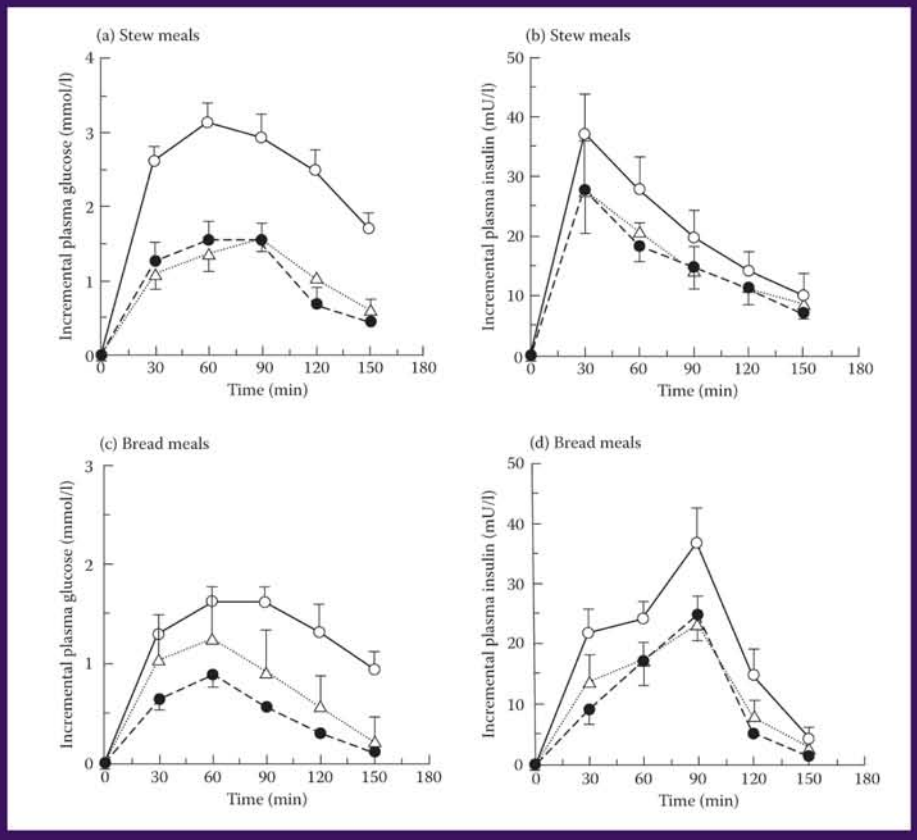
Traditional Herbal Medicines for Modern Times

Traditional Medicines for Modern Times

Antidiabetic Plants

Edited by

Amala Soumyanath



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Traditional Medicines for Modern Times

Antidiabetic Plants

Traditional Herbal Medicines for Modern Times

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Traditional Herbal Medicines for Modern Times

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Antidiabetic Plants

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Dedication

To our parents and forebears for their guidance and wisdom

Preface

Diabetes mellitus (diabetes) is a disease of worldwide significance and increasing prevalence. Plant materials have played an important role in the traditional treatment of diabetes, particularly the type II (non-insulin-dependent) form. In many regions of the world, herbal remedies continue to be more accessible and affordable than conventional drugs and represent the first line of treatment available to a diabetes patient. Concurrently, within societies with well-developed, modern health care systems, demand is growing for herbal remedies to complement prescribed, modern therapies for many diseases, including diabetes.

This volume is the first detailed compilation of information from across the world on plants used traditionally to treat diabetes and the scientific methods by which they can be and have been investigated. The book is divided into three main themes. It begins with an introduction to diabetes mellitus by a consultant physician and a major updated review and discussion of scientific information pertaining to traditional antidiabetic plants compiled by authors from the Royal Botanic Gardens, Kew, London. For those interested in performing research in this field, the next chapters provide an outline of clinical, *in vivo*, and *in vitro* methods for assessing antidiabetic activity of plant materials. Then follows a set of chapters by an international group of authors that describe traditional plant remedies used in Asia, the Americas, Africa, Europe, and Australia. The final chapters emphasize the role of particular phytochemical groups in the treatment of diabetes.

The potential role of plants in treating or preventing the complications of diabetes, is mentioned in the chapters on Chinese and Kampo medicines, a Western herbalist's perspective, and flavonoids, xanthones, and other antioxidant polyphenols. This latter chapter and that on plant polysaccharides highlight the important role of dietary plant materials in the prevention and control of diabetes. Indeed, it is believed that changes in diet from traditional plant foodstuffs containing beneficial components to richer, more processed and "junk" food is responsible for the increasing prevalence of diabetes worldwide.

A number of important points emerge from this volume. It is apparent that diversity as well as similarity can be found in the use of plants across the world. Understandably, each region of the world has developed a *materia medica* of antidiabetic remedies based on the local flora. However, the use of certain plants such as *Momordica charantia* L. (bitter melon) and *Trigonella foenum-graecum* L. (fenugreek) appears in more than one region. Climatic factors and cross-cultural communication play a role here. Generally, the use of a particular plant in a number of regions is strong evidence for its effectiveness. Diversity is also seen in the range of plant families and types of phytochemicals associated with antidiabetic activity. At the same time, certain groups, such as alkaloids, saponins, xanthones and flavonoids, and nonstarch polysaccharides appear to have effects of particular significance in diabetes treatment.

The extent to which various antidiabetic plants have been studied differs widely. For some (e.g., fenugreek, bitter melon, or gymnema [*Gymnema sylvestre* R. Br.]), detailed studies in humans, animals, and *in vitro* have resulted in the isolation of active compounds with recognizable modes of action. An interesting finding is that plants typically have more than one active component, often associated with more than one mode of action. Additive or synergistic effects between components undoubtedly occur, conforming to the view of traditional herbalists that the activity of a medicinal plant cannot be reproduced by the isolation of a single active component. Nevertheless, identification of actives and modes of action are important for drug development, and for the validation, standardization, and rational use of traditional herbal remedies.

To what extent has knowledge of traditional antidiabetic plants influenced the development of new antidiabetic drugs? Apart from the conventional drug metformin, which is based on the structure of galegine (a component of the European antidiabetic herb *Galega officinalis* L.), no new antidiabetic drugs derived from higher plants have been introduced into the market. This is rather surprising, given the large number of antidiabetic plants available and the wealth of documented information about them. One factor may be that research in the pharmaceutical industry has lately been heavily based on high-throughput *in vitro* screening programs. The capacity of these systems to handle large numbers of samples has led to random screening rather than selection from ethnobotanical materials. Complex extracts of natural products are, understandably, less attractive to the industry than screening single compounds from synthetic libraries because a "hit" would need to be followed up by isolation and identification of the active compound within the extract.

Legal access to plant material from other countries and conservation issues as covered by the Convention on Biodiversity and other international agreements are additional limiting factors. As a result, natural products derived from microbial sources have featured much more extensively in screening programs than have higher plants, let alone traditional plant remedies. A final factor is that high-throughput assays tend to be highly focused in their target mechanism and that, although effective in diabetes, the plant material may not work in that particular way. An alternate, more successful approach (pioneered by a smaller company) was to test ethnobotanically selected plants *in vivo* in experimental diabetic animals for initial determination of activity. This was followed by *in vivo* and *in vitro* testing to guide further fractionation. This approach has led to the identification of a number of active compounds as candidates for drug development. New investigational drugs must pass many hurdles relating to efficacy and toxicity issues before they are approved for use in the clinic; this, too, is a confounding factor in the introduction of new antidiabetic drugs from plant sources.

Much research on antidiabetic plants has been undertaken in academia. Indeed, the majority of the data described in this volume on activity and active components of these plants is from this source. This situation is likely to continue and, hopefully, increase in response to the growing prevalence of diabetes worldwide. Academia has traditionally been more inclined to follow ethnobotanical leads, but much of the early research led to publications rather than patents. A greater awareness of intellectual property issues coupled with greater synergy with the pharmaceutical industry may well lead to the development of new drugs from this route.

If not conventional drugs — what about herbal remedies for diabetes? Plant remedies have been and are being used by diabetic patients throughout the world. Research suggests that using an antidiabetic plant in whole form or as complex extracts may offer many benefits due to the presence of multiple active components. Of considerable benefit would be well researched herbal products based on traditional preparation methods and standardized to contain effective levels of the most important components for activity. Given the limited resources of most of the companies producing herbal products, research into these agents is, again, most likely to take place in an academic setting or by government-sponsored agencies as in many developing countries. It is also necessary for medicine's regulatory authorities to develop special criteria for the evaluation and licensing of herbal antidiabetic products. Finally, patients and health care providers need to be educated in the use of these products as sole or complementary treatments for diabetes in order to ensure their safe and effective use.

It is the hope of the editor that this volume will be of value to all those with an interest in antidiabetic plants and that it will facilitate the application of traditional knowledge to treatment of diabetes in modern and future times.

All the authors who contributed to this volume are very gratefully acknowledged.

Acknowledgments

I sincerely thank all the authors of this volume for their enthusiasm, their valuable contributions, and their patience with the editor during the long process of bringing this book to fruition. I express here my deep appreciation of my husband, K. Soumyanath, and my mother, Parvathi Raman. Their affection, encouragement, and practical support at a demanding time made it possible to undertake and complete this project.

Editor

Amala Soumyanath (née Amala Raman) is a classically trained pharmacognosist. She received a pharmacy degree from Chelsea College and a Ph.D. from King's College London (University of London, U.K.). She was senior lecturer in pharmacognosy in the Pharmacy Department, King's College London, until 2002, after which she moved to her present position as associate professor, Department of Neurology, Oregon Health & Science University, Portland. Her research centers on the identification of active components and mechanisms of action of traditional medicinal plants. At King's College London, Dr. Soumyanath led an active research group studying antidiabetic plants and developed a number of *in vitro* models to elucidate their modes of action and guide the isolation of active compounds. Her other research interests include plants used to treat skin diseases; her group discovered the potential of piperine and its analogs as treatments for the depigmentation disease, vitiligo. Currently, her research is focused on plants used for neurological disorders including diabetic neuropathy.

Dr. Soumyanath has served as a reviewer for numerous scientific journals in the fields of pharmacognosy, ethnopharmacology and phytotherapy and was reviews editor for the journal *Phytotherapy Research* from 1999 to 2002. She has also been involved in activities related to the use and quality control of botanical medicines and dietary supplements. Dr. Soumyanath has contributed as an author and advisor to the American Herbal Pharmacopoeia, as a member of the scientific advisory panel for the Medicinal Cannabis Research Foundation (U.K.), and served on the United States Pharmacopoeia Advisory Panel on Standards for Dietary Supplements and Natural Products. She currently holds a part-time position as director of research and development for Oregon's Wild Harvest, a grower and manufacturer of botanical dietary supplements. Dr. Soumyanath is the author of numerous peer-reviewed papers, reviews, and book chapters on the activity and quality control of traditional remedies and botanical dietary supplements.

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Table of Contents

1 Introduction to Diabetes Mellitus

Kevin C.R. Baynes

CONTENTS

WHAT IS DIABETES?

Diabetes mellitus is a metabolic disorder characterized by a predisposition to developing significantly raised blood glucose. The first recorded description of diabetes mellitus dates back to the Ebers papyrus in Egypt around 1500 B.C.[1] Diabetes mellitus has been noted in almost all ancient cultures with a tradition of written language such as Vedic, Chinese, Arabic, and Mediterranean

cultures. Diabetes is a major public health problem because it affects a significant minority of all populations and people with diabetes suffer more ill health and die younger.

Symptoms of diabetes mellitus include increased thirst as well as increased frequency and volume of urine production. These classical symptoms led to its naming from the Greek word for "a passing through," διαβητησ (δια — through or by; βαινω — a passing). Diabetes mellitus may lead to death if left untreated due to acute metabolic decompensation producing dehydration and acidosis. Even with treatment, over a period of years, elevated blood glucose levels result in damage to a number of organs, including the eyes, kidneys, nervous system, and blood vessels.

In normal individuals, glucose concentrations are tightly regulated by a number of hormonal factors. The disordered regulation of glucose metabolism that results in diabetes is usually due to a deficiency of insulin release from the pancreas and/or a reduced response to insulin.

PHYSIOLOGICAL ACTIONS OF INSULIN

Insulin Action on Glucose Metabolism

Insulin is the major regulator of blood glucose concentrations and has multiple actions on different tissues of the body. After an overnight fast, insulin levels are low and blood glucose concentrations are maintained by the supply of glucose from the liver. After complex carbohydrates are eaten, the intestine digests the food and the glucose produced is absorbed from the gut, causing an increase in blood glucose concentration. Release of insulin by pancreatic β-cells is stimulated by this rise in blood glucose concentration (Figure 1.1). Insulin reduces blood glucose mainly by reducing the supply of glucose from the liver, as well as by increasing the uptake of glucose by organs such as muscle and fat tissue. The concentration of insulin required to reduce glucose supply by the liver is probably lower than that needed to increase the uptake of glucose by muscle and fat. Once the blood glucose concentration starts to fall, the release of insulin is inhibited in a classical homeostatic negative feedback loop.

Insulin Action on Fat Metabolism

Energy is stored in fat tissue as droplets of triglycerides (fats) within cells. Triglycerides are formed biochemically by the combination of fatty acids with glycerol by enzymes found within fat cells. Breakdown of triglycerides stored in fat cells (lipolysis) by the enzyme hormone-sensitive lipase results in the appearance of fatty acids and glycerol in the bloodstream. Insulin, at relatively low concentrations, inhibits hormone-sensitive lipase, thus decreasing the release of fatty acids from fat tissue.[2] During fasting, fatty acids released from adipose tissue may be used by skeletal muscle

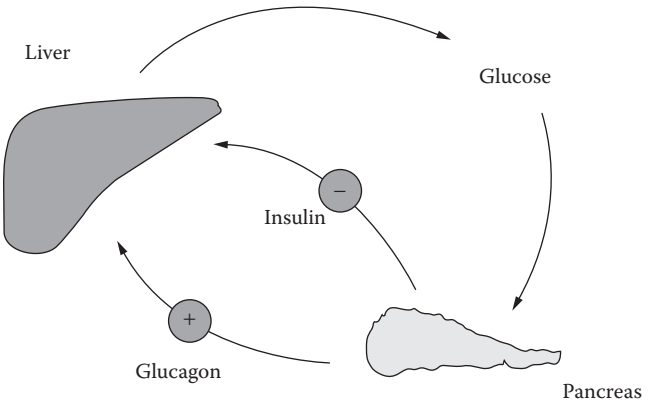

FIGURE 1.1 Actions of insulin and glucagon on hepatic glucose output.

and liver as a fuel source, thus reserving the supply of glucose as a fuel for other tissues, e.g., brain. During prolonged fasting, fatty acids may also be metabolized by the liver to form ketone bodies. Although the liver cannot use ketone bodies as a fuel source, other tissues are able to utilize them and they may become a major source of fuel in prolonged starvation.

Insulin Action on Protein Metabolism

Average protein turnover in a well-fed man is estimated to be 250 to 300 g daily — much greater than the average intake of protein of 75 to 100 g — so turnover of *endogenous* proteins accounts for the majority of daily protein turnover. Overall insulin has an anabolic action on protein turnover. *In vivo* studies suggest that the main effect of insulin appears to be a reduction in protein breakdown (proteolysis) in muscle and liver rather than a stimulation of protein synthesis.[3,4] In the insulin deficiency of diabetes, lack of insulin action on protein degradation contributes to weight loss by catabolism of lean tissue.

PHYSIOLOGICAL ACTIONS OF GLUCAGON

Although insulin is the main glucose-lowering hormone, a number of humoral factors may *increase* blood glucose concentrations, including glucagon, catecholamines, cortisol, and growth hormone. Glucagon is a peptide hormone released by α-cells of the pancreas in response to drops in blood glucose concentration. *In vivo* experiments in dogs have shown that glucagon secretion increases twofold in response to a fall in glucose from 100 mg/dl (5.6 mmol/l) to 80 mg/dl (4.5 mmol/l).[5] The principal target organ of glucagon action is the liver, in which it increases glycogenolysis and gluconeogenesis and inhibits glycogenesis and glycolysis.* Glucagon acts via hepatic cell surface G-protein-coupled receptors by a number of intracellular mechanisms whose net result is that hepatic glucose production increases and blood glucose rises. Increasing evidence suggests that, in type 2 diabetes, hyperglucagonemia and/or an imbalance between the glucagon:insulin ratio is present.[6]

MOLECULAR MECHANISMS OF INSULIN ACTION

Insulin exerts its effects on target organs (liver, muscle, fat) by binding to a cell surface receptor and activating a number of intracellular signaling cascades.[7,8] This is an area of intense scientific scrutiny because it is hoped that understanding the mechanism of action of insulin will reveal new drug targets that may be amenable to manipulation by small, nonpeptide agonists. The intracellular signaling cascades activated are, to some extent, tissue specific — one mechanism whereby insulin can have different effects on different organs. Even though a tissue may not possess many insulin receptors, it must also be remembered that insulin can exert an indirect effect by altering the flux of metabolites (e.g., fatty acids) delivered to or extracted from that tissue.[9,10]

Insulin binds reversibly to cell surface transmembrane receptors that are found in highest concentrations in insulin-sensitive tissues (Figure 1.2). The intracellular region of the insulin receptor possesses tyrosine kinase activity (enzymatic activity adding phosphate groups to tyrosine residues in proteins). Binding of insulin to its receptor is thought to induce a conformational change in the insulin receptor molecule; this increases its tyrosine kinase activity, which then autophosphorylates multiple tyrosine residues within its intracellular portion.[8] Phosphorylated tyrosine residues on the insulin receptor create binding sites for a number of soluble intracellular proteins that attach to the insulin receptor and are phosphorylated by the insulin receptor tyrosine kinase.[11] This initial event precipitates the activation of a number of diverging intracellular signaling cascades

* Glycogenolysis is the breakdown of glycogen into glucose; glycogenesis is the formation of glycogen from glucose precursors; gluconeogenesis is the formation of new glucose molecules from substrates such as lactate and amino acids; and glycolysis is the conversion of glucose into other molecules to release energy.

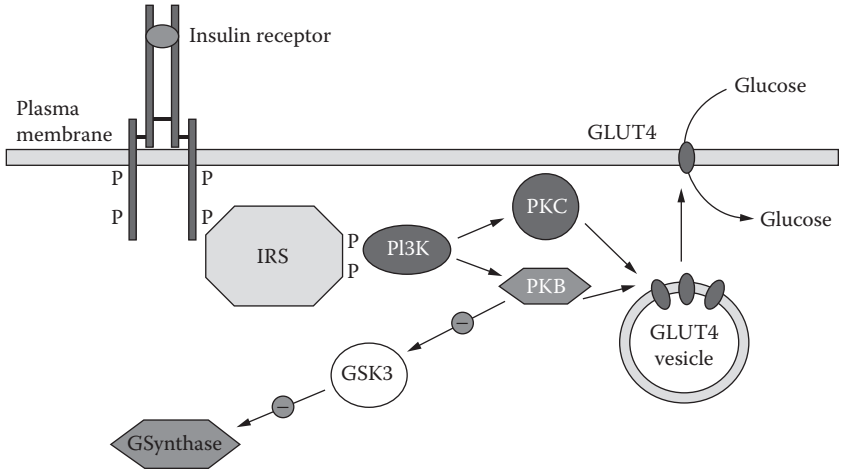

FIGURE 1.2 Simplified schematic of molecular effectors of insulin action. (IRS — insulin receptor substrate; PI3K — PI-3 kinase; PKC — protein kinase C; PKB — protein kinase B; GLUT4 — insulin-sensitive glucose transporter; GSK3 — glycogen synthase kinase-3; GSynthase — glycogen synthase; P — phosphate groups)

involving other tyrosine kinases, serine kinases, and lipid kinases. The principal molecules involved include the lipid kinase PI 3-kinase, protein kinase B, glycogen synthase kinase-3, and certain isoforms of protein kinase C (Figure 1.2).[12]

Two major endpoints of insulin action are stimulation of glucose uptake into skeletal muscle and adipose tissue, and stimulation of glycogen storage in the liver. Insulin stimulates the translocation of the glucose transporter GLUT4 from an intracellular location up to the plasma membrane in insulin-sensitive tissues, allowing glucose to enter cells down its concentration gradient.[13,14] This effect of insulin on cellular glucose uptake depends on the upstream signaling molecules PI 3-kinase and protein kinase C.[12] The effect of insulin on glycogen synthesis is partly due to PI 3-kinase-dependent inhibition of glycogen synthase kinase-3 (Figure 1.2).[12]

CLASSIFICATION OF DIABETES

Diabetes mellitus is not a single disorder, but a collection of conditions with a common end result of raised blood glucose. Two main types of diabetes account for more than 95% of all cases of diabetes; a minority of cases are due to various specific metabolic or genetic causes. Type 1 diabetes is a condition due to absolute insulin deficiency secondary to autoimmune destruction of the insulin-containing β-cells of the pancreas gland. Type 2 diabetes is a condition due to *relative* insulin deficiency and/or impaired biological response to insulin ("insulin resistance").[15] Type 1 diabetes probably represents 5 to 10% of all cases of diabetes, and type 2 diabetes accounts for 85% of all cases. Other forms of diabetes may be secondary to other metabolic disorders, such as the endocrine disorder acromegaly in which excessive production of growth hormone inhibits the action of insulin or due to pancreatic problems (e.g., after surgical removal of pancreas) (Table 1.1). Individuals are usually classified as having type 1 or 2 diabetes based on their presentation, age, and other clinical features.

DISEASE MECHANISMS IN DIABETES

Type 1 Diabetes

Immunology. Type 1 diabetes is almost always the result of an autoimmune disease process, which selectively destroys the insulin-producing β-cells of the pancreas. Histological examination of the

TABLE 1.1
Classification of Diabetes Mellitus

Type 1 diabetes mellitus
Type 2 diabetes mellitus
Gestational diabetes
Other forms:
Pancreatic disease: fibrocalculous pancreatopathy, chronic pancreatitis, pancreatectomy, cystic fibrosis, haemochromatosis, pancreatic carcinoma
Endocrine: Cushing's syndrome, acromegaly, thyrotoxicosis, phaeochromocytoma
Drug induced: corticosteroids, thiazide diuretics
Conditions with specific genetic causes: e.g., maturity-onset diabetes of the young

pancreas of subjects with type 1 diabetes shows infiltration of the islets of Langerhans with inflammatory white blood cells. Blood from subjects with type 1 diabetes has been found to contain a number of autoantibodies to components of the pancreas, including islet cell antibodies (ICA), insulin autoantibodies (IAA), and antibodies against glutamic acid decarboxylase (GAD) and insulinoma-associated autoantigen-2 (IA-2) (proteins found in pancreatic β-cells).[16] Family studies have shown that these antibodies may be found in a proportion of first-degree relatives of patients with type 1 diabetes, some of whom later develop diabetes.

Genetics. A number of lines of evidence suggest a genetic predisposition to developing type 1 diabetes. The lifetime risk of type 1 diabetes is 0.4% in white populations and rises to 5 to 6% if a first-degree relative is affected. Concordance rates for monozygotic (identical) twins are approximately 50%, but only 6% for dizygotic (nonidentical) twins.[17] Genome-wide screens for susceptibility genes for type 1 diabetes have identified more than ten chromosomal loci.[18–21] The two loci that contribute most to the risk of type 1 diabetes are the HLA region (tissue compatibility genes) and the insulin gene locus. Detailed analysis of the HLA region on chromosome 6 has shown that HLA DR3 and DR4 haplotypes increase and HLA DR2 haplotype decreases the risk of type 1 diabetes. Because HLA cell surface molecules are involved in activating T-cell immune responses, it is hypothesized that the DR3 and DR4 forms somehow induce an aberrant immune response, perhaps secondary to a viral infection.

Type 2 Diabetes

Type 2 diabetes is a more heterogeneous disease compared to type 1 diabetes. Most subjects with type 2 diabetes have a condition called insulin resistance. This is a state in which more than normal amounts of insulin are needed to produce a normal metabolic response to insulin.[22] Insulin resistance is asymptomatic and may be found in subjects years before they develop type 2 diabetes.[23,24] As long as the pancreas is able to secrete increased amounts of insulin to counter the reduced response to insulin, blood glucose levels stay within the normal range in individuals with insulin resistance. If the pancreas is unable to keep up with the demand for higher insulin secretion rates, blood glucose concentrations start to rise and diabetes may ensue. Biochemical investigation has shown that insulin concentrations are higher than normal in subjects with insulin resistance and are "normal" in patients with type 2 diabetes of short duration.[25] Thus, patients with type 2 diabetes have *relative* insulin deficiency.

Pancreatic defects. *In vitro* experiments show that insulin release by pancreatic β-cells has an initial first phase lasting about 10 minutes, followed by a more long lasting second phase of gradually increasing insulin release over 2 to 3 hours. The first phase corresponds to release of insulin granules near the plasma membrane and the second to increased synthesis of insulin and transport from storage granules to plasma membrane granules. Both phases of insulin release are blunted in individuals with type 2 diabetes and impaired glucose tolerance (a condition in which

blood glucose concentrations rise above normal, but not into the diabetic range).[26,27] It has been calculated that β-cell function is impaired by approximately 50% by the time diabetes occurs.[28] Dose–response experiments suggest that the defect in insulin secretion is due to a reduced capacity to secrete insulin rather than insensitivity to glucose as a stimulus for insulin secretion. This is partially, but not wholly, explained by the estimated 30% loss of β-cell mass found in type 2 diabetes. First-phase insulin release is also blunted in individuals with a family history of diabetes but normal glucose tolerance, suggesting a genetic contribution to β-cell function.[29]

Histological examination of pancreatic tissue from subjects with type 2 diabetes shows accumulation of fibrils of amyloid protein, but no inflammatory infiltrate. It is not clear whether the amyloid fibrils play a role in causing pancreatic damage or are a secondary phenomenon.

Genetics. Twin studies show a higher concordance rate for type 2 diabetes for monozygotic compared to dizygotic twins. A number of monogenic causes of apparent type 2 diabetes have been established, such as maturity onset diabetes of the young (MODY), an autosomal dominant form of diabetes affecting adults under the age of 25 years.[30–35] These monogenic forms of type 2 diabetes probably represent less than 5% of those with type 2 diabetes. Genome-wide scans for type 2 diabetes susceptibility genes have produced less uniform results compared to studies of type 1 diabetes. One locus on chromosome 2, originally identified as *NIDDM1*, has been shown to contain a protease (calpain-10) that appears to have a role in pancreatic function.[36] Overall, type 2 diabetes is thought to be a polygenic disorder with many genes contributing small effects to lifetime risk of diabetes combined with environmental factors. The difficulty in identifying these genes lies partly with the need for very large-scale studies to exclude the possibility of false positive results.

Insulin resistance. The most common associations with insulin resistance are obesity and lack of physical fitness. A wide range of other conditions is associated with insulin resistance (see Table 1.2) and many also increase the risk of developing diabetes. In prospective studies, obesity is the strongest modifiable risk factor that predicts future risk of diabetes in nondiabetic populations.[37] Body fat distribution is important also; visceral (abdominal) obesity, as measured by the waist:hip ratio, is a stronger predictor than body mass index.[38] It is thought that the increased fat mass in obese individuals augments insulin resistance by a number of different mechanisms, including increased release of free fatty acids and a number of adipocytokines including tumor necrosis factor-α, leptin, resistin, and interleukin-6. Some workers have also proposed, in the "lipotoxicity theory" that obesity not only affects insulin sensitivity, but also pancreatic function, with excess fatty acids inhibiting insulin release.[39]

Fetal nutrition. Epidemiological studies initiated by Barker and coworkers have suggested a novel theory of pathogenesis for type 2 diabetes.[40,41] Prevalence of type 2 diabetes has been shown to be higher in low-birth-weight babies compared to high-birth-weight babies. It has been suggested

TABLE 1.2
Factors Associated with Insulin Resistance

Obesity
Lack of physical fitness
First degree relative with type 2 diabetes
Essential hypertension
Coronary artery disease
Pregnancy
Polycystic ovary syndrome
Endocrine disorders — e.g., acromegaly, Cushing's syndrome
Drug therapies — e.g., protease inhibitors, corticosteroids, thiazide diuretics
Longstanding hyperglycemia
Elevated free fatty acids

that fetal undernutrition during pregnancy results in defective pancreatic organogenesis and a pancreas at risk of failure in later life, perhaps due to induction of longstanding "programmed" changes in metabolic function.[42]

CLINICAL PRESENTATION OF DIABETES

Type 1 Diabetes

Type 1 diabetes usually presents in children or young adults with acute symptoms of diabetes (thirst, increased urination, tiredness, blurred vision) associated with weight loss. Peak incidence is between 11 and 13 years, although it may present at any age. The incidence of type 1 diabetes appears to be increasing, especially in the under age 5 age group.[43] Sex distribution is roughly equal.[44]

Biochemical investigation of patients with type 1 diabetes shows that they have *absolute* insulin deficiency. Hyperglycemia occurs due to a lack of the effect of insulin to inhibit production of glucose by the liver, which continues unopposed. In the absence of insulin, fat stores are broken down (lipolysis) and increased amounts of free fatty acids reach the liver. Once at the liver, the fatty acids are further metabolized into ketone bodies that circulate in the bloodstream and, once present in excess, produce an acidosis of the bloodstream. Weight loss occurs in type 1 diabetes due to a combination of breakdown of fat and lean tissue and dehydration. Uncontrolled type 1 diabetes with high blood glucose, excess ketone bodies, and acidosis (diabetic ketoacidosis) is a medical emergency requiring hospital admission. Patients with type 1 diabetes have absolute insulin deficiency and require long-term insulin therapy for continued well-being.

Type 2 Diabetes

Type 2 diabetes usually presents in adults over the age of 30 with symptoms of diabetes or a complication related to diabetes or as a chance finding in an asymptomatic individual. The combination of insulin resistance and relative insulin deficiency contributes to the development of hyperglycemia in type 2 diabetes.[45] Lack of insulin action at the liver results in overproduction of glucose by the liver, especially in the fasting state; lack of insulin action in fat and skeletal muscle reduces the uptake of glucose by these tissues after food intake. Subjects with type 2 diabetes have a low risk for developing ketoacidosis because lipolysis is inhibited by the modest concentration of circulating insulin. Because overweight and obesity are major risk factors for type 2 diabetes, the majority of subjects are obese at presentation. Sex distribution is roughly equal, but with a slight preponderance in men in some studies (e.g., men 61%, women 39% in the UKPDS study).[46]

The prevalence of type 2 diabetes increases with age in all populations studied; for example, in the U.S., 6.8% of men aged 40 to 49 had diabetes compared to 21.1% of men aged over 75 years, according to NHANES III, 1994 (Figure 1.3).[47] Possible explanations for this phenomenon are the increase in body fat and reduction in lean body tissue with ageing, reduction in pancreatic capacity due to loss of β-cells by apoptosis, reduction in physical activity, and increased likelihood to be prescribed diabetogenic drugs.

Patients with type 2 diabetes may be managed by dietary change, exercise prescription, oral drug therapy, or insulin therapy. Despite treatment, the natural history of most subjects with type 2 diabetes is that increasing amounts of oral drugs are required to produce adequate glucose concentrations. Many patients need to transfer to treatment with insulin with the inconvenience of self-injection, requirement to monitor blood glucose levels, and increased risk of hypoglycemia (e.g., 38% of patients in the intensive glucose control group of the UKPDS study eventually received insulin).[46]

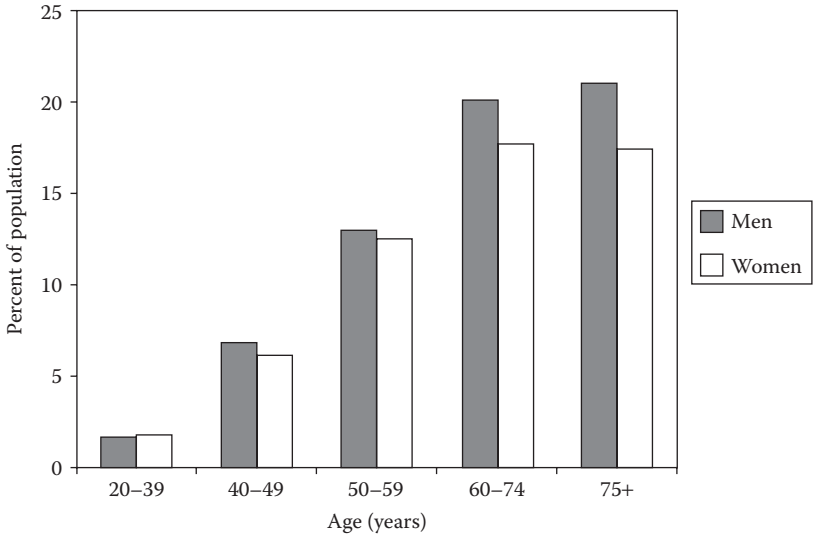

FIGURE 1.3 Effect of age on prevalence of diabetes in U.S. men and women in NHANES III (Third National Health and Nutrition Examination Survey), 1988–1994. (Reproduced from Harris, M.I. et al., *Diabetes Care* 21, 518–524, 1998. With permission.)

LONG-TERM COMPLICATIONS OF DIABETES

Diabetes mellitus is a long-term disorder associated with a number of clinical problems causing ill health and death. Disease affecting the small blood vessels in the retina, kidney, and peripheral nerves appears to be most directly related to the duration and severity of the raised blood glucose (hyperglycemia). These complications are termed "microvascular" and may result in blindness, chronic renal failure requiring dialysis, and nerve damage to the feet contributing to the formation of foot deformity and ulceration. Large blood vessels are also affected ("macrovascular" disease) in the heart, brain, and peripheral circulation. People with diabetes have higher rates of coronary heart disease,[48,49] stroke,[50] and peripheral vascular disease[51] compared to similar subjects of the same age and sex. This contributes significantly to the higher rates of ill health and early death in people with diabetes.

GLOBAL BURDEN OF DIABETES AND ETHNICITY

Diabetes mellitus is a worldwide disorder, but the incidence (number of new cases per year per unit of population) and prevalence (number of known cases per unit of population) vary significantly with geographical location. Type 1 diabetes has high prevalence in Scandinavian countries and Malta and low prevalence in Japan (Figure 1.4a). Type 2 diabetes has very high prevalence in Pima Indians (who originate from Arizona in the U.S.) and Pacific Islanders (e.g., Nauru) and high prevalence in South Asians, Hispanics, and Africans (Figure 1.4b). Relative risk of developing diabetes is approximately fourfold in South Asians from the Indian subcontinent and twofold in African–Caribbean people compared to white Caucasians from the same geographical area. Migration studies in a number of different populations have shown that the prevalence of type 2 diabetes increases with increasing "Westernization" of migrant populations. This is probably due to a mix of factors, such as reduction in physical activity level, increase in food availability, change in dietary patterns away from healthier traditional foodstuffs, and an increase in obesity.

Recent trends in diabetes prevalence over the last few decades have suggested significant increases in prevalence in most countries studied.[52,53] The total number of people with diabetes was

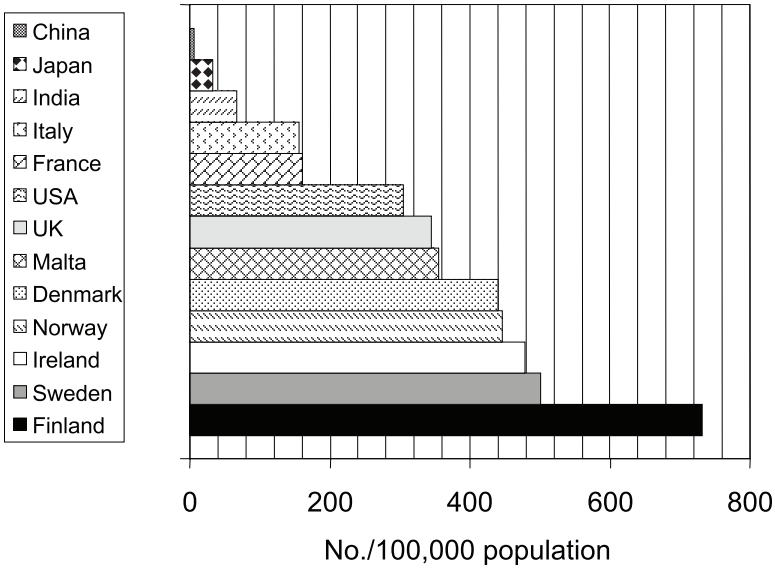

FIGURE 1.4a Estimated prevalence of Type I diabetes in different countries in 1995. Countries selected to display high to low range of prevalence. (Figure prepared with data from Amos, A.F. et al., *Diabetic Med.* 14, S7–S85, 1997.)

estimated to be 171 million in 2000 and is projected to be 366 million by 2030 (Figure 1.5).[54] The most dramatic increases have been recorded in developing countries such as India and China — almost all accounted for by cases of type 2 diabetes. This is due partly to an increase in longevity in these populations and partly to increasing prevalence of obesity. In developed countries, the increase in diabetes prevalence is mostly accounted for by the increasing prevalence of obesity.

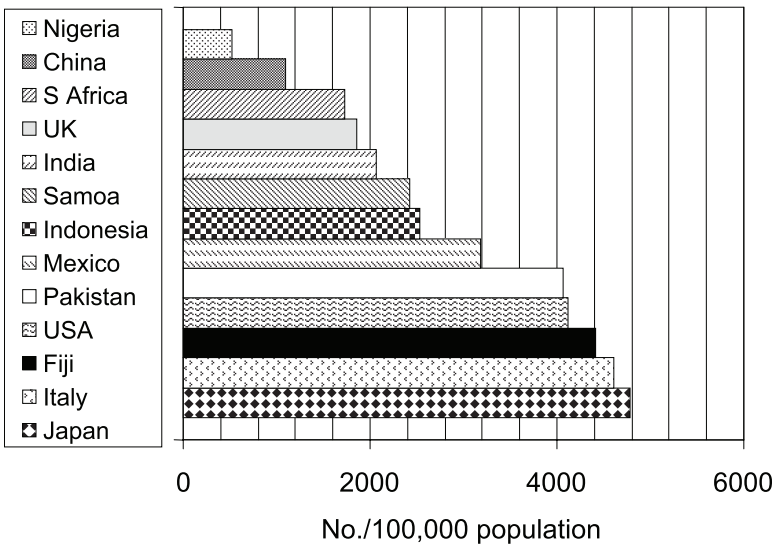

FIGURE 1.4b Estimated prevalence of Type II diabetes in different countries in 1995. Countries selected to display high to low range of prevalence. (Figure prepared with data from Amos, A.F. et al., *Diabetic Med.* 14, S7–S85, 1997.)

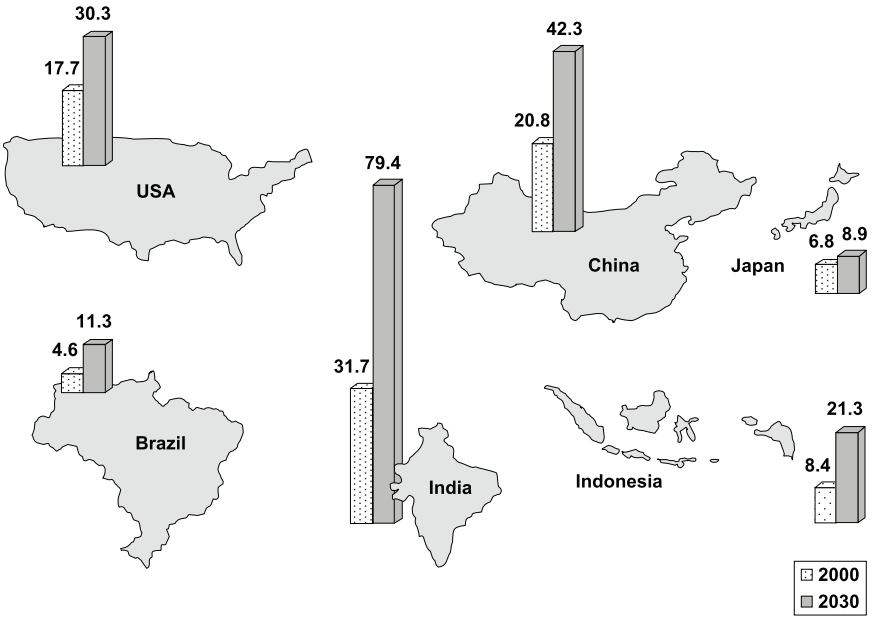

FIGURE 1.5 Estimated cases of diabetes (millions) in 13 countries in 2000 and projected to 2030. (Figure prepared with data from Wild, S. et al., *Diabetes Care* 27, 1047–1053, 2004.

DIABETES TREATMENT OPTIONS

Diabetes physicians have traditionally focused on treatments to reduce hyperglycemia. Good evidence from randomized, controlled trials now indicates that reducing hyperglycemia reduces the risk of microvascular complications of diabetes.[46,55] Subjects with diabetes also carry at least a doubling of risk of cardiovascular disease.[56] Whether lowering glucose improves cardiovascular risk is currently uncertain, but the effect, if present, is likely to be modest.[46,56–59] Potential treatments for lowering glucose in diabetes mellitus will be considered here in a rather theoretical way because this may illuminate the mechanisms by which some of the evaluated plant treatments have an effect (Table 1.3).

TABLE 1.3
General Mechanisms for Potential Diabetes Treatments

Mechanism	Example
Delay gastric emptying	GLP-1
Reduce absorption of dietary carbohydrate	Acarbose, guar gum
Increase pancreatic insulin secretion	Sulfonylureas, glitinides, GLP-1, liraglutide, exendin-4
Insulin replacement	Insulin injection, pancreas transplant
Insulinomimetic agents	
Reduce hepatic glucose output	Metformin, insulin, glucagon antagonists
Increase insulin sensitivity	Metformin, thiazolidinediones
Weight loss and exercise	
Alter renal glucose handling	

Delay Gastric Emptying

Reducing gastric motility will result in a slower delivery of carbohydrate-containing foods to the small intestine and may also increase gastric distension, resulting in a smaller volume of food being consumed. It has been suggested that part of the efficacy of the gut peptide glucagon-like peptide 1 (GLP-1) in type 2 diabetes is by decreasing gastric motility.[60] Cholecystokinin (CCK) has also been investigated as a peptide agent to reduce gastric emptying.[61] Reduction in food intake due to gastric distension does not necessarily reduce total calorie intake because the time gap between meals may be reduced in compensation. Any treatments that act primarily by slowing gastric motility are likely to have nausea and vomiting as adverse effects, thus limiting their acceptability as long-term treatments.

Reduce Absorption of Carbohydrate

Restriction of carbohydrate-containing foods is an obvious method of reducing alimentary absorption of carbohydrate. Foods that are high in soluble fiber (e.g., pulses) also slow absorption of carbohydrate (low glycemic index foods). Guar gum is a plant extract high in soluble fiber that has modest effects on glycemia in type 2 diabetes.[62] Complex carbohydrates need to be digested by intestinal enzymes — e.g., amylase — to monosaccharide subunits before absorption by the intestinal brush border. Inhibition of certain disaccharidase enzymes found at the intestinal epithelium is the basis of the α_1-glucosidase group of drugs, e.g., acarbose.[63] Absorption of glucose from the intestinal lumen occurs by an active process by sodium-linked glucose transporters, which are also a potential drug target.

Increase Pancreatic Insulin Secretion

Hyperglycemia occurs in type 2 diabetes due to impaired insulin secretion, often in the face of increased requirement for insulin due to insulin resistance. The sulfonylurea class of drugs increases insulin secretion by closing the ATP-sensitive potassium channel (K_{ATP}) on β-cells responsible for stimulus–response coupling of insulin secretion.[64] The more recently developed class of insulin secretagogues, the glitinides, also act by binding to the K_{ATP} channel, but with differing binding characteristics. Both these groups of drugs result in enhanced release of insulin from pancreatic islets and have the potential to cause hypoglycemia because insulin release is decoupled from prevailing glucose concentrations. The efficacy of sulfonylurea drugs is limited by progressive loss of β-cell reserve over time; after 10 years of use, they are often unable to stimulate sufficient insulin release to have a clinical effect. This "secondary sulfonylurea failure" is a major limitation to the treatment of type 2 diabetes.

Physiological release of insulin is also modulated by humoral factors secreted by the gut in response to food ingestion, including GLP-1 and GIP (gastric inhibitory peptide). These peptides enhance release of insulin stimulated by physiological triggers such as rise in blood glucose. One attraction of GLP-1 is that, because it enhances *glucose-dependent* insulin release, it is unlikely to cause hypoglycemia.[65] One problem with GLP-1 as a clinical treatment is that it has a short plasma half-life due to digestion by circulating proteases. This has led to the development of protease-resistant analogues such as liraglutide[66,67] and exendin 4 (a peptide found in the saliva of the Gila monster [a type of reptile]).

Insulin Replacement

Insulin deficiency is logically treated by replacing the absent insulin peptide. This is the mainstay of treatment for patients with the absolute insulin deficiency found in type 1 diabetes and is frequently necessary for many patients with type 2 diabetes when they fail to respond to oral drug therapy. Exogenous insulin therapy, given by subcutaneous injection, does not closely match

physiological release of insulin. Hypoglycemia may occur when a mismatch occurs between carbohydrate intake and circulating insulin concentrations. Insulin-treated patients have the highest risk of severe hypoglycemia and the risk increases when lower glucose levels are pursued. Fear of hypoglycemia and dislike of injections are major obstacles to uptake of insulin therapy. Insulin analogues with different pharmacokinetic profiles that are less likely to cause hypoglycemia when used appropriately have been developed; however, cost currently restricts their use in developing countries.[68] At the present time, insulin replacement by pancreatic transplantation or islet cell transplantation are treatment options for only a minority of patients with type 1 diabetes in developed countries.[69,70]

Insulinomimetic Agents

The need to inject insulin to bypass digestion of the peptide by gastrointestinal enzymes and increase its bioavailability is a major drawback to its acceptability. The insulin receptor is a cell surface protein, so it is theoretically possible that compounds will be discovered that are absorbed orally and can bind and activate the insulin receptor.[71] This might be by binding to the insulin-binding sites on the extracellular domain of the insulin receptor or by activating its intracellular domain tyrosine kinase activity by another mechanism. Alternatively, given the large number of protein kinases involved in insulin signaling to metabolic endpoints of insulin action, small molecules may potentially activate downstream intracellular second messengers of insulin action.

Reduce Hepatic Glucose Output

Fasting hyperglycemia in type 2 diabetes is mainly determined by unrestrained hepatic glucose output (HGO); thus, any treatments that reduce HGO will lower glucose levels. This is one major mechanism whereby metformin seems to have its antidiabetic activity, although the molecular/pharmacological mechanism by which it is achieved is debated. One of the main actions of insulin in lowering blood glucose concentrations is by a reduction in HGO. Because one of the main effects of glucagon is to increase HGO, any method to impair glucagon's action will also tend to reduce blood glucose.[6] The antidiabetic activity of GLP-1 in type 2 diabetes has been partially attributed to lowering of glucagon concentrations[65] and glucagon receptor antagonists are in development.[6] Alternatively, inhibiting the hepatic enzymes involved in glycogenolysis or hepatic gluconeogenesis would be expected to reduce HGO.[72]

Increase Insulin Sensitivity

Insulin resistance (the reduced biological effectiveness of the same quantity of insulin) is a pathophysiological hallmark of type 2 diabetes. Lifestyle changes and pharmacological methods to increase insulin sensitivity have been pursued as logical treatments for this condition. Metformin has long been known to increase insulin sensitivity. More recently, the thizolidinedione class of drugs — agonists of a nuclear hormone receptor PPAR-γ (peroxisome proliferator activated receptor γ) — have been introduced into clinical practice as a treatment for type 2 diabetes.[73,74] One mechanism by which PPAR-γ agonists increase insulin sensitivity is by increasing the transcription of certain insulin-sensitive genes. Other drugs that stimulate the transcription of insulin-sensitive genes via activation of other transcription factors are under consideration by pharmaceutical companies.[75]

Weight Loss and Exercise

Weight loss, especially loss of visceral (abdominal) fat tissue, is an effective treatment for type 2 diabetes. This is due partly to restriction of calorie and carbohydrate intake, but weight loss also improves insulin sensitivity so that glucose levels remain lower even if calorie intake is temporarily increased. High plasma fatty acid concentrations found in obesity have been hypothesized to

increase hepatic glucose output and inhibit insulin signaling in skeletal muscle.[10,76] Weight loss results in a lower total fat mass available to release fatty acids into the bloodstream so that plasma fatty acid levels fall.

Exercise improves insulin sensitivity by a number of mechanisms[77] and lowers glucose concentrations in type 2 diabetes. Long-term exercise reduces the amount of visceral fat[78] and also increases glucose disposal into skeletal muscle in the postprandial period. One mechanism by which acute exercise increases glucose disposal is to activate AMP kinase in skeletal muscle, which stimulates translocation of GLUT4 glucose transporters to the cell surface.[79] This effect is independent of insulin, making it an attractive potential drug target. Long-term exercise results in an increase in skeletal muscle content of GLUT4 glucose transporters[80] and increased use of fatty acids by skeletal muscle as a metabolic fuel.

Lifestyle change with increased exercise and weight loss has been shown to prevent the development of type 2 diabetes in those at high risk — indeed, lifestyle change is more effective than metformin alone in the same setting.[81–83] Promoting exercise and maintenance of a healthy weight is a major public health challenge for governments attempting to turn the tide of the increasing prevalence of type 2 diabetes.

Alter Renal Glucose Handling

Loss of glucose in the urine (glycosuria) usually occurs at a variable threshold when arterial glucose rises over 200 mg/dl (11 mmol/l) due to the limited capacity of glucose transporters in the renal tubules to reabsorb all the filtered load of glucose. Inhibition of these renal glucose transporters will theoretically result in glycosuria at lower arterial glucose concentrations, limiting the rise in blood glucose. The kidney also makes a 10% contribution to gluconeogenesis in the fasting state, so suppression of renal gluconeogenesis may hypothetically have a small effect on fasting hyperglycemia.

UNMET NEEDS

Treatment of diabetes mellitus poses a number of problems for the individual with the condition:

- Diabetes management requires input from health professionals to achieve optimum management over a lifetime.
- Often, in middle-aged individuals with longstanding habitually poor diet and exercise regimens, changes in diet and lifestyle are difficult to implement and maintain.
- Oral drug treatment often requires combinations of drugs with an increased potential for adverse effects.
- Oral drug treatments often fail to control hyperglycemia due to progressive loss of pancreatic β-cell function and insulin treatment is required.
- Insulin treatment is unpopular due to fear of injections (“needle phobia”), fear of stigmatization, fear of hypoglycemia, lack of money, or for reasons related to family stories.

The rising incidence and prevalence of diabetes, especially in developing countries, means that governments and individuals will be faced with challenges. People without access to modern medicines, as well as those in developed countries looking to avoid drug use, will look to use naturally occurring, botanically based therapies. Plant treatments may be more culturally acceptable for some people and exploiting foodstuffs as diabetes treatments may be easier to incorporate into a lifestyle than taking a tablet or injections. Using plant treatments on a daily basis, however, may not be possible for many because of seasonal availability of fresh produce or their unpalatability.

Many of the currently available treatments for type 2 diabetes aim to reduce hyperglycemia, but none have so far convincingly demonstrated that they can significantly alter the natural history

of the progressive loss of pancreatic insulin secretion that results in the need for insulin injection therapy. Treatments that preserve or, indeed, increase β-cell mass would be a major advance.

Current treatments to reduce the risk of diabetic microvascular complications concentrate on limiting hyperglycemia and meticulous control of blood pressure. It has been postulated that the cellular toxin is not glucose itself, but rather a metabolite of glucose such as methylglyoxal.[84,85] Theoretically, agents that reduce the accumulation of toxic metabolites of glucose may prevent diabetic complications without affecting glucose levels. This would be an advance because diabetes management would then be able to concentrate on preventing toxin accumulation rather than on glucose exposure alone. A treatment protocol combining moderate glucose lowering (and thus minimal risk of hypoglycemic events) with reduction in toxic glucose metabolites might be superior to intensive glucose lowering in preventing diabetic complications.

The predicted continuing surge in prevalence of diabetes mellitus worldwide will demand new solutions to be found for treatment and prevention. Because humanity does not appear inclined to take more exercise or avoid corpulence, the emphasis over the next few decades is likely to be on treating diabetes and perhaps screening for asymptomatic individuals. Despite major advances in knowledge about whole-body physiology and the molecular mechanisms involved in glucose homeostasis, this has not been translated into an armamentarium of new drug treatments for diabetes. Discovery of compounds with antidiabetic activity in traditional plant remedies remains a medically legitimate and potentially commercially rewarding activity.

REFERENCES

1. Tattersall, R.B., The history of diabetes mellitus, in *Textbook of Diabetes*, 3rd ed., Pickup, J.C. and Williams, G. Blackwell Science, Oxford, 2003, 1.1–1.22.
2. Bonadonna, R.C. et al., Dose-dependent effect of insulin on plasma free fatty acid turnover and oxidation in humans, *Am. J. Physiol.* 259, E736–E750, 1990.
3. Moller–Loswick, A.C. et al., Insulin selectively attenuates breakdown of nonmyofibrillar proteins in peripheral tissues of normal men, *Am. J. Physiol.* 29, E645–E652, 1994.
4. Louard, R.J. et al., Insulin sensitivity of protein and glucose metabolism in human forearm skeletal muscle, *J. Clin. Invest.* 90, 2348–2354, 1992.
5. Cherrington, A.D., Control of glucose uptake and release by the liver *in vivo*, *Diabetes* 48, 1198–1214, 1999.
6. Jiang, G. and Zhang, B.B., Glucagon and regulation of glucose metabolism, *Am. J. Physiol.* 284, E671–E678, 2003.
7. Saltiel, A.R. and Kahn, C.R., Insulin signaling and the regulation of glucose and lipid metabolism, *Nature* 414, 799–806, 2001.
8. White, M.F. and Kahn, C.R., The insulin signaling system, *J. Biological Chem.* 269(1), 1–4, 1994.
9. Barrett, E.J., Insulin's effect on glucose production: direct or indirect? *J. Clin. Invest.* 111(4), 434–435, 2004.
10. Boden, G. et al., FFA cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis, *Am. J. Physiol.* 283, E12–E19, 2002.
11. Keller, S.R. and Lienhard, G.E., Insulin signalling: the role of insulin receptor substrate 1, *Trends Cell Biol.* 4, 115–119, 1994.
12. Shepherd, P.R., Withers, D.J., and Siddle, K., Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling, *Biochem. J.* 333(Pt3), 471–490, 1998.
13. Bryant, N.J., Govers, R., and James, D.E., Regulated transport of the glucose transporter GLUT4, *Nat. Rev.: Molecular Cellular Biol.* 3, 267–277, 2002.
14. Shepherd, P.R. and Kahn, B.B., Glucose transporters and insulin action, *N. Engl. J. Med.* 341, 248–257, 1999.
15. World Health Organization, Definition, diagnosis and classification of diabetes mellitus and its complications — part 1: diagnosis and classification of diabetes mellitus, WHO, Geneva, 1999.

16. Petrovsky, N. and Schatz, D.A., The immunology of human type 1 diabetes, in *Textbook of Diabetes*, 3rd ed., Pickup, J.C. and Williams, G. Blackwell Science, Oxford, 2003, 18.11–18.14.
17. Kelly, M.A., Mijovic, C.H., and Barnett, A.H., Genetics of type 1 diabetes, *Best Prac. Res. Clin. Endocrinol. Metab.* 15(3), 279–291, 2001.
18. Concannon, P. et al., A second-generation screen of the human genome for susceptibility to insulin-dependent diabetes mellitus, *Nat. Genet.* 19, 292–296, 1998.
19. Cox, N.J. et al., Seven regions of the genome show evidence of linkage to type 1 diabetes in a consensus analysis of 767 multiplex families, *Am. J. Hum. Genet.* 69, 820–830, 2001.
20. Davies, J.L. et al., A genome-wide search for human type-1 diabetes susceptibility genes, *Nature* 371(6493), 130–136, 1994.
21. Mein, C.A. et al., A search for type 1 diabetes susceptibility genes in families from the United Kingdom, *Nat. Genet.* 19, 297–300, 1998.
22. Krentz, A.J., *Insulin Resistance*, Blackwell Science, Oxford, 2002.
23. Mahler, R.J. and Adler, M.L., Type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment, *J. Clin. Endocrinol. Metab.* 84(4), 1165–1171, 1999.
24. Reaven, G.M., Role of insulin resistance in human disease, *Diabetes* 37(12), 1595–1607, 1988.
25. Yalow, R.S. and Berson, S.A., Plasma insulin concentrations in nondiabetic and early diabetic subjects: determinations by a new sensitive immunoassay technique, *Diabetes* 9, 254–260, 1960.
26. Ferrannini, E. et al., Predominant role of reduced beta-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance, *Diabetologia* 46, 1211–1219, 2003.
27. Pratley, R.E. and Weyer, C., The role of impaired early insulin secretion in the pathogenesis of Type II diabetes mellitus, *Diabetologia* 44, 929–945, 2001.
28. U.K. Prospective Diabetes Study Group, U.K. Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease, *Diabetes* 44, 1249–1258, 1995.
29. O'Rahilly, S., Turner, R., and Matthews, D., Impaired pulsatile secretion of insulin in relatives of patients with noninsulin-dependent diabetes, *N. Engl. J. Med.* 318, 1225–1230, 1988.
30. Yamagata, K. et al., Mutations in the hepatocyte nuclear factor-4 alpha gene in maturity-onset diabetes of the young (MODY1), *Nature* 384, 458–460, 1996.
31. Horikawa, Y. et al., Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY, *Nat. Genet.* 17(4), 384–385, 1997.
32. Stoffel, M. et al., Missense glucokinase mutation in maturity-onset diabetes of the young and mutation screening in late-onset diabetes, *Nat. Genet.* 2, 153–156, 1992.
33. Stoffers, D.A. et al., Early-onset type-II diabetes mellitus (MODY4) linked to IPF1, *Nat. Genet.* 17(2), 138–139, 1997.
34. Vionnet, N. et al., Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus, *Nature* 356, 721–722, 1992.
35. Yamagata, K. et al., Mutations in the hepatocyte nuclear factor-1 alpha gene in maturity-onset diabetes of the young (MODY3), *Nature* 384, 455–458, 1996.
36. Horikawa, Y., Oda, N., and Cox, N.J., Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus, *Nat. Genet.* 26, 163–175, 2000.
37. Hu, F.B. et al., Diet, lifestyle, and the risk of type 2 diabetes mellitus in women, *N. Engl. J. Med.* 345, 790–797, 2001.
38. Bokyo, E.J. et al., Visceral adiposity and risk of type 2 diabetes, *Diabetes Care* 23(4), 465–471, 2000.
39. McGarry, J.D. and Dobbins, R.L., Fatty acids, lipotoxicity and insulin secretion, *Diabetologia* 42, 128–138, 1999.
40. Hales, C.N. and Barker, D.J.P., Type-2 (non-insulin-dependent) diabetes mellitus — the thrifty phenotype hypothesis, *Diabetologia* 35(7), 595–601, 1992.
41. Hales, C.N. et al., Fetal and infant growth and impaired glucose tolerance at age 64, *Br. Med. J.* 303(6809), 1019–1022, 1991.
42. Ozanne, S.E. et al., Poor fetal nutrition causes long-term changes in expression of insulin signaling components in adipocytes, *Am. J. Physiol.-Endocrinol. Metab.* 36(1), E46–E51, 1997.
43. Onkamo, P. et al., Worldwide increase in incidence of type I diabetes — the analysis of the data on published incidence trends, *Diabetologia* 42, 1395–1403, 1999.
44. Gale, E.A.M. and Gillespie, K.M., Diabetes and gender, *Diabetologia* 44, 3–15, 2001.

45. DeFronzo, R.A., The triumvirate — β-cell, muscle, liver. A collusion responsible for NIDDM, *Diabetes* 37(6), 667–687, 1988.
46. U.K. Prospective Diabetes Study Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet* 352, 837–853, 1998.
47. Harris, M.I. et al., Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994, *Diabetes Care* 21, 518–524, 1998.
48. Kannel, W.B. and McGee, D.L., Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study, *Diabetes Care* 2, 120–126, 1979.
49. Haffner, S.M. et al., Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction, *N. Engl. J. Med.* 339, 229–234, 1998.
50. Lehto, S. et al., Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes, *Stroke* 27, 63–68, 1996.
51. Chaturvedi, N. et al., Risk factors, ethnic differences and mortality associated with lower-extremity gangrene and amputation in diabetes. The WHO multinational study of vascular disease in diabetes, *Diabetologia* 44, S65–S71, 2001.
52. Amos, A.F., McCarty, D.J., and Zimmet, P., The rising global burden of diabetes and its complications: estimates and projections to the year 2010, *Diabetic Med.* 14, S7–S85, 1997.
53. Mokdad, A.H. et al., Diabetes trends in the U.S.: 1990–1998, *Diabetes Care* 23, 1278–1283, 2000.
54. Wild, S. et al., Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, *Diabetes Care* 27, 1047–1053, 2004.
55. Diabetes Control and Complications Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N. Engl. J. Med.* 329, 977–986, 1993.
56. Fuller, J.H. et al., Risk factors for cardiovascular mortality and morbidity: The WHO multinational study of vascular disease in diabetes, *Diabetologia* 44, S54–S64, 2001.
57. Stratton, I.M. et al., Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study, *Br. Med. J.* 321, 405–412, 2000.
58. U.K. Prospective Diabetes Study Group, Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), *Lancet* 352, 854–865, 1998.
59. Nakagami, T. and DECODA Study Group, Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin, *Diabetologia* 47, 385–394, 2004.
60. Nauck, M.A. et al., Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans, *Am. J. Physiol.-Endocrinol. Metab.* 36(5), E981–E988, 1997.
61. Wynne, K., Stanley, S., and Bloom, S., The gut and regulation of body weight, *J. Clin. Endocrinol. Metab.* 89, 2576–2582, 2004.
62. Groop, P.H. et al., Long-term effects of guar gum in subjects with non-insulin dependent diabetes mellitus, *Am. J. Clin. Nutr.* 58, 513–518, 1993.
63. Coniff, R. et al., Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM, *Diabetes Care* 18, 817–824, 1995.
64. Ashcroft, F.M. and Gribble, F.M., ATP-sensitive K+ channels and insulin secretion: their role in health and disease, *Diabetologia* 42, 903–919, 1999.
65. Perry, T. and Greig, N.H., The glucagon-like peptides: a double-edged therapeutic sword? *Trends Pharm. Sci.* 24, 377–383, 2003.
66. Harder, H., Nielson, L., and Astrup, A., The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes, *Diabetes Care* 27, 1915–1921, 2004.
67. Madsbad, S. et al., Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial, *Diabetes Care* 27, 1335–1342, 2004.
68. Bolli, G.B. et al., Insulin analogues and their potential in the management of diabetes mellitus, *Diabetologia* 42, 1151–1167, 1999.
69. Sachs, D.H. and Bonner–Weir, S., New islets from old, *Nat. Med.* 6, 250–251, 2000.

70. White, S.A. et al., Human islet cell transplantation — future prospects, *Diabetic Med.* 18, 78–103, 2001.
71. Flier, J.S., Big deal about a little insulin, *Nat. Med.* 5, 614–615, 1999.
72. Martin, W.H. et al., Discovery of a human liver glycogen phosphorylase inhibitor that lowers blood glucose *in vivo*, *Proc. Natl. Acad. Sci. USA* 95(4), 1776–1781, 1998.
73. Nolan, J.J. et al., Rosiglitazone once daily provides effective glycaemic control in patients with type 2 diabetes mellitus, *Diabetic Med.* 17, 287–294, 2000.
74. Tan, M.H., How pioglitazone affects glucose and lipid metabolism, *Exp. Clin. Endocrinol. Diabetes* 108, S224–S233, 2000.
75. Moller, D.E., New drug targets for type 2 diabetes and the metabolic syndrome, *Nature* 141, 821–827, 2001.
76. Boden, G., Role of fatty acids in the pathogenesis of insulin resistance and NIDDM, *Diabetes* 46(1), 3–10, 1997.
77. Duncan, G.E. et al., Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults, *Diabetes Care* 26, 557–562, 2003.
78. Thomas, E.L. et al., Preferential loss of visceral fat following aerobic exercise, measured by magnetic resonance imaging, *Lipids* 35, 769–776, 2000.
79. Winder, W.W. and Hardie, D.G., AMP-activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes, *Am. J. Physiol.* 40, E1–E10, 1999.
80. Zierath, J.R., Krook, A., and Wallberg–Henriksson, H., Insulin action and insulin resistance in human skeletal muscle, *Diabetologia* 43, 821–835, 2000.
81. Diabetes Prevention Program Research Group, Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, *N. Engl. J. Med.* 346, 393-403, 2002.
82. Pan, X.R. et al., Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and diabetes study, *Diabetes Care* 20, 537–544, 1997.
83. Tuomilehto, J. et al., Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance, *N. Engl. J. Med.* 344, 1343–1350, 2001.
84. Thornalley, P.J., Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs, *Cellular Molecular Biol.* 44, 1013–1023, 1998.
85. Beisswenger, P.J. et al., Alpha-oxoaldehyde metabolism and diabetic complications, *Biochem. Soc. Trans.* 31, 1358–1363, 2003.

2 Plants Used in the Treatment of Diabetes

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CONTENTS

BACKGROUND

The *Ebers Papyrus* written in approximately 1550 B.C. provides the earliest documentation about the use of plants in the treatment of conditions associated with diabetes (Bailey and Day, 1989). In India, the early Ayurvedic texts such as the *Sushruta Samhita* and the *Charaka Samhita* written in the 4th to 5th century B.C. describe the use of about 760 and 500 species of medicinal plants, respectively, including those prescribed for conditions such as glycosuria, polyphagia, and polyuria associated with diabetes (Nagarajan et al., 1982). In China, *Ben Jing*, written in about 104 B.C., contains detailed descriptions of 252 species with reference to those used to treat diabetes. It is easier to track the traditional and modern uses of species in the treatment of diabetes in cultures with a strong written culture like those in India, China, and the Middle East than it is in South America and Africa, where much less documentation is available to the researcher.

Despite their long tradition of use in most parts of the world, very few of these species have been exposed to modern, large-scale, clinical-type trials to test their efficacy. Some species used in the ancient civilizations of India and China have been used for hundreds of years and some people would suggest this indicates that they are effective. However, it is clear that more research needs to be undertaken on these species because, in most cases, the active compounds and their mode of action still remain unclear. For example, hundreds of species are used in Chinese medicine for treating diabetes, but only seven multiple-species antidiabetic products have been approved for clinical use in China (Shang, 2000).

Currently, many countries face large increases in the number of people suffering from diabetes. The World Health Organization estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000 (www.who.int/diabetes/facts/world-figures). Wild et al. (2004) estimate the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years. This is in contrast to the developed world in which most people diagnosed with diabetes are over 64 (Wild et al., 2004). Despite the lack of robust scientific data to support the efficacy of many species of plants, they remain the main source of medication for patients with diabetes in many parts of the world and are sometimes taken in preference to other treatments. If

the species were all effective, many communities still using the plants would be able to treat diabetes. However, this is not the case.

Plants thought to play a role in the treatment of diabetes are taken as food or as medication. Marles and Farnsworth (1995) provided an overview of the species of plants reported to be used to treat diabetes. Their review remains a classic reference work for those involved in using ethnobotanical data to study the potential use of plants in the treatment of diabetes. It was based on a search of information about antidiabetic plants up to the year 1994 available in the computer database NAPRALERT at the College of Pharmacy, University of Illinois, Chicago. In their review, they identified about 1200 species of plants from 725 genera representing 183 families. A later review by Perez et al. (1998a) identified about 800 species.

In the 10 years since Marles and Farnsworth (1995) completed their review, knowledge about the potential uses and chemistry of the plants that they listed has increased. This review provides an update. We have looked at the literature since 1994 using a range of different databases, including the ISI Web of Knowledge (www.isiknowledge.com), CABI International (www.cabdirect.org), and SEPASAL (www.rbgkew.org.uk/ceb/sepasal). We also include references to some of the earlier work on species that have been used and, in some cases, species currently used to treat diabetes but poorly studied. The results of this review are outlined in Table 2.1.

SELECTION OF SPECIES

It is clear that a case can be made for further research on these potentially antidiabetic species. However, how should the plants to study be selected? Marles and Farnsworth (1995) suggested that to "accelerate" research on the antidiabetic activity of plants, five criteria could be used to prioritize the selection of species:

- Traditional use in one or more countries
- Experimentally determined hypoglycemic activity
- Lack of detailed information on hypoglycemic constituents
- Experimental evidence for low toxicity
- Botanical abundance

These criteria are useful but depend on whether the aim of the research project is to find novel leads or increase the use of a proven species. In fact, the five criteria focus on the search for new leads rather than the development of existing leads.

The first criterion cited by Marles and Farnsworth (1995) highlights the selection of species in parts of the world with a tradition of documenting the uses of their plants. This gives a bias to India and China. The information in Table 2.1 shows that a high proportion of species come from India and other parts of Asia, including China. However, as more research is done on medicinal plants in other parts of the world, better understanding of the range of species used to treat diabetes will ensue. In some cases, related species with similar types of chemistry are used in different geographical areas. For example, species that belong to the Lamiales often contain flavonoids, terpenoids, and polysaccharides that have activity in the treatment of diabetes or related conditions. Representatives from this group of species are used in most countries.

Currently, because of the lack of ethnobotanical information, especially from parts of Africa, it is difficult to establish how widely some of these species are used. *Plectranthus barbatus* (known previously as *Coleus forskohlii*) contains the diterpene, forskolin, a compound that activates adenylate cyclase and stimulates the biosynthesis of intracellular cAMP (Kuznetsova et al., 2004). The release of cAMP results in an increase in cholecystokinin- and glucose-stimulated release of insulin. Thus, species that contain this compound could have a use in the treatment of diabetes. However, there is very little documentation about the traditional use of *P. barbatus* in the treatment of diabetes, although it is sold at village markets in Ghana and Uganda for this use.

TABLE 2.1
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Filicopsida				
Oleandraceae	*Oleandra pistillaris* (Sw.) C. Chr.	India	All	Shows hypoglycemic activity in rats (Abraham et al., 1986)
Gnetopsida				
Ephedraceae	*Ephedra distachya* L.	E. Asia	All	Glycan ephedrans A, B, C, D, and E and L-ephredrine have antihyperglycemic activity; regenerate atrophied pancreatic islets and restore secretion of insulin (Xiu et al., 2001)
Gymnospermae				
Cupressaceae	*Juniperus communis* Thunb.	Europe, India	Fruit	Extracts decrease blood glucose (Gallagher et al., 2003)
Pinaceae	*Abies pindrow* Spach.	India	Aerial parts	Ethanol extracts increase insulin release from INS-1 cells (Hussain et al., 2004)
Pinaceae	*Pinus densiflora* Siebold & Zucc.	Japan	Bark, leaf	Ethanol extracts inhibit carbohydrate-hydrolysing enzymes (Kim et al., 2004)
Pinaceae	*Pinus roxburghii* Sarg.	Africa, India	Bark, root	Used to treat diabetes (Marles and Farnsworth, 1995)
Taxaceae	*Taxus cuspidata* Siebold and Zucc.		Bark, leaf	Used to treat diabetes (Lewis, 1977)
Angiospermae				
Primitive Angiosperms				
Nymphaeceae	*Nymphaea lotus* L.	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Nymphaeceae	*Nymphaea nouchali* Burm.f.	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Magnoliids				
Magnoliales				
Annonaceae	*Annona squamosa* L.	India, Africa, Tropics	Leaf	Extracts modulate levels of glucose, insulin, and lipids in STZ-treated rats. The aqueous extract was as active as glibenclamide (Shirwaikar et al., 2004)
Magnoliaceae	*Michelia champaca* L.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Magnoliaceae	*Schisandra chinensis* (Turcz.) Baill	Asia	Fruit	Lignans are reported to inhibit aldose reductase (Li et al., 2004)
Magnoliaceae	*Talauma ovata* A. St. Hil.	C. America		Used to treat diabetes (Marles and Farnsworth, 1995)
Laurales				
Lauraceae	*Actinodaphne hookeri* Meisn.	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Lauraceae	*Cinnamomum cassia* D. Don.	Africa, Asia, India	Leaf, bark	Cinnamaldehyde isolated from bark inhibits aldose reductase (Lee, 2002)
Lauraceae	*Cinnamomum tamala* T. Nees & Eberm.	Tropics	Bark	Extracts decrease blood glucose in alloxan-treated rats (Kar et al., 2003)
Lauraceae	*Cinnamomum zeylanicum* Blume	Europe	Bark	Antinociceptive *in vivo* (Atta and Alkofahi, 1998)
Lauraceae	*Laurus nobilis* L.		Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Lauraceae	*Persea americana* Mill.	Africa	Leaf	Extracts could decrease absorption of glucose (Gallagher et al., 2003)
Lauraceae	*Persea gratissima* Gaertn.	Canaries	Seed, bark	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Lauraceae	*Phoebe wightii* Meisn.	India	Aerial parts	Shows hypoglycemic activity in rats (Abraham et al., 1986)
Piperales				
Piperaceae	*Piper cubeba* Bojer	E. Asia, Europe, India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Piperaceae	*Piper longum* Blume	India, S.E. Asia	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Piperaceae	*Piper nigrum* L.	Africa, S.E. Asia, India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Monocots				
Alismatales				
Araceae	*Amorphophallus konjac* K. Kock	E. Asia	Rhizome	Used as health food for weight loss because it lowers blood glucose. Active compounds are konjak oligosaccharides and galactomannan (Yang et al., 2001)
Araceae	*Pinellia ternata* (Thunb.) Breit.	Asia	Rhizome	Flavone-*C*-glycosides have antidiabetic activity (Nishimura et al., 1992)
Araceae	*Scindapsus officinalis* Schott Melet	India	Fruit	Fruit reported to have antidiabetic activity (Marles and Farnsworth, 1995)
Potamogetonaceae	*Potamogeton crispus* L.		All	Used to treat diabetes (Dhawan et al., 1980)
Dioscoreales				
Dioscoreaceae	*Dioscorea asclepiadea* Prain & Burkill	E. Asia	Bulb	Used to treat diabetes (Marles and Farnsworth, 1995)
Dioscoreaceae	*Dioscorea batatas* Decne.	E. Asia	Tuber	Extract lowers blood glucose (Marles and Farnsworth, 1995)
Dioscoreaceae	*Dioscorea bulbifera* L.	Asia	Bulb	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Dioscoreaceae	*Dioscorea dumetorum* Pax.	Africa	Tuber	Reduces glucose in alloxan-treated rabbits (Ivorra et al., 1989)
Dioscoreaceae	*Dioscorea gracillima* Miq.	E. Asia	Bulb	Used to treat diabetes (Marles and Farnsworth, 1995)
Dioscoreaceae	*Dioscorea japonica* Herb. Madr. ex. Wall.	E. Asia	Tuber	Dioscorans A to F have hypoglycemic activity (Hikino et al., 1986)
Liliales				
Liliaceae	*Lilium auratum* Lindl.	Japan	Bulb	Used to treat diabetes (Marles and Farnsworth, 1995)
Liliaceae	*Lilium speciosum* Andrews	Japan	Bulb	Used to treat diabetes (Marles and Farnsworth, 1995)
Smilacaceae	*Smilax canariensis* Willd.	Canaries	Aerial parts	Used to treat diabetes (Darias et al., 1989)
Asparagales				
Agavaceae	*Anemarrhena asphodeloides* Bunge	E. Asia	Rhizome	Polysaccharides anemarans A, B, C and D lower levels of blood sugar (Wang et al., 2000)
Alliaceae	*Allium cepa* L.	Universal	Bulb	Improves metabolic status in diabetic condition and lowers blood cholesterol. Active compounds allyl propyldisulfide and *S*-methylcysteine sulfoxide (Kumari et al., 1995)
Alliaceae	*Allium sativum* L.	Universal	Bulb	Lowers blood sugar at a level comparable to tolbutamide. Allicin and *S*-allyl cysteine sulfoxide are the active compounds. Stimulates insulin secretion from β-cells, improves glucose tolerance and increases liver glycogen synthesis (Li et al., 2004)
Amaryllidaceae	*Lycoris radiata* Herb.	Asia	Bulb	Glucomannans show hypoglycemic activity in mice (Tomoda et al., 1987)
Amaryllidaceae	*Lycoris squamigera* Maxim.	Asia	Bulb	Lycoris-*S*-glucomannan has antidiabetic activity, although the plant is toxic (Marles and Farnsworth, 1995)
Amaryllidaceae	*Narcissus tazetta* L.	Asia, Europe	Bulb	Glucomannans have antidiabetic activity (Marles and Farnsworth, 1995)
Asparagaceae	*Asparagus gonocladus* Baker	India	Bulb	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Asparagaceae	*Convallaria majalis* L.	Asia	Bulb	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Asparagaceae	*Polygonatum odoratum* subsp. *glaberrimum* (K. Koch) Elenevsky & A.S. Zernov	China	Rhizome (bulb)	Steroidal glycosides decrease blood glucose and stimulate glycogen synthase. Promotes peripheral sensitivity to insulin rather than altering secretion of insulin (Choi and Park, 2002)
Asparagaceae	*Polygonatum officinale* All.	Europe, Asia	Rhizome (bulb)	Extracts lower blood glucose and increase sensitivity to insulin (Miura and Kato, 1995)
Asphodelaceae	*Aloe arborescens* Mill.	E. Asia	Leaf	Variety *natalensis*: protects pancreatic islet β-cells from toxins by acting as a radical scavenger (Beppu et al., 2003); antihyperglycemic in STZ-treated mice (Beppu et al., 1993)
Asphodelaceae	*Aloe vera* (L.) Burm. f.	India, W. Indies, E. Asia	Leaf	Maintains glucose homeostasis *in vivo* (Rajasekaran et al., 2004)
Hyacinthaceae	*Scilla sibirica* Andrews		Bulb	Contains polyhydroxyalkaloids that have antidiabetic properties (Yamashita et al., 2002)
Hyacinthaceae	*Urginea indica* Kunth.	India	Bulb	Hypoglycemic activity in rats (Dhar et al., 1968)
Orchidaceae	*Dendrobium chrysanthum* Wall.ex. Lindl.	China	Stem	Reported to have antihyperglycemic activity (Li et al., 2004)
Orchidaceae	*Dendrobium loddigesii* Rolfe	China	Stem	Reported to have antihyperglycemic activity (Li et al., 2004)
Orchidaceae	*Dendrobium nobile* Lindl.	China	Stem	Reported to have antihyperglycemic activity (Li et al., 2004)
Orchidaceae	*Orchis latifolia* L.	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Orchidaceae	*Orchis mascula* Crantz.	Europe, India, Middle East	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Commelinids				
Poales				
Bromeliaceae	*Tillandsia usneoides* L.	N. America	All	Extracts from whole plant have antidiabetic activity in rats (Ivorra et al., 1989)
Cyperaceae	*Cyperus iria* L.		Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Cyperaceae	*Kyllinga triceps* Thunb.	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Poaceae	*Andropogon citratus* Hort ex. DC	Asia	Aerial parts	Lowers blood glucose in rabbits (Garcia, 1944)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Poaceae	*Avena sativa* L.	Temperate	All	Lowers blood glucose (Marles and Farnsworth, 1995)
Poaceae	*Bambusa arundinacea* Willd.	India	Aerial parts	Some oat bran concentrate bread products improve glycemic, insulinemic, and lipidemic responses in NIDDM patients (Pick et al., 1996)
Poaceae	*Bambusa nutans* Wall. ex. Munro	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Poaceae	*Coix lachryma-jobi* L.	E. Asia	Seed	Coixans A, B, and C (polysaccharides) reduce blood glucose in alloxan-treated mice (Takahashi et al., 1986)
Poaceae	*Eragrostis bipinnata* Schum. in Engl.			Used to treat diabetes (Marles and Farnsworth, 1995)
Poaceae	*Hordeum vulgare* L.	Universal	Root, seed	May stimulate mobilization of insulin in NIDDM (Shukla et al., 1991)
Poaceae	*Oryza sativa* L.	Subtropics	Root, seed	Contains oryzabrans with antidiabetic activity (Hikino et al., 1988)
Poaceae	*Panicum miliaceum* L.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Poaceae	*Poa pratensis* Pollich	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Poaceae	*Saccharum officinarum* L.	Africa, C. and S. America	Juice	Contains saccharans with hypoglycemic activity (Takahashi et al., 1985)
Poaceae	*Zea mays* L.	Universal	Styles, seed	Contains "resistant starch" thought to have antidiabetic properties (Morell et al., 2004)
Commelinales				
Arecaceae	*Acrocomia mexicana* Karw. ex. Mart.	C. America	Root	Methanol extract decreases blood glucose in mice (Perez et al., 1992)
Arecaceae	*Cocos nucifera* L.	Universal		Coconut flour added to bakery products could decrease blood glucose due to its high dietary fibre content (Trinidad et al., 2003)
Arecaceae	*Serenoa serrulata* Hook. f.	Europe	Fruit	Used to treat diabetes (Lust, 1986)
Zingiberales				
Costaceae	*Costus schlechteri* H. Winkler	Africa		Lowers blood glucose (Marles and Farnsworth, 1995)
Musaceae	*Ensete superbum* (Roxb.) Cheesman	India		Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Musaceae	*Musa paradisiaca* L.	India, tropics	Flower, root	Chloroform extract of flowers reduces blood glucose in alloxan-treated rats (Pari and Umamaheswari, 2000)
Strelitziaceae	*Ravenala madagascariensis* J.F. Gmel.	Africa		Used to treat diabetes (Sussman, 1980)
Zingiberaceae	*Alpinia galanga* Willd.	India	Rhizome	Reduces blood glucose in rabbits (Akhtar et al., 2002)
Zingiberaceae	*Amomum aromaticum* Roxb.	India	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Zingiberaceae	*Amomum subulatum* Roxb.	India	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Zingiberaceae	*Curcuma longa* L.	India	Root	Forms part of a mixture, "hyponidd," that reduces blood glucose in STZ-treated rats (Babu and Prince, 2004)
Zingiberaceae	*Hedychium gardnerianum* Wall. ex. Spreng.	India	Leaf	Shows hypoglycemic activity in rats (Abraham et al., 1986)
Zingiberaceae	*Hedychium spicatum* Lodd.	India	Rhizome	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Zingiberaceae	*Zingiber officinale* Rosc.	Tropics, India	All	Ethanol extract reduces blood glucose in alloxan-treated rats (Kar et al., 2003)
Zingiberaceae	*Zingiber zerumbet* Rosc. ex. Sm	India	Leaf	Although used traditionally to treat diabetes, an aqueous extract did not decrease blood glucose in STZ-treated rats (Husen et al., 2004)
Eudicots				
Ranunculales				
Berberidaceae	*Berberis aristata* DC	India	Root	Contains berberine (Soffar et al., 2001), which reduces levels of fasting blood glucose, triglycerides, and total cholesterol (Leng et al., 2004) and decreases glucose absorption (Pan et al., 2003)
Berberidaceae	*Berberis vulgaris* Vell.	India, Africa, Europe	Root	Berberine administration to impaired glucose tolerance rats reduces levels of fasting blood glucose, triglycerides and total cholesterol (Leng et al., 2004)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Berberidaceae	*Epimedium brevicornum* Maxim.	China	All	Used as a tonic (Li et al., 2004)
Berberidaceae	*Epimedium sagittatum* (Sieb. et Zucc.) Maxim	China	All	Used as a tonic (Li et al., 2004)
Menispermaceae	*Cocculus cordifolius* Miers	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Menispermaceae	*Fibraurea chloroleuca* Miers	S.E. Asia		Used to treat diabetes (Marles and Farnsworth, 1995)
Menispermaceae	*Stephania glabra* Miers	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Menispermaceae	*Stephania tetradra* S. Moore	Asia	Root	Protects β-cells of pancreatic islets (You and Wang, 2000)
Menispermaceae	*Tinospora cordifolia* Miers	India	All	Extracts from stems, leaves, and roots have antidiabetic properties. In alloxan-treated rats, the root extract reduces blood glucose and lipids and prevents weight loss (Stanely Mainzen Prince and Menon, 2003)
Menispermaceae	*Tinospora crispa* Miers	Asia	Stem	Reduces blood glucose in alloxan-treated rats (Noor et al., 1989)
Papaveraceae	*Chelidonium majus* L.	Europe		Used to treat diabetes (Marles and Farnsworth, 1995)
Papaveraceae	*Fumaria parviflora* Lam.	India	Aerial parts	Extracts have hypoglycemic activity in alloxan-treated rabbits (Akhtar et al., 1984)
Papaveraceae	*Glaucium flavum* Crantz.		Leaf	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Papaveraceae	*Papaver somniferum* L.	Universal	Fruit	Alkaloids have hypoglycemic activity (Marles and Farnsworth, 1995)
Ranunculaceae	*Aconitum carmichaelii* Debeaux	E. Asia	Root	Care needs to be taken in preparation of the roots. Aconitans A, B, C, and D lower blood glucose (Konno et al., 1985a)
Ranunculaceae	*Aconitum moschatum* Stapf	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Ranunculaceae	*Aconitum violaceum* Jacquem. ex. Stapf	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Ranunculaceae	*Cimicifuga racemosa* (L.) Nutt.			Used to treat diabetes (Marles and Farnsworth, 1995)
Ranunculaceae	*Clematis armandii* Franch	E. Asia		Used to treat diabetes (Marles and Farnsworth, 1995)
Ranunculaceae	*Clematis chinensis* Osbeck	China	Root	Used to treat diabetes complications (Li et al., 2004)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Ranunculaceae	*Coptis chinensis* Franch.	E. Asia	Root, aerial parts	Decreases serum glucose, berberine has hypoglycemic activity (Chen and Xie, 1986)
Ranunculaceae	*Coptis deltoidea* C.Y. Cheng et Hsiao	Asia	Root	Decreases serum glucose, berberine has hypoglycemic activity (Chen and Xie, 1986)
Ranunculaceae	*Coptis teeta* Wall.	India	Rhizome	Used to treat diabetes (Marles and Farnsworth, 1995)
Ranunculaceae	*Hydrastis canadensis* L.	Universal		Used to treat diabetes (Lewis, 1977)
Ranunculaceae	*Nigella sativa* L.	Brunei		Volatile oil from seeds can reduce blood glucose via a mechanism that does not involve insulin. Also has antioxidant properties and decreases levels of lipid peroxidases (Ali and Blunden, 2003)
Proteales				
Nelumbonaceae	*Nelumbo nucifera* Gaertn.	India	Flower	Methanol extracts decrease blood glucose in STZ-treated rats (Mukherjee et al., 1995); tryptophan is an active compound and a protein fraction also shows activity (Ibrahim and El-Eraqy, 1996)
Core Eudicots				
Caryophyllales				
Amaranthaceae	*Achyranthes aspera* L.	Africa, India, Australia	All	Lowers blood glucose levels in alloxan-treated rabbits (Akhtar and Iqbal, 1991)
Amaranthaceae	*Aerva sanguinolenta* Blume	S.E. Asia	All	Reported to have antidiabetic activity (Marles and Farnsworth, 1995)
Amaranthaceae	*Atriplex halimus* L.	Middle East	Leaf	Extract is reported to have an insulin-potentiating effect (Shani et al., 1972)
Amaranthaceae	*Beta vulgaris* L.	International	Root, leaf	Betavulgarosides II and IV and oleanane triterpenoid saponins have hypoglycemic activity (Murakami et al., 1999) Extracts reduce serum lipids, sialic, and uric acid, glucose, and lipid peroxidation in rats. The extracts protect the liver (Ozsoy–Sacan et al., 2004)
Amaranthaceae	*Chenopodium ambrosioides* L.	India		Used to treat diabetes (Neame and Pillay, 1964)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Amaranthaceae	*Hammada salicornica* R. Br.	Arabia	Aerial parts	Reduces blood glucose in alloxan-treated dogs (Handa et al., 1989)
Amaranthaceae	*Spinacia oleracea* L.	Africa, Europe, India		Extracts have antidiabetic activity (Marles and Farnsworth, 1995)
Cactaceae	*Lophophora williamsii* (Salm–Dyck) J.M. Coult.			Extracts have antidiabetic activity, but plant is toxic (Marles and Farnsworth, 1995)
Cactaceae	*Opuntia ficus-indica* (L.) Mill.	Africa, Europe, America	Aerial parts	Aqueous extract lowers blood glucose level in STZ-treated rats (Enigbokan et al., 1996)
Cactaceae	*Opuntia lindheimeri* Englem.		Aerial parts	Aqueous extract lowers blood glucose level in STZ-treated pigs (Laurenz et al., 2003)
Cactaceae	*Opuntia streptacantha* Lemair	C. America	Aerial parts	Reduces blood glucose (Handa et al., 1989)
Cactaceae	*Opuntia vulgaris* Mill.	Africa	Aerial parts	Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Nyctaginaceae	*Boerhavia diffusa* L.	India	Leaf	Extracts of leaves lower blood glucose in alloxan-treated rats (Pari and Satheesh, 2004)
Nyctaginaceae	*Bougainvillea spectabilis* Willd.	India	Leaf	Leaves contain pinitol, a compound with antidiabetic activity (Narayanan et al., 1987)
Nyctaginaceae	*Salpianthus arenarius* Humb. & Bonpl.	C. America	Flower	Used to treat diabetes (Marles and Farnsworth, 1995)
Polygalaceae	*Polygala senega* L.	Asia	Root	Variety *latifolia*: triterpenoid glycosides, senegins II and III reduce blood glucose in mice (Kako et al., 1997)
Polygonaceae	*Polygonum aviculare* L.	Europe, Africa, India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Polygonaceae	*Polygonum cuspidatum* Sieb et Zucc.	Asia	Rhizome	Antidiabetic activity could be because it improves blood circulation (You and Wang, 2000)
Polygonaceae	*Polygonum multiflorum* Thunb.	Asia	Aerial parts	Aqueous extracts form part of a preparation sold as "Slimax" that regulates glucose utilization and lipid metabolism (Wijaya et al., 1995)
Polygonaceae	*Rheum officinale* Baill.	China	Root	Polysaccharides could be active compounds for treating diabetic nephropathy (Li et al., 2004)
Polygonaceae	*Rheum palmatum* L.	China	Root	Polysaccharides could be active compounds for treating diabetic nephropathy (Li et al., 2004)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Polygonaceae	*Rheum tanguticum* Maxim. ex. Balf	China	Root	Polysaccharides could be active compounds for treating diabetic nephropathy (Li et al., 2004)
Polygonaceae	*Rumex abyssinicus* Jacq.	Africa	Root	Used to treat diabetes (Abdulkadir, 1985)
Portulacaceae	*Portulaca oleracea* L.	Africa, India, Europe		Used to treat diabetes (Marles and Farnsworth, 1995)
Portulacaceae	*Talinum portulacifolium* Aschers. ex. Schweinf.	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Santalales				
Loranthaceae	*Loranthus curviflorus* Benth.	Middle East		Used to treat diabetes (Marles and Farnsworth, 1995)
Loranthaceae	*Loranthus micranthus* Hook, f.	New Zealand		Methanolic extract lowers blood glucose in alloxan-treated rats (Osadebe et al., 2004)
Loranthaceae	*Psittacanthus calyculatus* G. Don	C. America	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Santalaceae	*Viscum album* L.	Asia, Europe, India	Aerial parts	Extracts inhibit α-glucosidase (Onal et al., 2005)
Saxifragales				
Paeoniaceae	*Paeonia emodi* Royal	Asia	All	Pinane monoterpenoids paeoniflorin and 8-debenzoylpaeoniflorin lower blood glucose and increase glucose utilization in STZ-treated rats (Hsu et al., 1997)
Paeoniaceae	*Paeonia lactiflora* Pall.	China	Root	Paeoniflorin and 8-debenzoylpaeoniflorin lower blood sugar (Hsu et al., 1997)
Paeoniaceae	*Paeonia moutan* Sims	China	All	A pentagalloylglucose, 090002, inhibits squalene synthase and is hypocholesterolemic *in vivo* (Park et al., 2002)
Paeoniaceae	*Paeonia veitchii* Lynch	China	Root	Tetra and penta-*O*-galloyl-β-D-glucose inhibit aldose reductase (Aida et al., 1989)
Saxifragaceae	*Bergenia stracheyi* Stein	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Rosids				
Crossosomatales				
Geraniaceae	*Geranium maculatum* L.	Europe	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Stachyuraceae	*Stachyurus himalaicus* C.Y. Wu	China		Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Myrtales				
Combretaceae	*Terminalia bellirica* (Gaertn) Roxb.	India, S.E. Asia	Fruit	Hypoglycemic effect of fruit pulp in alloxan-treated rats (Kar et al., 2003)
Combretaceae	*Terminalia catappa* L.	Africa	Fruit	Extracts from fruits reduce blood glucose in alloxan-treated rats (Nagappa et al., 2003)
Combretaceae	*Terminalia chebula* Retz.	India, S.E. Asia	Fruit	Decreases blood glucose in alloxan-treated rats (Sabu and Kuttan, 2002)
Lythraceae	*Lagerstroemia parviflora* Roxb.	Asia, India, Australia	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Lythraceae	*Lagerstroemia speciosa* (L.) Pers	S.E. Asia	Leaf, bark, root, seed	Reduces blood glucose (Ivorra et al., 1989)
Lythraceae	*Lythrum salicaria* L.	Mediterranean	Stem, flower	Reduces blood glucose (Ivorra et al., 1989)
Lythraceae	*Punica granatum* L.	India	Fruit	Methanol seed extract reduces glucose levels in STZ-treated rats (Das et al., 2001)
Melastomataceae	*Memecylon umbellatum* Blume	India	Leaf	Alcoholic extract lowers blood glucose in alloxan-treated mice (Amalraj and Ignacimuthu, 1998)
Myrtaceae	*Eucalyptus citriodora* Hook	Africa, India	Leaf	Myrtillin has hypoglycemic activity (Marles and Farnsworth, 1995)
Myrtaceae	*Eucalyptus globulus* Labill.	Africa, America	Leaf	Extracts decrease blood glucose (Gallagher et al., 2003)
Myrtaceae	*Eugenia jambolana* Lam.	Africa	Seed, bark	Extract lowers blood glucose, urea, and urine sugar in STZ-treated rats (Ravi et al., 2003)
Myrtaceae	*Hexachlamys edulis* (O. Berg) Kausel & D. Legrand	S. America		Reduces blood glucose in alloxan-treated rats without signs of toxicity (Rodriguez et al., 1992)
Myrtaceae	*Myrcia uniflora* Bard. Robr.			Extracts decrease blood glucose in diabetes patients (Russo et al., 1990)
Myrtaceae	*Myrtus communis* L.	Africa	Leaf, stem	Reduces blood glucose (Ivorra et al., 1989)
Myrtaceae	*Pimenta officinalis* Lindl.	America	Leaf, fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Myrtaceae	*Psidium guajava* L.	Africa, E. Asia, India	Leaf	Lowers blood glucose. Glycoprotein with molecular weight of 50,000–100,000 has activity (Basnet et al., 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Myrtaceae	*Syzygium alternifolium* Walp.	India	Seed	Aqueous extracts lower blood glucose in alloxan-treated rats (Rao and Rao, 2001)
Myrtaceae	*Syzygium cerasoides* (Roxb.) Raiz.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Myrtaceae	*Syzygium cumini* (L.) Skeels	India	Fruit, bark	Jambosine associated with hypoglycemic activity (Rajan et al., 2002)
Onagraceae	*Epilobium hirsutum* L.	Canaries	Aerial parts	Used to treat diabetes (Darias et al., 1989)
Onagraceae	*Epilobium royleanum* Hausskn.	India	Whole plant	Shows hypoglycemic activity in rats (Aswal et al., 1984)
Onagraceae	*Oenothera biennis* L.	Europe	Seed	Proanthocyanidins are associated with hypoglycemic activity (Aitani et al., 2003)
Eurosid 1				
Celastrales				
Celastraceae	*Catha edulis* Forssk.	Africa	Leaf	Khat chewing increases levels of serum glucose and C-peptides in diabetic patients (Saif–Ali et al., 2003)
Celastraceae	*Euonyrnus alatus* (Thunb.) Sieb.	Asia	Whole plant	Lowers blood glucose and lipids (Yao et al., 2000)
Celastraceae	*Maytenus senegalensis* (Lam.) Exell	Africa, India	Leaf	Used to treat diabetes (Bever, 1980)
Celastraceae	*Salacia macrosperma* Wight	India	Leaf, root	Methanol extract has antidiabetic activity in rats (Venkateswarlu et al., 1993)
Celastraceae	*Salacia reticulata* Wight	India	Root bark	Extract reduces glucose and insulin and increases breath hydrogen. These features are similar to α-glucosidase inhibitors (Heacock et al., 2005)
Malpighiales				
Euphorbiaceae	*Aporosa lindleyana* Baill.	Tropics	All	Reduces blood glucose in alloxan-treated rats (Jayakar and Suresh, 2003)
Euphorbiaceae	*Bridelia ferruginea* Benth.	Africa	Leaf	Reduces blood glucose (Ivorra et al., 1989)
Euphorbiaceae	*Clutia richardiana* L.	Middle East	Leaf	Labdane-type diterpenes (richardianidin-1, richardianidin-2, saudin) have hypoglycemic activity. Compounds present in hot infusions of leaves (Mossa et al., 1988)
Euphorbiaceae	*Cnidoscolus aconitifolius* (Mill.) I.M. Johnst.	C. America	Young leaf, shoot	Shows hypoglycemic activity (Grubben and Denton, 2004)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Euphorbiaceae	*Croton cajucara* Benth.	S. America		*Trans*-dehydrocrotonin, a diperpene, lowers blood glucose in STZ-treated rats (Silva et al., 2001)
Euphorbiaceae	*Croton niveus* Billb. ex. Beurl.	S. America		Used to treat diabetes (Marles and Farnsworth, 1995)
Euphorbiaceae	*Euphorbia hirta* L.	Australia, India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Euphorbiaceae	*Euphorbia pilulifera* L.	India		Used to treat diabetes (Marles and Farnsworth, 1995)
Euphorbiaceae	*Euphorbia prostrata* Ait.	India	Aerial parts	Reduces blood glucose in rabbits (Handa et al., 1989)
Euphorbiaceae	*Glochidion hohenackeri* (Müll. Arg.) Bedd	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Euphorbiaceae	*Mallotus philippinensis* Müll. Arg.	India, E. Asia, Australia	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Euphorbiaceae	*Manihot esculenta* Crantz			Results in high levels of glucose released into the blood (Ramdath et al., 2004)
Euphorbiaceae	*Phyllanthus amarus* Schumach. & Thonn.	India	All	Aqueous extract of aerial parts used traditionally to treat diabetes. However, no evidence of hypoglycemic activity in NIDDM patients (Moshi et al., 2001). Plant contains oleanolic acid
Euphorbiaceae	*Phyllanthus emblica* L.	India	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Euphorbiaceae	*Phyllanthus niruri* L.	India, Africa	All	Although used traditionally to treat diabetes, an aqueous extract did not decrease blood glucose in STZ-treated rats (Husen et al., 2004)
Euphorbiaceae	*Phyllanthus sellowianus* Müll. Arg.	India, S. America	All	Flavonoids such as rutin and isoquercitrin lower blood glucose in STZ-treated mice (Hnatyszyn et al., 2002)
Euphorbiaceae	*Ricinus communis* L.	Universal	All	Has proven hypoglcemic activity (Moshi and Mbwambo, 2002)
Passifloraceae	*Passiflora quadrangularis* L.	Tropical America	Fruit, leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Rhizophoraceae	*Kandelia rheedii* Wight & Arn.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Rhizophoraceae	*Rhizophora mangle* Roxb.	India	Bark, root	Reduces blood glucose in hyperglycemic rabbits (Alarcon Aguilar et al., 1998)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Rhizophoraceae	*Rhizophora mucronata* Lam.	Tropics, India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Salicaceae	*Casearia glauca* Lam.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Salicaceae	*Casearia esculenta* Roxb.	India	Root	Root extract is antioxidant in STZ-treated rats (Prakasam et al., 2003)
Turneraceae	*Turnera diffusa* Willd.	C. America	All	Recent research showed that water-ethanol extracts did not reduce blood glucose (Alarcon–Aguilar et al., 2002)
Oxalidales				
Elaeocarpaceae	*Elaeocarpus ganitrus* Roxb. & G. Don	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Oxalidaceae	*Averrhoa bilimbi* L.	Tropics	Leaf	Extracts decrease blood glucose and increase release of insulin from pancreatic islets (Latha et al., 2004)
Oxalidaceae	*Biophytum sensitivum* (L.) DC	S.E. Asia	All	Leaf extracts are hypoglycemic (Puri, 2001) and hypocholesterolemic (Puri, 2003) *in vivo*
Oxalidaceae	*Xanthoxalis corniculata* (L.) Small			Used to treat diabetes (Marles and Farnsworth, 1995)
Rosales				
Moraceae	*Artocarpus altilis* (Parkinson) Fosberg	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Moraceae	*Ficus benghalensis* L.	S.E. Asia	Bark	Used traditionally in Ayurveda for the treatment of diabetes (Elder, 2004)
Moraceae	*Ficus carica* L.	Europe, Australia, Asia	Leaf, bark	Reduces levels of blood lipids in STZ-treated rats (Perez et al., 1999)
Moraceae	*Ficus glomerata* Roxb.	India	Bark, fruit, sap	Ethanolic extracts show hypoglycemic activity in alloxan-treated rats (Kar et al., 2003)
Moraceae	*Ficus racemosa* L.	Tropics, India	Bark	Methanol extract lowers blood glucose in alloxan-treated rats. The extract was as active as glibenclamide (Rao et al., 2002)
Moraceae	*Ficus religiosa* L.	India, S.E. Asia	Bark, root bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Moraceae	*Morus alba* L.	India, E. Asia, Africa	Leaf, root bark	The glycoprotein moran A lowers blood glucose (Hikino et al., 1985); phenolics kaempferol and quercetin glycosides, and ursolic acid could be important (Basnet et al., 1993)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Moraceae	*Morus australis* (T. Hotta) S. Kitamura	E. Asia	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Moraceae	*Morus nigra* L.	India, Asia, Europe	Leaf	Used in herbal mixtures to lower blood glucose (Petlevski et al., 2001)
Rhamnaceae	*Rhamnus purshiana* DC.	C. America	Bark	Used to treat diabetes (Winkelman, 1989)
Rhamnaceae	*Ziziphus mauritiana* Lam.	Tropics	Leaf	Aqueous extracts reduce blood glucose in rabbits (Diallo et al., 2004)
Rhamnaceae	*Ziziphus rugosa* Lam.	India	Bark	Quercetin-3-*O*-rhamnoside and myricetin-3-*O*-rhamnoside associated with hypoglycemic activity (Marles and Farnsworth, 1995)
Rhamnaceae	*Ziziphus sativa* Gaertn	Asia		Reduces glucose levels (Anand et al., 1989)
Rosaceae	*Agrimonia eupatoria* L.	Europe	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Rosaceae	*Agrimonia pilosa* Ledeb.	China	Leaf	Lower blood glucose (Li et al., 2002)
Rosaceae	*Alchemilla vulgaris* Wight	Europe		Used to treat diabetes (Marles and Farnsworth, 1995)
Rosaceae	*Cotoneaster aitchisoni* C.K. Schneid.	India	Aerial parts	Hypoglycemic activity in rats (Abraham et al., 1986)
Rosaceae	*Eriobotrya japonica* (Thunb.) Lindl.	India	Leaf	Sesquiterpene glycosides and polyhydroxylated triterpenoids are the active compounds thought to promote insulin release (De Tommasi et al., 1991)
Rosaceae	*Poterium ancistroides* Guir. ex. Nym.	Europe	Aerial parts	Tormentic acid influences insulin secretion in rats (Ivorra et al., 1989b)
Rosaceae	*Poterium spinosum* L.	Middle East	Stem, root	Aqueous extract has hypoglycemic activity in rabbits (Mishkinsky et al., 1966)
Rosaceae	*Prunus amygdalus* Stokes	Universal	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Rosaceae	*Prunus persica* (L.) Batsch	S.E. Asia, India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Rosaceae	*Pyrus communis* L.	Asia, Europe, India		Used to treat diabetes (Marles and Farnsworth, 1995)
Rosaceae	*Rosa brunonii* Lindl.		Aerial parts	Shows hypoglycemic activity in rats (Dhawan et al., 1980)
Rosaceae	*Rosa canina* L.	Europe	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Rosaceae	*Rubus fruticosus* L.	Europe	Leaf	Reduces blood glucose (Ivorra et al., 1989)
Rosaceae	*Rubus strigosus* Michx.	Europe	Leaf	Used to treat diabetes (Lust, 1986)
Rosaceae	*Rubus ulmifolius* Schott.	C. America	Leaf	Reduces blood glucose level in blood of alloxan-treated rats (Lemus et al., 1999)
Rosaceae	*Sanguisorba minor* Scop.			Contains triterpenes with hypoglycemic activity (Reher et al., 1991)
Rosaceae	*Sanguisorba officinalis* L.			Contains triterpenes with hypoglycemic activity (Reher et al., 1991)
Rosaceae	*Sarcopoterium spinosum* Spach	Middle East	Root	Reduces blood glucose (Handa et al., 1989)
Urticaceae	*Cecropia obtusifolia* Bertol	C. America	Leaf, stem	Extracts reduce blood glucose, cholesterol and triglycerides in patients with type 2 diabetes that did not respond to conventional treatments (Herrera–Arellano et al., 2004)
Urticaceae	*Cecropia peltata* L.	C. America	Leaf, stem	Used to treat diabetes (Winkelman, 1989)
Urticaceae	*Myrianthus arboreus* Beauv.	Africa	Bark	Used to treat diabetes (Abbiw, 1990)
Urticaceae	*Urtica dioica* L.	Temperate zones	All	Extracts inhibit α-glucosidase (Onal et al., 2005)
Urticaceae	*Urtica urens* L.	Europe	All	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Fabales				
Fabaceae	*Abrus precatorius* L.	India	Leaf	Precatorine shown to have hypoglycemic activity (Marles and Farnsworth, 1995)
Fabaceae	*Acacia arabica* Willd.	India	Bark	Reduces glucose levels (Handa et al., 1989)
Fabaceae	*Acacia benthami* Rochbr.	Africa	Seed, bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Acacia catechu* Brandis	India, S.E. Asia	Stem	Extracts reported to have hypoglycemic activity (Singh et al., 1976)
Fabaceae	*Acacia melanoxylon* R. Br.	Africa, India, Australia	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Acacia modesta* Wall	India	Seed	Reduces glucose levels (Handa et al., 1989)
Fabaceae	*Acacia nilotica* Delile	India	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Fabaceae	*Acacia suma* Buch.-Ham. ex. Voigt	Africa, India	Seed	Extracts reported to have hypoglycemic activity (Singh et al., 1976)
Fabaceae	*Albizia lebbek* Benth.	Africa, India, Asia	Bark, seed pod	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Albizia moluccana* Miq.	India	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Albizia procera* Benth.	Africa, India, Australia	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Alhagi maurorum* Medik.	Africa, S.W. Asia	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Arachis hypogaea* L.	Asia, America	Nut	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Astragalus membranaceus* (Fisch.) Bunge	Asia	Root	Polysaccharides can regulate blood glucose level (Zhang et al., 2001); has activity on diabetic complications, inhibits lipid peroxidation (Chen et al., 2001)
Fabaceae	*Bauhinia candicans* Benth.	C. America, S.E. Asia, Australia		Decreases blood glucose in alloxan-treated rats (Lemus et al., 1999) Extracts increase the peripheral metabolism of glucose (Fuentes et al., 2004)
Fabaceae	*Bauhinia forficata* Benth.	Brazil, S. America	Leaf	Leaves contain kaempferitrin that lowers blood glucose and stimulates glucose uptake by muscles (Jorge et al., 2004)
Fabaceae	*Bauhinia purpurea* Wall.	Africa	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Bauhinia retusa* Roxb.	India	Seed	Reported to be hypoglycemic *in vivo* (Singh and Chandra, 1977)
Fabaceae	*Bauhinia variegata* L.	Tropics	Flower, leaf	Extracts stimulate the release of insulin (Hussain et al., 2004)
Fabaceae	*Butea monosperma* (Lam.) Taub.	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Caesalpinia bounducella* Flem.	India		Caesalpin, bonducellin, and amino acids associated with hypoplycemic activity (Rajan et al., 2002)
Fabaceae	*Caesalpinia digyna* Rottl.	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Caesalpinia sappan* L.	Asia	Leaf, root	Caesalpin P, sappanchalcone, 3-deoxysappanone, brazilin and protosappanin A inhibit aldose reductase (Morota et al., 1990)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Fabaceae	*Cajanus cajan* (L.) Millsp	Africa, India	Seed	Frequently used to treat patients with diabetes, especially in India (Grover, 2002)
Fabaceae	*Caragana brevispina* Benth.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Cassia alata* L.	Asia	Leaf	Extracts reported to have antidiabetic activity (Palanichamy et al., 1988)
Fabaceae	*Cassia auriculata* L.	Africa, India	Seed, leaf, flower	Part of an ayurvedic formula "hyponida" that has antihyperglycemic and antioxidant activity (Babu and Prince, 2004)
Fabaceae	*Cassia fistula* L.	Tropics, India	Bark	Reported to have antidiabetic activity but Hussain et al. (2004) showed it did not stimulate insulin secretion
Fabaceae	*Cassia occidentalis* L.	India	Leaf, flower	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Cassia sophera* L.	India	Bark, leaf, seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Ceratonia siliqua* L.	Middle East	Seed	Used traditionally to treat diabetes in Israel (Yaniv et al., 1987)
Fabaceae	*Cyamopsis tetragonolobus* Taub	Arabia, India, S. America	Seed	Gum extracts have a short-term influence on the lowering of blood glucose (Frias and Sgarbieri, 1998)
Fabaceae	*Dolichos biflorus* L.	India	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Dolichos lablab* L.	India	Seed	Protein concentrates from seeds are hypocholesterolemic *in vivo* (Chau et al., 1998)
Fabaceae	*Erythrina indica* Lam	India	Root, stem bark	Oleanolic acid from stem bark (Nkengfack et al., 2001) lowers blood glucose in normal and diabetic mice (Perez et al., 1998b) and inhibits α-amylase (Ali et al., 2002)
Fabaceae	*Erythrina suberosa* Roxb.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Eysenhardtia polystachya* Sarg.	C. America	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Galega officinalis* L.	Europe, India	Leaf, seed	Reduces blood glucose in alloxan-treated rats (Lemus et al., 1999)
Fabaceae	*Glycine max* Merrill.	Universal	Seed	D-pinitol lowers blood glucose and is a major component in soya leaves (Streeter, 2001)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Fabaceae	*Glycyrrhiza glabra* L.	Universal	Root	Hydrophobic flavonoids in licorice decrease blood glucose and abdominal fat. These effects may be mediated via peroxisome proliferator-activated receptor-γ (Nakagawa et al., 2004)
Fabaceae	*Indigofera arrecta* Hochst.	Africa	Leaf	Traditionally used to treat diabetes in Ghana but extracts did not have hypoglycemic activity in nondiabetic humans and showed some overt toxicity by lowering the immune status (Sittie and Nyarko, 1998)
Fabaceae	*Indigofera tinctoria* L.	Tropics	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Lablab purpureus* (L.) Sweet	Africa, India	Leaf	Used to treat diabetes (Grubben and Denton, 2004)
Fabaceae	*Lathyrus japonicus* Fernald		Seed	Active compounds are lathyrine, L-glutamyl-L-lathyrine (Marles and Farnsworth, 1995)
Fabaceae	*Lathyrus palustris* S. Watson	America	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Leucaena glauca* Benth.	India	Seed	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Leucaena leucocephala* (Lam.) de Wit	S. America, S.E. Asia, India	Leaf, seed	Reduces glucose levels (Ivorra et al., 1989)
Fabaceae	*Lupinus albus* L.	India, Mediterranean	Seed	Extracts lower blood glucose in alloxan-treated rats but also decrease activity of cytochrome P450 and other enzymes in the liver that detoxify metabolites (Sheweita et al., 2002)
Fabaceae	*Lupinus hirsutus* L.	Mediterranean	Seed	Active compounds lupanine, coumarin, and sparteine are toxic (Marles and Farnsworth, 1995)
Fabaceae	*Lupinus termis* Forssk.	N. Africa	Seed	Extracts decrease blood levels of glucose, urea, creatinine, and bilirubin in alloxan-treated rats (Mansour et al., 2002)
Fabaceae	*Medicago sativa* L.	Africa		Decreases levels of blood glucose (Gallagher et al., 2003)
Fabaceae	*Millettia cinerra* Benth.	Burma	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Mimosa pudica* Mill.			Extracts with mimosine cited as having hypoglycemic activity (Rajan et al., 2002)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Fabaceae	*Mucuna pruriens* DC	Africa, E. Asia, India	Fruit	Extracts decrease glucose level in blood. Increase in peripheral utilization of glucose and release of insulin in a way that differs from insulin (Rathi et al., 2002)
Fabaceae	*Mucuna prurita* Hook	India	Fruit	Extracts decrease blood glucose level in alloxan-treated rats (Kar et al., 2003)
Fabaceae	*Parkia speciosa* Hassk.	Africa, India		Stigmast-4-en-3-one from pods lowers blood glucose in alloxan-treated rats (Jamaluddin et al., 1995)
Fabaceae	*Phaseolus coccineus* L.	Europe, India, America	Seed	Active compound gluckinin (Marles and Farnsworth, 1995); glycoprotein (MAI-2) from seeds inhibits α-amylase (Sawada et al., 2002)
Fabaceae	*Phaseolus multiflorus* Willd.	India	Seed	Inhibits α-amylase (Labbé, 1936)
Fabaceae	*Phaseolus mungo* L.	India	Seed	Addition of blackgram fibre to a rat diet decreases blood glucose level (Boby and Leelamma, 2003)
Fabaceae	*Phaseolus vulgaris* L.	Africa, Europe, India	Seed	Inhibitor of α-amylase from kidney beans reduces blood glucose in rats (Tormo et al., 2004)
Fabaceae	*Pisum sativum* L.	Universal	Seed	Saponins decrease blood glucose level but can be lost during food processing (Shi et al., 2004)
Fabaceae	*Pithecellobium dulce* (Roxb.) Benth.	India	Leaf	Lowers blood glucose (Garcia, 1944)
Fabaceae	*Pongamia pinnata* (L.) Pierre	India	Flower	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Prosopis farcta* Macbride	Middle East	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Pterocarpus marsupium* Roxb.	Africa, India, S. America	Wood, bark	Extracts with kinotanic acid associated with antidiabetic activity (Rajan et al., 2002)
Fabaceae	*Pterocarpus santalinus* Blanco	India	Seed, wood	Epicatechin and pterostilbene have antidiabetic activity (Marles and Farnsworth, 1995)
Fabaceae	*Pueraria lobata* (Willd.) Ohwi.	China	Root	Puerarin, an isoflavone, has been associated with lowering of blood glucose (Shen and Xie, 1985)
Fabaceae	*Pueraria thunbergiana* Benth.	China	Flower	Tectorigenin and kaikasaponin III alleviate STZ-induced toxicity and have hypoglycemic activity (Lee et al., 2000)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Fabaceae	*Saraca indica* L.	India	Flower, bulb	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Securigera securidaca* L.	India, Middle East	Seed	Aqueous extracts of seeds reduce blood glucose level. Extract containing flavonoids is active in alloxan-treated mice by a mechanism different from the sulphonylurea glibenclamide (Hosseinzadeh et al., 2002)
Fabaceae	*Spartium junceum* L.	Canaries	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Tamarindus indica* L.	Universal	Seed	Aqueous extracts of seeds decrease blood glucose in STZ-treated rats (Maiti et al., 2004)
Fabaceae	*Tephrosia purpurea* (L.) Pers	India	Root, seed	Lupeol has antidiabetic activity (Marles and Farnsworth, 1995)
Fabaceae	*Tephrosia villosa* (L.) Pers	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Fabaceae	*Teramnus labialis* (L.f.) Spreng.	India	All	Mixture of coumarins including fraxidin, isolated from aerial material show hypoglycemic activity (Fort et al., 2000)
Fabaceae	*Tetrapleura tetraptera* (Taub)	Africa	Fruit	Decreases blood glucose in STZ-treated rats (Ojewole and Adewunmi, 2004)
Fabaceae	*Trifolium alexandrinum* L.	India, Middle East	Flower, seed	Extracts alleviate hyperglycemia in STZ-diabetic rats (Amer et al., 2004)
Fabaceae	*Trigonella foenum-graecum* L.	Africa, India, Middle East	Seed, leaf	Saponins, a high fibre content and the amino acid 4-hydroxyisoleucine have been associated with antidiabetic effects (Al-Habori and Raman, 1998; Sauvaire et al., 1998)
Fagales				
Betulaceae	*Alnus nepalensis* D. Don	India	Bark	Extracts show antidiabetic activity but plant is toxic (Marles and Farnsworth, 1995)
Fagaceae	*Quercus infectoria* Oliv.	India	Gall, fruit	Hexagalloylglucose from galls inhibits α-glycosidases such as sucrase, maltase, and isomaltase (Hwang et al., 2000)
Fagaceae	*Quercus lamellosa* Sm.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Fagaceae	*Quercus lanceaefolia* Roxb.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Fagaceae	*Quercus lineata* Miq.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Fagaceae	*Quercus robur* Pall.		Gall	Grandinin reduces blood glucose in STZ-treated mice (Moharram et al., 2003)
Fagaceae	*Quercus spicata* Sm.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Juglandaceae	*Juglans mandshurica* Maxim.	E. Asia	Leaf	Used to treat diabetes (Moskalenko, 1987)
Juglandaceae	*Juglans regia* L.	Africa, Asia, Europe		A tetralone derivative has antidiabetic activity by inhibiting protein tyrosine phosphatase (An et al., 2003)
Cucurbitales				
Cucurbitaceae	*Benincasa hispida* (Thunb.) Cogn.	India, S.E. Asia	Fruit	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Cucurbitaceae	*Bryonia alba* Bull.	Asia, Europe, Africa	All	Reduces glucose level in alloxan-treated rats (Ivorra et al., 1989)
Cucurbitaceae	*Bryonia cretica* L.	Europe	Aerial parts	Trihydroxyoctadecadienoic acid reported to be an active compound (Marles and Farnsworth, 1995)
Cucurbitaceae	*Bryonia epigaea* Blume	India	Aerial parts	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Citrullus colocynthis* Schrad.	Middle East	All	Aqueous extracts of seeds reduce aspartate aminotranferase and lactic dehydrogenase in STZ-treated rats, thus could treat some symptoms of diabetes (Al-Ghaithi et al., 2004)
Cucurbitaceae	*Citrullus lanatus* (Thunb.) Mansf.	Tropics, subtropics	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Coccinia grandis* (L.) Voigt	Africa, India	Root	Used to treat diabetes (Grubben and Denton, 2004)
Cucurbitaceae	*Coccinia indica* W. & A.	India	All	Ethanolic extracts of leaves used in Ayurvedic medicine to treat diabetes. Depress the activity of glucose 6-phosphatase and stimulate insulin release (Venkateswaran and Pari, 2002)
Cucurbitaceae	*Coccinia indica* Wight et Arn.	India	Leaf	A review of 108 different trials showed good evidence for the antidiabetic activity (Yeh et al., 2003)
Cucurbitaceae	*Cogniauxia podoleana* Baillon			Non-flavonoid compounds lower blood glucose in alloxan-treated rats (Diatewa et al., 2004)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Cucurbitaceae	*Cyclanthera pedata* (L.) Schrad	S. America, E. Africa	Shoot, leaf	Has hypoglycemic activity (Grubben and Denton, 2004)
Cucurbitaceae	*Gynostemma pentaphyllum* (Thunb.) Mak		Stem, leaf	Saponins decrease blood glucose (Jang et al., 2001); phanoside stimulates insulin release (Norberg et al., 2004)
Cucurbitaceae	*Lagenaria vulgaris* Ser.	India	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Luffa acutangula* (L.) Roxb.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Luffa aegayptiac* Mill.		Aerial parts	Reduces blood glucose in STZ-treated rats (El-Fiky et al., 1996)
Cucurbitaceae	*Luffa echinata* Roxb.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Momordica balsamina* L.	C. America	Root	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Momordica charantia* L.	Africa, India, C. America, Australia, Middle East	Fruit, leaf	Widespread use for the treatment of diabetes; polypeptide (p-insulin) and a mixture of sterols have been identified as the active compounds (Li et al., 2004)
Cucurbitaceae	*Momordica cochinchinensis* (Lour.) Spreng.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Momordica foetida* Schum.	Africa	Aerial parts	Extracts and foetidin lower blood glucose (Marquis et al., 1977)
Cucurbitaceae	*Trichosanthes bracteata* Voight.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Cucurbitaceae	*Trichosanthes dioica* Wall.	India	Aerial parts	Lowers blood glucose (Marles and Farnsworth, 1995)
Cucurbitaceae	*Trichosanthes kirilowii* Maxim.	India, E. Asia	Aerial parts	Five glycans, trichosans A, B, C, D, and E show hypoglycemic activity (Hikino et al., 1989)
Not yet placed in an order				
Krameriaceae	*Krameria triandra* Ruíz & Pav.		Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Zygophyllaceae	*Balanites aegyptiaca* Delile	Africa	Fruit	Used to treat diabetes (Elsaadany et al., 1986)
Zygophyllaceae	*Larrea tridentata* Coville	C. America, Laminaria Ocean	Root, stem, bark, leaf	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Zygophyllaceae	*Peganum harmala* L.	Africa, Europe, Asia, India	Seed	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Zygophyllaceae	*Tribuluks terrestris* L.	Asia	Stem, leaf	Decreases blood glucose and improves glucose tolerance (You and Wang, 2000)
Zygophyllaceae	*Zygophyllum cornutum* Coss	N. Africa		Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Eurosid II				
Brassicales				
Brassicaceae	*Brassica napiformis* (Paill. & Bois) L.H. Bailey	E. Asia		Used to treat diabetes (Marles and Farnsworth, 1995)
Brassicaceae	*Brassica oleracea* L.	Europe, India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Brassicaceae	*Brassica rapa* L.	Europe	Root	Reported to lower blood glucose (Marles and Farnsworth, 1995)
Brassicaceae	*Capparis spinosa* L.	Middle East	Fruit	Polar extract of fruit decreases blood glucose in STZ-treated rats but does not change insulin levels. Antidiabetic activity is independent of insulin release (Eddouks et al., 2004)
Brassicaceae	*Cleome droserifolia* Delile	Middle East	Leaf	Extract suppresses the rise in peripheral blood glucose, in the fasting state and after glucose intake, and is reported to be hypocholesterolemic (Nicola et al., 1996)
Brassicaceae	*Descurainia sophia* (L.) Webb ex. Prantl.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Brassicaceae	*Lepidium ruderale* L.	Asia	Aerial parts	Reduces blood glucose in alloxan-treated rats (Handa et al., 1989)
Brassicaceae	*Megacarpaea polyandra* Benth.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Brassicaceae	*Nasturtium officinale* R. Br.	Canaries, India	Aerial parts	Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Brassicaceae	*Raphanus sativus* L.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Caricaceae	*Carica papaya* L.	India, Africa	Fruit	Extracts used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Moringaceae	*Moringa oleifera* Lam.	Middle East	Fruit	Niazicin, 1-*O*-phenyl-α-L-rhamnopyranoside, 4-[(β-D-glucopyranosyl)-(1>3)-α-L-rhamnopyranosyl]phenylacetonitrile, methyl N-{4-[(α-L-rhamnopyranosyl)benzyl]}carbamate and methyl N-[4-[{4′-*O*-acetyl-α-L-rhamnopyranosyl) benzyl]} carbamate stimulate insulin release (Francis et al., 2004)
Moringaceae	*Moringa pterygosperma* (L.) Gaertn.	India	Flower, bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Salvadoraceae	*Salvadora persica* L.	Middle East	Aerial parts	Extracts reduce blood glucose and increase insulin release in rats (Trovato et al., 1998)
Sapindales				
Anacardiaceae	*Anacardium occidentale* L.	Tropics, Europe	Stem, leaf	Regulates glucose level in blood of STZ-treated rats (Kamtchouing et al., 1998)
Anacardiaceae	*Mangifera indica* L.	India	Leaf	Regulates glucose level in blood of STZ-treated rats (Sharma et al., 1997)
Anacardiaceae	*Poupartia birrea* (Hochst.) Aubrév.	Africa	Leaf	Extracts inhibit aldose reductase (Laurens et al., 1985)
Anacardiaceae	*Rhus chinensis* Mill.	E. Asia, India, N. America	Aerial parts	Extracts contain compounds that inhibit α-glucosidase, thus decreasing glucose level in the blood (Shim et al., 2003)
Anacardiaceae	*Rhus coriaria* L.	Asia	Fruit	Extracts from fruits have potent antioxidant activity against lipid peroxidation (Candan and Sokman, 2004)
Anacardiaceae	*Rhus glabra* L.	Europe	Bark, leaf, fruit	Extracts inhibit lipid peroxidation and as antioxidants these could relate to the antidiabetic uses of the plant (Candan and Sokmen, 2004)
Anacardiaceae	*Rhus succedanea* L.	India	Aerial parts	Ethanolic extracts have antidiabetic activity (Marles and Farnsworth, 1995)
Anacardiaceae	*Rhus typhina* L.	N. America	Leaf	Extracts have hypoglycemic activity (Lewis, 1977)
Anacardiaceae	*Sclerocarya birrea* (A. Rich.) Hochst.	Africa	Leaf	Lowers blood glucose in STZ-treated rats (Ojewole, 2003)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Anacardiaceae	*Semecarpus anacardium* L.f.	India	Fruit	Modulates glucose metabolism by decreasing activity of glycolytic enzymes and increasing gluconeogenic enzymes (Premalatha et al., 1997)
Burseraceae	*Commiphora molmol* Engl. ex. Tschirch	Middle East		Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Meliaceae	*Amoora wallichi* Bulm. F.		Stem	Used to treat diabetes (Marles and Farnsworth, 1995)
Meliaceae	*Azadirachta indica* A. Juss	India, E. Asia, America,	Leaf, seed, flower	Reduces blood glucose (Handa et al., 1989)
Rutaceae	*Aegle marmelos* Correa	India	Leaf, root, fruit	Aqueous extract reduces blood glucose and has antioxidant activity in STZ-treated rats (Kamalakkannan and Prince, 2004)
Rutaceae	*Atalantia racemosa* Wight et Arn	India	Aerial parts	Shows hypoglycemic activity in rats (Bhakuni et al., 1988)
Rutaceae	*Boenninghausenia albiflora* Rchb.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Rutaceae	*Citrus aurantium* L.	Subtropics	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Rutaceae	*Citrus bergamia* Risso	Europe, India	Fruit	Diphenylamine could be associated with antidiabetic activity (Marles and Farnsworth, 1995)
Rutaceae	*Feronia limonia* Swingle	India	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Rutaceae	*Murraya koenigii* L.	Africa, India	Leaf	Extract is reported to have hypoglycemic activity (Kesari et al., 2005)
Rutaceae	*Paramignya monophylla* Wight	India	Aerial parts	Shows hypoglycemic activity in rats (Bhakuni et al., 1988)
Rutaceae	*Phellodendron amurense* Rupr.	India, China	Bark	Reduces lipid peroxidation and protein carbonylation (Lee et al., 2000)
Rutaceae	*Phellodendron chinensis* Schneid	Asia	Bark	Reduces lipid peroxidation and protein carbonylation (Lee et al., 2000)
Rutaceae	*Ruta chalepensis* L.	Africa	Leaf	Used to treat diabetes (Abdulkadir, 1985)
Rutaceae	*Toddalia asiatica* Lam.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Rutaceae	*Zanthoxylum alatum* Roxb.	Africa, India, E. Asia	Stem	Used to treat diabetes (Marles and Farnsworth, 1995)
Rutaceae	*Zanthoxylum armatum* DC.	India	Stem	Shows hypoglycemic activity in rats (Dhar et al., 1968)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Sapindaceae	*Blighia sapida* Kon	Africa, C. America, Tahiti	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Sapindaceae	*Dodonaea viscosa* Jacq.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Simaroubaceae	*Ailanthus altissima* Swingle	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Simaroubaceae	*Eurycoma longifolia* Jack	Africa		Aqueous extract decreases blood glucose in STZ-treated rats (Husen et al., 2004)
Malvales				
Bixaceae	*Bixa orellana* L.	C. America	Seed	Extracts from seeds have antidiabetic activity in dogs (Ivorra et al., 1989)
Malvaceae	*Abelmoschus manihot* (L.) Medik.	India	Root	Mucilage has hypoglycemic activity (Marles and Farnsworth, 1995)
Malvaceae	*Althaea officinalis* L.	Europe, Asia	Root, leaf	Mucilage (O and OL) has hypoglycemic activity (Marles and Farnsworth, 1995)
Malvaceae	*Ceiba pentandra* (L.) Gaertn.	Tropics	Bark	Polar extracts of bark decrease blood glucose in STZ-treated rats (Ladeji et al., 2003)
Malvaceae	*Decaschistia crotonifolia* Wight et Arn	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Malvaceae	*Gossypium herbaceum* L.	Africa, India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Malvaceae	*Hibiscus rosa-sinensis* L.	India	Flower	Hypoglycemic effect in STZ-treated rats is not mediated through insulin release (Sachdewa and Khemani, 2003)
Malvaceae	*Hibiscus syriacus* L.	Asia	Leaf	Mucilage has hypoglycemic activity (Marles and Farnsworth, 1995)
Malvaceae	*Hibiscus tiliaceus* L.	Tropics, subtropics	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Malvaceae	*Malva verticillata* L.	E. Asia	Seed	Glycan polysaccharides could have hypoglycemic activity (Tomoda et al., 1990)
Malvaceae	*Salmalia malabarica* Schott & Endl.	India, E. Asia, Australia	Bark	Extracts shown to have antidiabetic activity (Marles and Farnsworth, 1995)
Malvaceae	*Sida cordifolia* Forssk.	India	Aerial parts, root	Methanol extract of root is hypoglycemic (Kanth and Diwan, 1999)

TABLE 2.1 (CONTINUED)
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Sterculiaceae	*Abroma augusta* L.f.	India		Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Sterculiaceae	*Helicteres isora* L.	S.E. Asia, Australia, India	Seed, bark, root juice	Extracts reduce blood glucose in rats (Venkatesh et al., 2004)
Sterculiaceae	*Heritiera minor* Lam.	Indonesia	Aerial parts	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Sterculiaceae	*Sterculia guttata* Roxb.	India	Leaf	Shows hypoglycemic activity in rats (Bhakuni et al., 1988)
Tiliaceae	*Corchorus olitorius* L.		Leaf	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Tiliaceae	*Grewia asiatica* L.	India	Bark	Reduces blood glucose (Handa et al., 1989)
Not yet placed in an order				
Vitaceae	*Leea crispa* M. Laws	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Vitaceae	*Leea indica* Merr.	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Asterids				
Cornales				
Cornaceae	*Cornus officinalis* Sieb. et Zucc.	Asia	Fruit, seed	Ursolic acid and oleanolic acid reduce blood glucose in STZ-treated rats (Yamahara et al., 1981)
Hydrangeaceae	*Hydrangea paniculata* Sieb		Bark	Hypoglycemic activity in mice (Tomoda et al., 1987)
Hydrangeaceae	*Hydrolea zeylanica* (L.) J. Vahl	Tropics, India	All	Hypoglycemic activity in rats (Dhar et al., 1968)
Ericales				
Ebenaceae	*Diospyros peregrina* Gürke	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Ericaceae	*Agapetes sikkimensis* Airy Shaw	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Ericaceae	*Agarista mexicana* (Hemsl) Judd	C. America	Aerial parts	Water extract used to treat diabetes. Triterpene compound 12-ursene isolated from chloroform extract reduces blood glucose in alloxan-treated mice. As active as tolbutamide (Perez and Vargas, 2002)
Ericaceae	*Arctostaphylos uva-ursi* (L.) Spreng.	C. America	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Ericaceae	*Vaccinium leschenaultii* Wight	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Ericaceae	*Vaccinium myrtillus* L.	Europe, Africa, Asia	Leaf	Reduces blood glucose (Handa et al., 1989)
Ericaceae	*Vaccinium oxycoccus* L.		Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Ericaceae	*Vaccinium vitis-idaea* L.	Europe, N. Asia	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Lecythidaceae	*Barringtonia acutangula* (L.) Gaertn.	S.E. Asia, Australia	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Sapotaceae	*Madhuca longifolia* Macbride	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Sapotaceae	*Mimusops elengi* L.	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Sapotaceae	*Pouteria tomentosa* (Roxb.) Baehni	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Styracaceae	*Symplocos theaefolia* D. Don	India	Root, leaf	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Theaceae	*Camellia sinensis* Kuntze	India	Leaf	Theophylline, diphenylamine, epicatechin, epigallocatechin, and caffeine associated with antidiabetic activity. Epigallocatechin represses hepatic glucose production (Waltner–Law et al., 2002)
Euasterid I				
Lamiales				
Acanthaceae	*Adhatoda vasica* Nees	India	Leaf, root	Shows hypoglycemic activity in rats (Dhar et al., 1968)
Acanthaceae	*Andrographis paniculata* Nees	Asia	All	Aqueous extract decreases blood glucose in STZ-treated rats (Husen et al., 2004)
Acanthaceae	*Asteracantha longifolia* Nees	India, Africa	All	Used to treat diabetes (Bever, 1980)
Acanthaceae	*Barleria cristata* L.	India	All	Used to treat diabetes (Dhar et al., 1968)
Acanthaceae	*Barleria noctiflora* L.f.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Acanthaceae	*Barleria prionotis* L.	Africa, India	Bark, leaf, root	Used to treat diabetes (Marles and Farnsworth, 1995)
Acanthaceae	*Dipteracanthus prostratus* Nees	India	All	Used to treat diabetes (Rastogi and Dhawan, 1982)
Acanthaceae	*Jacobinia suberecta* E. Andre	S. America	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Acanthaceae	*Strobilanthes crispus* Blume			Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Bignoniaceae	*Heterophragma quadriloculare* K. Schum	Indonesia	Aerial parts	Extracts have antidiabetic activity (Marles and Farnsworth, 1995)
Bignoniaceae	*Spathodea campanulata* Buch.-Ham. ex. DC.	Asia		Polar extracts from the bark show antidiabetic activity in mice (Niyonzima et al., 1999)
Bignoniaceae	*Stereospermum suaveolens* DC.	India	Root	Extracts have antidiabetic activity (Marles and Farnsworth, 1995)
Bignoniaceae	*Tecoma mollis* H.B.K.	Africa, India	All	Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Bignoniaceae	*Tecoma stans* H.B. et K.	India, C. America	All	Extracts from leaves have antidiabetic activity (Shapiro and Gong, 2002)
Lamiaceae	*Ajuga bracteosa* Benth.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Lamiaceae	*Ajuga iva* Schreb.	Canaries	Aerial parts	Decreases blood glucose in STZ-treated rats (El Hilaly and Lyoussi, 2002)
Lamiaceae	*Ajuga remota* Benth.	Africa	Leaf	Used to treat diabetes (Abdulkadir, 1985)
Lamiaceae	*Calamintha macrostema* Benth.	C. America	Root, stem	Used to treat diabetes (Marles and Farnsworth, 1995)
Lamiaceae	*Calamintha officinalis* Moench	Morocco	Aerial parts	Hypoglycemic effect in normal and STZ-treated rats (Lemhadri et al., 2004a)
Lamiaceae	*Calamintha umbrosa* Rchb.	India	All	Hypoglycemic activity in rats (Dhar et al., 1968)
Lamiaceae	*Cedronella canariensis* Webb & Berthel.	Canaries	Aerial parts	Extracts have hypoglycemic activity (Lopez Garcia et al., 1996)
Lamiaceae	*Clerodendranthus spicatus* (Thunb.) C.Y. Wu	Brunei		Triterpenoids ursolic and oleanolic acids (Yoshimura et al., 2003) could explain antidiabetic activity of plant
Lamiaceae	*Clerodendron phlomoides* L.f.	India	All	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Lamiaceae	*Hyptis suaveolens* Poit.	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Lamiaceae	*Lavandula multifida* Burm. f.		Flower	Extracts reported to have hypoglycemic activity (Gamez et al., 1987)
Lamiaceae	*Lavandula stoechas* L.	Europe	Leaf, flower	Extracts reported to have hypoglycemic activity (Gamez et al., 1987)
Lamiaceae	*Leonotis leonurus* (L.) R. Br.	Africa		Used to treat diabetes (Marles and Farnsworth, 1995)
Lamiaceae	*Lycopus virginicus* L.			Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Lamiaceae	*Mentha longifolia* Huds.	India	All	Used to treat diabetes (Aswal et al., 1984)
Lamiaceae	*Nepeta ciliaris*	India	All	Shows hypoglycemic activity in rats (Abraham et al., 1986)
Lamiaceae	*Ocimum americanum* Sims	S.E. Asia	Seed	Reduces blood glucose (Ivorra et al., 1989)
Lamiaceae	*Ocimum gratissimum* Forssk.	Africa	Leaf	Extracts lower blood glucose in alloxan-treated rats (Aguiyi et al., 2000)
Lamiaceae	*Ocimum tenuiflorum* L.	India	All	Extracts used traditionally to treat diabetes (Rajan et al., 2002)
Lamiaceae	*Origanum syriacum* L.	Middle East	Leaf	Used traditionally to treat diabetes in Israel (Yaniv et al., 1987)
Lamiaceae	*Origanum vulgare* L.			Aqueous extract decreases blood glucose in STZ-treated rats. Insulin secretion was not affected (Lemhadri et al., 2004b)
Lamiaceae	*Orthosiphon aristatus* Miq.	S.E. Asia	Leaf	Presence of ursolic and oleanolic acids (Yoshimura et al., 2003) could explain antidiabetic use
Lamiaceae	*Orthosiphon spiralis* Merr.		Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Lamiaceae	*Orthosiphon stamineus* Benth.	India	Leaf	Contains oleanolic acid and ursolic acid (Tezuka et al., 2000), which lower blood glucose in normal and diabetic mice (Perez et al., 1998b)
Lamiaceae	*Prunella vulgaris* L.	Worldwide	Whole plant	Reported to be antihyperglycemic (Li et al., 2004)
Lamiaceae	*Salvia lavandulifolia* Vahl.	Europe, C. America	Flower	Reduces blood glucose in alloxan-treated rats (Ivorra et al., 1989)
Lamiaceae	*Salvia canariensis* L.	Canaries	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Lamiaceae	*Salvia fruticosa* Mill.	Mediterranean	Leaf	Extracts reduce blood glucose by reducing absorption of glucose in intestines (Perfumi et al., 1991)
Lamiaceae	*Salvia miltiorrhiza* Bunge.	China	Root	Reported to treat diabetic nephropathy (Li et al., 2004)
Lamiaceae	*Salvia officinalis* L.	Europe	Leaf	Extracts decrease blood glucose level in alloxan-treated mice (Alarcon–Aguilar et al., 2002)
Lamiaceae	*Solenostemon rotundifolius* (Poir.) J.K. Morton	Africa	Tuber	Used to treat diabetes (Abbiw, 1990)
Lamiaceae	*Teucrium oliverianum* R. Br.	Middle East	Aerial parts	Reduces blood glucose (Ivorra et al., 1989)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Lamiaceae	*Teucrium polium* L.	India, Middle East	Leaf	Aqueous extracts lower blood glucose and enhance insulin secretion in STZ-treated rats (Esmaeili and Yazdanparast, 2004)
Lamiaceae	*Teucrium royleanum* Wall.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Oleaceae	*Ligustrum lucidum* Ait.	China	Fruit	Lowers blood glucose levels; oleanolic acid an active compound (Hao et al., 1992)
Oleaceae	*Olea europaea* L.	Universal	Leaf	Extract of leaves contains luteolin and oleanolic acid, which are antihyperglycemic; oleanolic acid also inhibits α-amylase (Komaki et al., 2003)
Oleaceae	*Syringa vulgaris* L.	E. Asia	Bud	Used to treat diabetes (Moskalenko, 1987)
Pedaliaceae	*Sesamum indicum* L.	India	Seed	Hot water and methanol extracts fed to mice reduce blood glucose associated with a delay in glucose absorption (Takeuchi et al., 2001)
Plantaginaceae	*Plantago himalaica* Pilg.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Plantaginaceae	*Plantago ovata* Phil	Chile		Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Capraria biflora* L.	C. America	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Cistanche tubulosa* Wight	Africa, India, Asia	All	Shows hypoglycemic activity in rats (Dhawan et al., 1980)
Scrophulariaceae	*Cymbalaria muralis* Gaertn.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Isoplexis canariensis* Steud	Canaries	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Isoplexis isabelliana* (Webb & Berthel.) Morris	Canaries	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Kickxia ramosissima* (Wall.) Janchen	India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Mazus surculosus* D. Don	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Pedicularis rhinanthoides* Larranaga	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Scrophulariaceae	*Rehmannia glutinosa* Libosch	China	Root	Oligosaccharide exhibits hypoglycemic activity by stimulating release of insulin (Zhang et al., 2004) Iridoid glycosides, rehmanniosides A, B, C, and D (Oshio and Inouye, 1982), and phenethyl alcohol derivatives, leucosceptoside A and purpureaside C (Nishimura et al., 1990a, b) have antidiabetic activity.
Scrophulariaceae	*Rehmannia lutea* Maxim.		All	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Scoparia dulcis* L.	India, Africa	Leaf, stem	Extracts from fresh leaves lower blood glucose level in alloxan-treated rats (Pari and Venkateswaran, 2002)
Scrophulariaceae	*Scrophularia buergeriana* Miq.	China	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Scrophularia ningpoensis* Hemsl.	China	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Striga gesnerioides* Vatke ex. Engl.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Scrophulariaceae	*Torenia asiatica* Herb. Madr. ex. Wall.	India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Verbenaceae	*Gmelina arborea* Roxb.	India	Wood, bark	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Verbenaceae	*Premna integrifolia* L.	India	Root, bark	Ethanol extract reduces blood glucose in alloxan-treated rats (Kar et al., 2003)
Verbenaceae	*Premna latifolia* Thwaites	India	Leaf, bark	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Verbenaceae	*Premna obtusifolia* R. Br.		Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Verbenaceae	*Verbena bonariensis* L.	Africa, S. America, India	All	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Solanales				
Convolvulaceae	*Argyreia cuneata* Ker. Gawl.	Africa	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Convolvulaceae	*Argyreia nervosa* Bojer	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Convolvulaceae	*Calystegia japonica* Choisy	E. Asia	Flower	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Convolvulaceae	*Convolvulus microphyllus* Sieber. ex. Spreng.	India		Used to treat diabetes (Marles and Farnsworth, 1995)
Convolvulaceae	*Ipomoea aquatica* Forssk.	America, E. Asia, India	Leaf	Aqueous extract of leaves is as effective as tolbutamide at reducing blood glucose level in Wistar rats (Malalavidhane et al., 2001)
Convolvulaceae	*Ipomoea batatas* (L.) Lam.	America, tropics	Leaf	Decreases blood glucose in patients with type 2 diabetes (Ludvik et al., 2004)
Convolvulaceae	*Ipomoea nil* (L.) Roth	America, E. Asia, India	Leaf	Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Convolvulaceae	*Rivea ornata* Choisy	India	Juice	Used to treat diabetes (Marles and Farnsworth, 1995)
Solanaceae	*Anisodus tanguticus* Pascher	China	Tuber	Lowers blood glucose (Li et al., 2004)
Solanaceae	*Atropa belladonna* L.	India	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Solanaceae	*Capsicum annuum* L.	Tropics	Fruit	Capsaicin has hypoglycemic activity (Marles and Farnsworth, 1995)
Solanaceae	*Capsicum frutescens* L.	India	Fruit	Capsaicin decreases blood glucose level and increases insulin secretion in dogs (Tolan et al., 2001)
Solanaceae	*Datura quercifolia* H.B. & K.	N. America, India	All	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Solanaceae	*Lycium barbatum* L.	Africa, China	Fruit, root cortex	Lowers serum glucose; polysaccharides active compounds (Wang et al., 1999)
Solanaceae	*Lycopersicon esculentum* Mill.	Universal		Used to treat diabetes (Marles and Farnsworth, 1995)
Solanaceae	*Nicotiana tabacum* L.	America	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Solanaceae	*Solanum lycocarpum* St Hil	S. America	Fruit	Polysaccharides slow gastric emptying, lower blood glucose, and decrease cholesterol (Dall'Agnol and von Poser, 2000)
Solanaceae	*Solanum melongena* L.	Middle East, Africa	Fruit	Used to treat diabetes (Grubben and Denton, 2004)
Solanaceae	*Solanum sanitwongsei* Craib.	S.E. Asia	Fruit	Lupeol has hypoglycemic activity (Marles and Farnsworth, 1995)
Solanaceae	*Solanum torvum* Sw.	India	Fruit	Lupeol has hypoglycemic activity (Marles and Farnsworth, 1995)
Solanaceae	*Solanum tuberosum* L.	C. America		Lupeol has hypoglycemic activity (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Gentianales				
Apocynaceae	*Alstonia macrophylla* Wall. & G. Don	S.E. Asia	All	Extracts from the whole plants have antidiabetic activity (Marles and Farnsworth, 1995)
Apocynaceae	*Alstonia scholaris* (L.) R. Br.	Africa, India, S.E. Asia	All	Extracts from the whole plants have antidiabetic activity (Marles and Farnsworth, 1995)
Apocynaceae	*Carissa edulis* Vahl.	India	Leaf	Leaf extracts lower glucose level in STZ-treated rats (El-Fiky et al., 1996)
Apocynaceae	*Catharanthus roseus* (L.) G. Don	Tropics	All	Lowers blood glucose, active compounds include vindoline, vindolinine, and leurosine (Li et al., 2004)
Apocynaceae	*Cryptostegia grandiflora* R. Br.	Africa, India		Rhodexin B and gitoxigenin associated with hypoglycemic activity (Rajan et al., 2002)
Apocynaceae	*Decalepis hamiltonii* Wight et Arn	India	Tuber	Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Apocynaceae	*Gymnema sylvestre* (Retz.)	Tropics	All	Gymnemic acids III, IV, V, VII, and gymnemoside B tested for antidiabetic activity (Yoshikawa et al., 1997a, b); A polyol conduritol A suppresses cataracts (Miyatake et al., 1994)
Apocynaceae	*Holarrhena antidysenterica* Wall ex. A. DC.	Tropics, India	Fruit	Extracts from fruits have antidiabetic activity (Handa et al., 1989)
Apocynaceae	*Holostemma annularis* Schum	India	Root	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Apocynaceae	*Hoodia currorii* (Hook.) Decne.	Central Africa	Stem	Used to treat diabetes (Grubben and Denton, 2004)
Apocynaceae	*Ichnocarpus frutescens* (L.) R. Br.	India	Leaf	Used to treat diabetes (Nagaraja and Rao, 1989)
Apocynaceae	*Periploca laevigata* Bal ex. Boiss			Extract used to treat diabetes (Marles and Farnsworth, 1995)
Apocynaceae	*Plumeria rubra* L.	Africa, C. America, India	Stem	Extracts from the whole plants have antidiabetic activity (Marles and Farnsworth, 1995)
Apocynaceae	*Rauwolfia serpentina* Benth. ex. Kurz	Tropics	All	Antidiabetic activity in cats (Handa et al., 1989)
Apocynaceae	*Rhazya stricta* Decne.	Middle East	Leaf	Reduces blood glucose and increases insulin release in rats; could adversely interfere with glycemic control if used with glibenclamide (Ali, 1997)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Apocynaceae	*Vinca erecta* Regel & Schmalh.	Asia	All	Vinca alkaloids have been reported to have antidiabetic activity. Extracts from the whole plants have antidiabetic activity (Marles and Farnsworth, 1995)
Apocynaceae	*Vinca minor* L.	Africa, Europe, Middle East	All	Range of alkaloids including isoreserpiline and reserpiline have antidiabetic activity (Marles and Farnsworth, 1995)
Gentianaceae	*Canscora decussata* (Roxb.) Roem. & Schult.	India		Contains mangiferin (Chaudhuri and Ghosal, 1971), which reduces the blood glucose level in diabetic mice (Ichiki et al., 1998; Miura et al., 2001)
Gentianaceae	*Enicostema hyssopifolium* (Willd.) Verdoorn	Africa, India	All	Used to treat diabetes (Marles and Farnsworth, 1995)
Gentianaceae	*Enicostema litoralis* Blume	India		Reduces blood glucose (Maroo et al., 2002)
Gentianaceae	*Swertia chirata* Buch. Ham	Africa, India	All	Swerchirin reduces blood glucose (Asthana et al., 1991)
Loganiaceae	*Anthocleista nobilis* G. Don	Africa	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Loganiaceae	*Anthocleista rhizophoroides* Baker	Madagascar	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Loganiaceae	*Anthocleista vogelii* Planch.	Africa	Root	Extracts shown to have hypoglycemic activity (Abuh et al., 1990)
Loganiaceae	*Gelsemium sempervirens* (L.) J. St.-Hil.			Used to treat diabetes (Marles and Farnsworth, 1995)
Loganiaceae	*Strychnos nux-vomica* L.	India, S.E. Asia	Fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Loganiaceae	*Strychnos potatorum* L.f.	India	Fruit	Extract has hypoglycemic activity in rabbits (Mathuram et al., 1981)
Rubiaceae	*Anthocephalus indicus* A. Rich.	India	Bark	Used to treat diabetes (Marles and Farnsworth, 1995)
Rubiaceae	*Cephalanthus glabratus* K. Schum	S. America	Wood	Used to treat diabetes (Marles and Farnsworth, 1995)
Rubiaceae	*Coffea arabica* L.	Asia	Seed	Extracts reported to have hypoglycemic activity (Rajan et al., 2002)
Rubiaceae	*Coutarea hexandra* K. Schum	S. America		Used to treat diabetes (Marles and Farnsworth, 1995)
Rubiaceae	*Coutarea latiflora* (Sessé & Moc.) ex. DC.	C., S. America	All	Geniposide have hypoglycemic activity (Marles and Farnsworth, 1995)
Rubiaceae	*Hamiltonia suaveolens* D. Don	India	Root	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Rubiaceae	*Hedyotis biflora* (L.) Lam.	India	All	Reduces blood glucose in alloxan-treated rabbits (Ivorra et al., 1989)
Rubiaceae	*Hintonia latiflora* Bullock	C. America	Bark	Neoflavonoid, coutareagenin reduces blood glucose in STZ-treated rats (Korec et al., 2000)
Rubiaceae	*Morinda citrifolia* L.	S.E. Asia	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Rubiaceae	*Morinda lucida* Benth.	Africa	Leaf	Methanol extract reduces blood glucose in STZ-treated rats (Olajide et al., 1999)
Rubiaceae	*Randia dumetorum* Lam.	India	Bark, fruit	Used to treat diabetes (Marles and Farnsworth, 1995)
Rubiaceae	*Rubia cordifolia* Hochst. ex. A. Rich.	Africa, India	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Not yet placed in an order				
Boraginaceae	*Heliotropium subulatum* Hoclist. ex. DC.	India	All	Extracts have antidiabetic activity but plant is toxic (Marles and Farnsworth, 1995)
Boraginaceae	*Lithospermum erythrorhizon* Sieb. & Zucc.	China	Root	Glycans lithospermans A, B, and C lower blood glucose (Konno et al., 1985b)
Boraginaceae	*Symphytum officinale* L.	Asia, Europe		Extracts used to treat diabetes but plant is toxic (Marles and Farnsworth, 1995)
Euasterid II				
Aquifoliales				
Aquifoliaceae	*Ilex guayusa* Loes	Europe	Aerial parts	Guanidine thought to be the main active component when tested (Marles and Farnsworth, 1995)
Apiales				
Apiaceae	*Ammi visnaga* (L.) Lam.	Middle East	Seed	Dihydrosamidin associated with antidiabetic activity (Marles and Farnsworth, 1995)
Apiaceae	*Anethum graveolens* L.	N. America, Asia, India	Fruit	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Apiaceae	*Apium graveolens* L.	Europe		Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Apiaceae	*Arracacia brandegei* J. M. Coult. & Rose	C. America	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Apiaceae	*Coriandrum sativum* L.	Middle East, Africa, Asia	Seed	Extracts reduce blood glucose in alloxan-treated rats (Sabu and Kuttan, 2003)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Apiaceae	*Daucus carota* L.	Europe, India	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Apiaceae	*Eryngium creticum* Jan ex. Guss.	Middle East	Leaf	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Apiaceae	*Ferula assa-foetida* L.	Asia, India	Leaf	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Apiaceae	*Petroselinum crispum* (Mill) Nyman	Asia		Reduces blood glucose in STZ-treated rats (Tunali et al., 1999)
Araliaceae	*Acanthopanax senticosus* (Rupr. et Maxim) Harms.	E. Asia	Bark	Senticoside A lowers blood glucose (Sui et al., 1994)
Araliaceae	*Acanthopanax sessiliflorum* Seem	Asia	Bark	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Araliaceae	*Aralia chinensis* Blume	E. Asia	All	Contains oleanolic acid (Wang et al., 1998), which lowers blood glucose in normal and diabetic mice (Perez et al., 1998b) and inhibits α-amylase (Ali et al., 2002)
Araliaceae	*Aralia decaisneana* Hance.	Asia	Branch bark, root bark	Triterpenoids (oleanolic acid and ursolic acid) and their glycosides are active compounds (Lin et al., 2000) and lower blood glucose and cholesterol
Araliaceae	*Aralia elata* (Miq.) Seem	E. Asia	Bark	Decreases levels of cholesterol in rats (Chung and Jung, 2003)
Araliaceae	*Eleutherococcus senticosus* Maxim	America, Siberia	Root	Polysaccharides, eleutherans F and G, lower blood sugar level (Wang et al., 2000)
Araliaceae	*Panax ginseng* C.A. Mey	America, E. Asia	Root	Many antidiabetic properties. Saponin ginsenosides Rb1, Rg1 (Lee et al., 1998), Re (Attele et al., 2002), Rg3 (Li et al., 2004), Rb2, (Kitamura et al., 1997) regulate enzymes associated with glucose metabolism. Panaxans and polypeptides also active (Li et al., 2004)
Araliaceae	*Panax notoginseng* (Burk.) F.H. Chen	Asia	Root	Ginsenoside Rg1 lowers plasma glucose (Gong et al., 1991); used to treat diabetic nephropathy (Lang et al., 1998)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Araliaceae	*Panax quinquefolium* L.	N. America, E. Asia	Root	Saponins (Li et al., 2004), and polysaccharides, quinquefolans A, B, and C (Oshima et al., 1987), have antidiabetic activity
Araliaceae	*Tetrapanax papyrifer* K. Kock	Asia	Root	Extracts used to treat diabetes (Marles and Farnsworth, 1995)
Asterales				
Asteraceae	*Achillea fragrantissima* Sch. Bip.	Middle East	All	Used traditionally to treat diabetes in Israel (Yaniv et al., 1987)
Asteraceae	*Achillea millefolium* L.	Europe	Leaf	Reduces blood glucose in alloxan-treated mice (Petlevski et al., 2001)
Asteraceae	*Ainsliaea latifolia* (D. Don) Sch. Bip.	India	All	Extracts show antidiabetic activity (Marles and Farnsworth, 1995)
Asteraceae	*Arctium lappa* L.	Africa, Asia, India, Europe	Fruit, root, leaf	Shows antihyperglycemic activity (You and Wang, 2000)
Asteraceae	*Artemisia abyssinica* Sch. Bip.	Arabia	All	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Artemisia afra* Jacq.	Africa	All	Extract used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Artemisia capillaris* Thunb.	India	Leaf, flower bud	Inhibits hyperglycemia and hypocholesterolemia *in vivo* (Pan et al., 1998)
Asteraceae	*Artemisia dracunculus* L.	N. America	Leaf	Reduces the hyperphagia and polydipsia associated with STZ-diabetes in mice (Swanston–Flatt et al., 1989)
Asteraceae	*Artemisia herba-alba* Asso.	Middle East	Aerial parts	Extract from stems and leaves has antidiabetic activity in humans (Ivorra et al., 1989)
Asteraceae	*Artemisia vulgaris* L.	India	All	Extract lowers blood glucose but plant is toxic (Marles and Farnsworth, 1995)
Asteraceae	*Atractylodes japonica* Kiodz.	E. Asia	Rhizome	Atractans A, B, and C have hypoglycemic activity (Konno et al., 1985c)
Asteraceae	*Atractylodes lancea* (Thunb.) DC.	China	Rhizome	Atractans A, B, and C have antidiabetic activity (Konno et al., 1985c)
Asteraceae	*Atractylodes macrocephala* Koidz.	China	Aerial parts	Atractans A, B, and C have antidiabetic activity (Konno et al., 1985c)
Asteraceae	*Atractylodes ovata* DC.	China	Rhizome	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Atracylodes chinensis* (DC.) Koidz.	China	Rhizome	Atractans A, B, and C have antidiabetic activity (Konno et al., 1985c)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Asteraceae	*Bidens leucantha* Willd.	C. America	All	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Bidens pilosa* L.	C. America	All	Reduces glucose levels in blood of alloxan-treated mice (Alarcon–Aguilar et al., 2002)
Asteraceae	*Brachylaena elliptica* Less	Africa		Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Cacalia decomposita* A. Gray	C. America	Root, stem	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Calea zacatechichi* Schlecht	C. America	Aerial parts	Decreases hyperglycemia *in vivo* (Roman Ramos et al., 1992)
Asteraceae	*Centaurea aspera* L.	Europe	Aerial parts	Reported to be hypoglycemic (Masso and Adzet, 1976)
Asteraceae	*Centaurea calcitrapa* L.	Africa, Europe, India	Aerial parts	Cnicin lowers blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Centaurea corcubionensis* Lainz	Europe	Leaf, flower	Extracts from leaves and flowers lower blood glucose in rats (Ivorra et al., 1989)
Asteraceae	*Centaurea melitensis* L.	Canaries, Europe	Aerial parts	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Centaurea salmantica* L.	Europe, Africa	All	Extract lowers blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Centaurea seridis* L.	Europe	Flower	Extracts from flowers lower glucose in glucose induced rats (Handa et al., 1989)
Asteraceae	*Centaurea solstitialis* L.	Africa, Europe	Aerial parts	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Cheirolophus arbutifolius* (Svent) G. Kundel	Canaries	Leaf	Extract lowers blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Cheirolophus canariensis* (Willd.) Holub	Canaries	Aerial parts	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Cichorium endivia* L.	Asia, Europe, India, Africa	Leaf, root	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Cichorium intybus* L.	Africa, India, Europe	Leaf, root, flower	Chicory contains carbohydrates called fructans that modulate levels of insulin and glucagon, thus regulating metabolism of blood glucose. Inulin can be used to make fructose syrups (Kaur and Gupta, 2002)
Asteraceae	*Cirsium dipsacolips* Matsum	America	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Cirsium ochrocentrum* A. Gray	C. America	Root	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Asteraceae	*Cirsium pascuarense* (H.B.K.) Spreng.	C. America	Leaf	Water extract of fresh leaves used locally to treat diabetes. Hexane extract decreases blood glucose level in alloxan-treated rats; activity similar to tolbutamide (Perez et al., 2001)
Asteraceae	*Dahlia pinnata* Cav.	India	Aerial parts	Antidiabetic activity could be related to fructans
Asteraceae	*Elytropappus rhinocerotis* Less	Africa	Root	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Erigeron annuus* Pers		Leaf, stem	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Erigeron canadensis* L.			Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Eupatorium purpureum* L.	Europe	Root, flower	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Helianthus annuus* L.	N. America		Extract lowers blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Helianthus tuberosus* L.	N. America, Europe, India		Antidiabetic activity could be associated with fructans
Asteraceae	*Inula britannica* L.	Asia	Flower	Aqueous extract of flowers has a preventative effect on autoimmune diabetes by regulation of cytokine production (Kobayashi et al., 2002)
Asteraceae	*Inula helenium* L.	Europe	Root	Alantolactone reported to lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Inula racemosa* Hook f.	C. America, India	Root	Hypoglycemic activity could be via regulation of corticosteroid concentration (Gholap and Kar, 2004)
Asteraceae	*Inula viscosa* (Dryand.)	Middle East	Leaf	Extract lowers blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Lactuca sativa* L.	Europe	Leaf	Extracts lower blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Launaea nudicaulis* Hook f.	Asia	Leaf	Reduces glucose in alloxan-treated rats (Handa et al., 1989)
Asteraceae	*Matricaria aurea* Sch. Bip.	Middle East	Leaf	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Neurolaena lobata* R. Br.	C. America	Leaf	Extract lowers blood sugars (Gupta et al., 1984)
Asteraceae	*Psacalium decompositum* H.B.K. (Cass)	C. America	Root	Extracts decrease blood glucose levels in alloxan-treated mice (Alarcon–Aguilar et al., 2002)
Asteraceae	*Siegesbeckia orientalis* L.	Asia, India, Africa	All	Used to treat diabetes (Marles and Farnsworth, 1995)

TABLE 2.1 (CONTINUED)
Species of Plants Reported to Be Used Traditionally to Treat Diabetes

Order/Family	Species	Distribution and Area Traditionally Used	Part Used	Comments about Activity
Asteraceae	*Sphaeranthus indicus* L.	India		Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Stevia rebaudiana* (Bert.) Hemsl.	Indonesia	Leaf	Sweetener stevioside stimulates insulin release by action on β-cells (Jeppesen et al., 2002)
Asteraceae	*Taraxacum officinale* F.H. Wigg	Europe, India, Africa	All	Extracts stimulate release of insulin (Hussain et al., 2004)
Asteraceae	*Trixis radialis* (L.) Kuntze	C. America		Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Verbesina crocata* Less.	C. America	Leaf, flower	Daucosterol, galegine, lupeol, and lupeol acetate decrease blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Verbesina encelioides* (Cav.) A. Gray	America	Flower, root	Used to treat diabetes (Marles and Farnsworth, 1995)
Asteraceae	*Verbesina persicifolia* DC.	C. America	Leaf, flower	Extracts decrease blood glucose in alloxan-treated mice and rats (Perez et al., 1996)
Asteraceae	*Vittadinia australis* A. Rich.	India	All	Extracts decrease blood glucose (Marles and Farnsworth, 1995)
Asteraceae	*Xanthium strumarium* Patr.	Africa, India, Europe	Fruit, root, seed	Lowers blood sugar, similar mechanism to phenethyl biguanide (You and Wang, 2000)
Campanulaceae	*Platycodon grandiflorum* (Jacq.) A. DC.	China	Root	Decreases blood lipids and cholesterol (Kim et al., 2000)
Dipsacales				
Caprifoliaceae	*Lonicera japonica* Wall			Extract dose dependently inhibits α-amylase, sucrase and isomaltase, and improves the glucose tolerance in genetically diabetic mice (Kwon et al., 2004)
Caprifoliaceae	*Sambucus nigra* L.	Europe		Extract shows an insulin-releasing effect *in vitro* (Gray et al., 2000)
Valerianaceae	*Valeriana edulis* Nutt	C. America	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Valerianaceae	*Valeriana mexicana* DC.	C. America	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)
Valerianaceae	*Valeriana officinalis* L.	C. America	Root	Extracts have hypoglycemic activity (Marles and Farnsworth, 1995)

Notes: Plants are listed according to their phylogenetic relationships based on DNA data (Figure 2.1; Chase, 2005). Abbreviations: NIDDM = non-insulin dependent-diabetes mellitus; STZ = streptozotocin.

Also, ethical issues surround the use of traditional information in what is described as bioprospecting. Some parts of the world fear that commercial companies could exploit ethnobotanical information about biologically active plants. One way around this issue is for the traditional uses to be well documented and in the public domain so that, if they are used, acknowledgment could be given to the traditional users. Many biodiversity-rich countries now want the use of traditional knowledge to be recognized in drug discovery programs so that a patent would cite what information had been used. This opens up a complex series of questions about ownership and benefit sharing if products are going to be developed commercially, especially if the "inventors" have used traditional knowledge in the selection of the species.

The second selection criterion cited by Marles and Farnsworth (1995) requires experimental evidence of hypoglycemic activity. Although a high proportion of the species in Table 2.1 have been subject to some form of experimentation, in most cases the only parameter monitored was the influence of taking an extract on the level of blood glucose. This parameter is important, but it is not a robust selection character for assessing activity in a species because it is known that many species not used traditionally to treat diabetes also lower blood glucose. Thus, further experimentation is required on a high proportion of species listed in Table 2.1.

The third criterion proposed by Marles and Farnsworth (1995) places weight on the selection of species in which the active ingredients have not been identified. A comparison of the data in Table 2.1 with those in the list provided by Marles and Farnsworth shows that, since 1995, knowledge about the diversity of active compounds in the antidiabetic species and, in some cases, their mode of action has increased. Marles and Farnsworth (1995) suggest that priority should be given to species about which this information is lacking. Nevertheless, a strong case can be made for further research into species that contain compounds with proven efficacy to enable them to be developed as treatments. Such knowledge could not only validate the traditional use but also enable more people to benefit from the existing "leads." It would greatly assist the case for supporting plant-based research on antidiabetic plants if more examples of treatments for diabetes could be established.

Most natural product and pharmacology groups still tend to search for new actives in poorly studied species instead of undertaking further research on species with proven activity. This could be due in part to researchers finding it difficult to find funds to support work on plants with proven activity and commercial companies not wanting to invest funds into developing a product in which they will not be able to protect the intellectual property. These reasons are justified, but more research needs to be undertaken on species containing compounds with proven activity in order to turn a "potential" into an "actual" lead. Very few examples of plant-based leads, such as metformin, a biguanide derived from two linked guanidine units (guanidine derivatives are reported to be the active constituents of *Galega officinalis* [Fabaceae]), are currently prescribed in mainstream Western medicine (Hundal and Inzucchi, 2003). The challenge will be to see whether any of these species or the active compounds in the species progress through the validation system. This is unlikely unless they attract financial resources.

In the last 5 years, the species that received the most citations for their antidiabetic activity include species of *Panax* and *Phyllanthus, Momordica charantia*, *Allium cepa*, and *A. sativum*. A growing body of evidence indicates that the traditional uses of these species can be supported by scientific evidence. Many of the active compounds in these species have been identified (Table 2.1), but more research needs to be completed if products are going to be developed from these species. Currently, *Panax ginseng* is included in some of the products currently prescribed in China for treating diabetes and the same is true in India for the use of products containing *Momordica charantia*.

Knowledge about the toxicity of the species is an important criterion for selection. For example, species of plants used as vegetables that have been shown to have hypoglycemic activity could be of high priority. Onion and garlic meet this criterion; they have been well studied and contain compounds that modulate biochemical processes involved in diabetes. Allicin and *S*-allylcysteine

sulfoxide, from *Allium sativum* bulbs, are reported to be the active constituents associated with prevention of diabetic cardiovascular complications (Patumraj et al., 2000). Administration of *S*-methylcysteine sulfoxide and *S*-allylcysteine sulfoxide, from *Allium* species, to alloxan-diabetic rats ameliorated glucose intolerance, weight loss, and depletion of liver glycogen; however, they were not as effective as glibenclamide and insulin in relation to glucose utilization (Sheela et al., 1995).

To dismiss a plant because it contains toxic compounds could result in dropping species with potent antidiabetic leads, such as the vinca alkaloids. The alkaloids vindoline, vindolinine, and leurosine isolated from the leaves of *Catharanthus roseus* are reported to be antidiabetic (Li et al., 2004). Conophylline, a vinca alkaloid from *Ervatamia microphylla* leaves, induced insulin expression in pancreatic cells *in vitro* (Takatsuna and Umezawa, 2004; Umezawa et al., 2003) and induced differentiation of pancreatic precursor cells (Ogata et al., 2004). However, because neuropathy is associated with the use of vinca alkaloids, their clinical potential in the management of diabetes is limited.

Another group of alkaloids, the polyhydroxylated piperidines, pyrrolidines indolizidines, pyrrolizidines, and nortropanes have potential in the management of a range of different diseases (Simmonds et al., 1999) including diabetes. These compounds are found in species used to treat diabetes, such as 1-deoxynojirimycin (DNJ). DNJ is a piperidine alkaloid (also known as moranoline) from roots of *Morus alba* that inhibits α-glucosidase activity *in vitro*; however, its efficacy *in vivo* has not been quite as promising (Asano et al., 2000). Other polyhydroxyalkaloids have been isolated from species known to be toxic. For example, the 7-*O*-β-D-glucoside of the piperidine alkaloid α-homonojirimycin from *Aglaonema treubii* plants and *Hyacinthus orientalis* bulbs has been investigated as a potential antidiabetic drug.

Several nitrogen-containing compounds isolated from *Xanthocercis zambesiaca* root and leaves have been evaluated for potential antihyperglycemic effects *in vivo*. An aqueous methanol extract and the isolated compounds fagomine, 4-*O*-β-D-glucopyranosylfagomine, (2*R*, 5*R*)-dihydroxymethyl-(3*R*, 4*R*)-dihydroxypyrrolidine (DMDP), and castanospermine reduced blood glucose level in streptozotocin diabetic mice; fagomine was also shown to increase the plasma insulin level (Nojima et al., 1998). Isolated from the pods and bark of *Angylocalyx pynaertii*, 2, 5-imino-1, 2, 5-trideoxy-L-glucitol, β-homofuconojirimycin, and 2, 5-dideoxy-2, 5-imino-D-fucitol were identified as specific inhibitors of α-L-fucosidase (Yasuda et al., 2002).

Toxicity is a relative term and will vary on the part of the plant being extracted or eaten and the amounts taken. However, it is critical that the crude extract and individual compounds are tested for toxicity, although most tests currently only measure acute toxicity. These tests do not provide information about adverse responses that might result from long-term exposure to the species. Knowledge about whether compounds taken in low amounts over time could result in the accumulation of a toxic dose is important because diabetes is a chronic condition and a patient might need to take a daily supply of a medication over a long period.

Thus, it is very important to gather data on the profile of compounds in a proposed antidiabetic plant to see whether they have been shown to cause any adverse responses. For example, ephedrine, from *Ephedra* species, is reported to suppress hyperglycemia in diabetic mice (induced by streptozotocin) and to promote the regeneration of pancreas islets following atrophy induced by streptozotocin (Xiu et al., 2001). Ephedrine is also reported to improve microcirculation in the diabetic neuropathic foot (Wollersheim et al., 1989). However, in view of the adverse effects associated with administration of ephedrine, such as hypertension, it should be used with caution in those with cardiovascular disease and diabetes.

The availability of a species is another important selection criterion. Publicizing the medicinal properties of a species is always a concern because this may result in overharvesting unless the species is already commercially produced. Thus, as part of a research project on a species with relatively restricted geographical distribution, procedures need to be considered at an early stage to establish their sustainable production.

Overall, many challenges face researchers interested in furthering understanding of the value of plants in the control of diabetes. These include not only the criteria used to select the plants, the selection of appropriate bioassays, and the isolation of the active compounds but also issues associated with ownership of the plant material being studied. The implementation of the Convention on Biodiversity (CBD) (www.biodiv.org) by different countries has resulted in a complex array of procedures that need to be in place to enable scientists to gain access to plant material. All scientists involved in plant-based research, especially those involved in research that might result in the discovery of a lead molecule, need to keep copies of the appropriate paperwork to enable them to trace the source of their plant material and any knowledge they used to assist their research. Readers are referred to the CBD Website to obtain information about how different countries implement the CBD and which authorities need to be contacted in these countries to obtain "prior informed consent" before collecting genetic resources.

WHERE DO WE GO NEXT?

When prioritizing species that need further study, the criteria used by Marles and Farnsworth (1995) can still apply, but more use should be made of taxonomic information about the relationship among plants' families and genera. Molecular data have enabled significant advances to be made in understanding of the phylogenetic relationships among different plant families (Chase, 2005). Species used to treat diabetes can be found distributed throughout the plant kingdom (Figure 2.1). However, some trends justify further study.

Of the 656 species of flowering plants identified in this study, a high proportion of the 437 genera, representing 111 families, come from the rosids and asteroids (Table 2.1; Figure 2.1). However, there are representatives with potent activity in the magnoliids and monocots (Table 2.1). Within the Ranunculales, alkaloids with potential antidiabetic activity have been isolated from the Berberidaceae, Menispermaceae, Papaveraceae, and Ranunculaceae. The best studied example is berberine from rhizomes of *Coptis chinensis* (Ranunculaceae). It is reported to be hypoglycemic in normal and in diabetic mice (Chen and Xie, 1986). Treating impaired glucose tolerance rats with berberine resulted in a reduction in levels of fasting blood glucose, triglycerides, and total cholesterol (Leng et al., 2004). Berberine also aided insulin secretion of HIT-TI5 cells and murine pancreatic islets in a dose-dependent manner *in vitro* (Leng et al., 2004). It has been shown that oral administration of berberine to hypercholesterolemic patients reduced serum cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol; *in vitro*, berberine elevated LDL receptor expression through a post-transcriptional mechanism that stabilizes mRNA (Kong et al., 2004).

Other studies suggest that berberine may mediate antihyperglycemic effects by inhibiting α-glucosidase and decreasing glucose transport through the intestinal epithelium (Pan et al., 2003). Some *in vitro* investigations suggest that berberine exerts a glucose-lowering effect in hepatocytes that is insulin independent and similar to the action of metformin, but has no effect on insulin secretion (Yin et al., 2002). Other alkaloids with potential use in the treatment of diabetes from this group of plants include dehydrocorydaline from *Corydalis turtschaninovii* (Papaveraceae) tuber (Kubo et al., 1994) and tetrandrine from *Stephania tetrandra* (Menispermaceae) root (Liang et al., 2002; Lieberman et al., 1992). Polysaccharides from this group of plants also justify further study including aconitans A, B, C, and D from the roots of *Aconitum carmichaelii* (Ranunculaceae), which lower blood glucose in normal and diabetic mice (Konno et al., 1985c).

The diversity of active compounds increases within the rosids, including examples of alkaloids, flavonoids, and terpenoids. The legume family (Fabaceae) contains a large number of species, of which 81 are identified as having hypoglycemic activity (Table 2.1). For example, (–)-multiflorine was isolated from seeds of species of *Lupinus* (Fabaceae) (Abdel–Halim et al., 1999). It produced a hypoglycemic effect when administered to mice with streptozotocin-induced diabetes; in addition, synthetic compounds also containing the quinolizidin-2-one ring system were active *in vivo* (Kubo et al., 2000). Some other quinolozidine alkaloids, lupanine, 13-α-hydroxylupanine, and

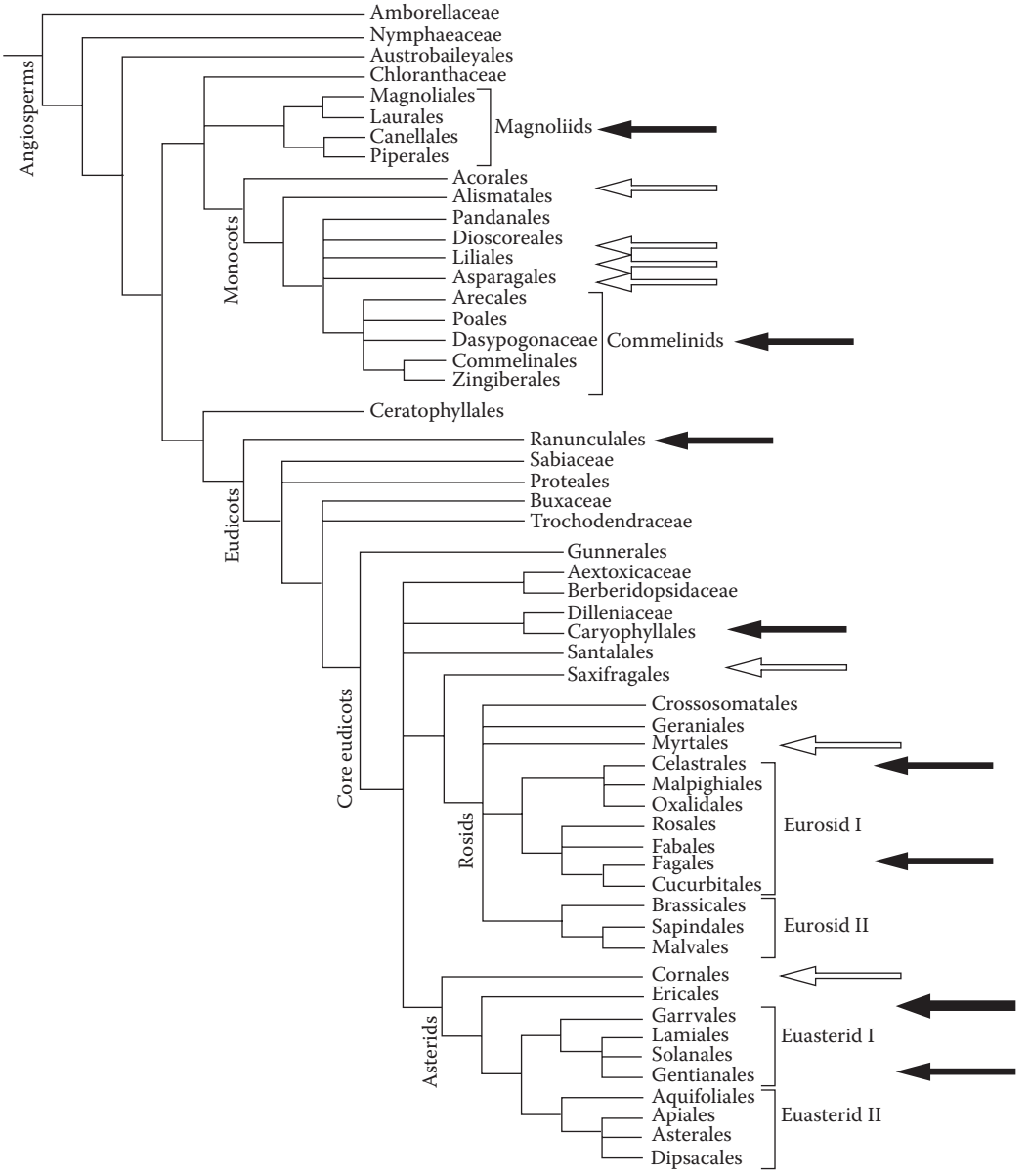

FIGURE 2.1 Phylogenetic distribution of species of plants used traditionally to treat diabetes. The phylogeny of the flowering plants is based on molecular data (Chase, 2005). Arrows indicate groups (clades) of families that contain species with antidiabetic activity. Solid arrows point to clades that contain more species than unfilled arrows with the greatest number of species occurring in the euasterid I clade. Species are listed in Table 2.1.

17-oxolupanine isolated from *Lupinus* species, enhance insulin secretion *in vitro*, an effect that could be explained by blocking β-cell K_{ATP}-sensitive channels (Garcia López et al., 2004).

Flavonoids that ameliorate the condition of patients with diabetes occur in many plant families and have been well studied in members of the Fabales. Quercetin dose dependently decreased the plasma glucose level in streptozotocin-induced diabetic rats, which may be related to an increase in the number of pancreatic islets (Vessal et al., 2003). Quercetin may also be of value in diabetic nephropathy because treatment of diabetic rats with quercetin attenuated renal dysfunction and oxidative stress (Anjaneyulu and Chopra, 2004). Diabetic neuropathy may also be attenuated by

treatment with quercetin because antinociceptive activity has been associated with quercetin in a mouse model of diabetic neuropathic pain (Anjaneyulu and Chopra, 2003). Quercetin-3-*O*-methyl ether may have some potential in treating diabetic complications (Enomoto et al., 2004).

Isorhamnetin-3, 7-di-*O*-β-D-glucopyranoside isolated from *Brassica juncea* (Brassicaceae) leaf appears to be metabolized to isorhamnetin *in vivo*, and intraperitoneal (ip) administration of isorhamnetin reduced serum glucose in diabetic rats (Yokozawa et al., 2002). Kaempferitrin isolated from *Bauhinia forficata* (Fabaceae) leaves lowered blood glucose in diabetic rats (Jorge et al., 2004). Administration of naringin to hyperglycemic rats dose dependently decreased the blood glucose level, increased insulin level, and increased the total antioxidant status (Ali and Abd El Kader, 2004).

The possible mechanisms to explain the hypoglycemic effect of brazilin from *Caesalpinia sappan* (Fabaceae) wood have been investigated and some studies suggest an association with insulin action. It has been shown that brazilin increases the rate of glucose oxidation and lipogenesis in the presence of insulin and that it may regulate the enzymatic processes involved in glucose metabolism (Moon et al., 1993). The hypoglycemic effect of brazilin may be associated with enhancement of insulin receptor function by a decrease in serine phosphorylation (Kim et al., 1998). Other studies show that brazilin stimulates glucose transport *in vitro* (Kim et al., 1995) and decreases gluconeogenesis in hepatocytes isolated from diabetic rats (Won et al., 2004). Brazilin is also reported to inhibit aldose reductase activity (Moon et al., 1985).

Hypoglycemic and hypolipidemic effects were observed when streptozotocin-induced diabetic rats were treated with tectorigenin, an isoflavone isolated from the flowers of *Pueraria thunbergiana* (Fabaceae); these effects were proposed to be associated with the antioxidant effects of tectorigenin (Lee et al., 2000). Oral administration of tectorigenin, an aldose reductase inhibitor isolated from *Belamcanda chinensis* (Iridaceae) rhizomes, to streptozotocin-induced diabetic rats caused a significant inhibition of sorbitol accumulation in tissues such as lens, sciatic nerves, and red blood cells, thus indicating the potential of tectorigenin in the prevention or treatment of some diabetic complications (Jung et al., 2002). It has been proposed that 6″-*O*-xylosyltectoridin and tectoridin isolated from the flowers of *Pueraria thunbergiana* act as prodrugs because they are metabolized to tectorigenin by human intestinal bacteria; tectorigenin showed more potent hypoglycemic activity than 6″-*O*-xylosyltectoridin and tectoridin (Bae et al., 1999).

Puerarin isolated from the roots of *Pueraria lobata* increased glucose utilization and lowered plasma glucose in diabetic rats lacking insulin (Hsu et al., 2003). Daidzein is reported to inhibit the activities of α-amylase and α-glucosidase (Kim et al., 2000). Daidzein and genistein occur in many species of legumes and they have been associated with a reduction in glucose toxicity-induced cardiac mechanical dysfunction and thus may be beneficial against diabetes-associated cardiac defects (Hintz and Ren, 2004). Long-term (6 months) oral administration of genistein to streptozotocin-induced diabetic rats inhibited retinal vascular leakage, which may have some clinical relevance (Nakajima et al., 2001).

An oleanane triterpenoid, kaikasaponin III (KS III), isolated from the flowers of *Pueraria thunbergiana*, also showed hypoglycemic and hypolipidemic effects when given to streptozotocin-induced diabetic rats. These effects were proposed to be associated with the antioxidant effect of KS III (Lee et al., 2000). More recent studies show that KS-III may exhibit its hypoglycemic and hypolipidemic effects by up-regulating or down-regulating antioxidant mechanisms via the changes in phase I and II enzyme (e.g., superoxide dismutase [SOD], glutathione peroxidase and catalase) activities (Choi et al., 2004).

Another taxonomic clade that contains many active species is euasterid I (Figure 2.1). This clade contains families with numerous species that, in traditional practices of medicine, have been reputed to possess antidiabetic activity. Many of these species contain oleanolic and ursolic acids, which have been isolated from the dried stem of *Bouvardia ternifolia* (Rubiaceae) and have lowered blood sugar levels in normal and alloxan-diabetic mice (Perez et al., 1998b).

Another study identified oleanolic acid as an anti-α-amylase compound from *Olea europaea* leaves; it inhibited postprandial hyperglycemia in diabetic rats (Komaki et al., 2003). The mechanism of action of oleanolic acid glycosides and some other triterpenoids has been investigated. It has been proposed that oral administration of oleanolic acid 3-*O*-glucuronide, momordin Ic, escins Ia and IIa, and *E*, *Z*-senegin II do not initiate insulin-like activity or promote insulin release; however, they may exert their hypoglycemic activity by suppressing the transfer of glucose from the stomach to the small intestine and by inhibiting glucose transport at the brush border of the small intestine (Matsuda et al., 1998a, b). In contrast, an *in vitro* study has suggested that oleanolic acid may act via a different mechanism. Using an INS-1 cell assay, oleanolic acid and oleanolic aldehyde isolated from grape skin were shown to stimulate insulin production dose dependently (Zhang et al., 2004). Oleanolic acid is also reported to inhibit α-glucosidase (Ali et al., 2002).

Some oleanolic acid 3-*O*-monodesmosides (oleanolic acid 3-*O*-glucuronide, momordin Ic, momordin I and 28-*O*-deglucosyl-chikusetsusaponins IV and V) have been associated with inhibition of gastric emptying in mice, but oleanolic acid 3, and 28-*O*-bisdesmosides (momordin IIc, chikusetsusaponins IV and V, oleanolic acid 28-*O*-monodesmoside) and their aglycone oleanolic acid were not associated with this activity (Matsuda et al., 1999). It has been proposed that the 3-*O*-monodesmoside structure and 28-carboxyl group were important for such activity, and that the 28-ester glucoside moiety and 2′-*O*-β-D-glucopyranoside moiety reduced the activity (Matsuda et al., 1999).

Luteolin-7-*O*-β-glucoside and luteolin-4′-*O*-β-glucoside were identified as anti-α-amylase compounds from *Olea europaea* (Oleaceae) leaves, and luteolin inhibited postprandial hyperglycemia in diabetic rats (Komaki et al., 2003). Luteolin, amentoflavone, and luteolin-7-*O*-glucoside are reported to inhibit the activities of α-amylase and α-glucosidase (Kim et al., 2000). However, other studies indicate that, when administered orally to rats treated with maltose or sucrose, luteolin does not suppress the glucose production from carbohydrates through the inhibition of α-glucosidase action in the gut (Matsui et al., 2002).

Epicatechin protected pancreatic β-cells against IL-1β-induced toxicity *in vitro* (Kim et al., 2004). From *Apocynum venetum* (Apocynaceae) leaves, (±)-gallocatechin, (–)-epigallocatechin, (±)-catechin, (–)-epicatechin, epicatechin-(4β-8)-gallocatechin, epigallocatechin-(4β-8)-epicatechin, and procyanidin B_2 were isolated and shown to inhibit the formation of advanced glycation endproducts, which have been implicated in the pathogenesis of atherosclerosis (Yokozawa and Nakagawa, 2004). Polysaccharides from *Lycium barbarum* fruit are associated with antihyperglycemic effects *in vivo* (Luo et al., 1997). An extract from *L. barbarum* was purified and fractionated to yield polysaccharide fractions that were associated with hypoglycemic and hypolipidemic effects *in vivo* (Luo et al., 2004).

When ethnobotanical information about the uses of plants in diabetes is superimposed onto a phylogeny of the angiosperms, it is clear that clusters of related species of plants are reported to have activity. Within the asterids, the clade that contains the Lamiales, Solanales, and Gentianales has 134 species of plants used traditionally to treat diabetes. This represents 20% of the species covered in this review. Whether the activity could be explained by a similar group of compounds seems highly unlikely because the families in these orders contain a high diversity of compounds — many with a diverse range of biological properties.

Thus, the combination of ethnobotanical and phylogenetic information can be used to assist target plant selection. If, after further research, similar types of compounds were identified, the phylogenies could be used for dereplication because species from related families often contain similar types of compounds. It is hoped researchers will be stimulated to increase the number of species studied for their antidiabetic properties not only to validate the ethnobotanical uses but also to increase understanding of the different types of plant-derived compounds that can be used to treat diabetes and diabetes-related conditions.

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REFERENCES

Abbiw, D., 1990. *Useful Plants of Ghana*. Intermediate Technology Publications, London.

Abdel–Halim, O.B., El-Gammal, A.A., Abdel–Fattah, H., Takeya, K., 1999. Glycosidic alkaloids from *Lupinus varius*. *Phytochemistry* 51: 5–9.

Abdulkadir, J., 1985. Utilisation of traditional treatment among Ethiopian diabetes. *Ethiopian Med. J.* 23: 117–121.

Abraham, Z., Bhakuri, D.S., Garg, H.S., Mehrolra, B.N., Patnaik, G.K., 1986. Screening of Indian plants for biological activity. Part XII. *Indian J. Exp. Biol.* 24: 48–68.

Abuh, F.Y., Wambebe, C., Rai, P.P., Sokomba, E.N., 1990. Hypoglycemic activity of *Anthocleista vogelli* (Planch) aqueous extract in rodents. *Phytother. Res.* 4: 20–24.

Aguiyi, J.C., Obi, C.I., Gang, S.S., Igweh, A.C., 2000. Hypoglycaemic activity of *Ocimum gratissimum* in rats. *Fitoterapia* 71: 444–446.

Aida, K., Tawata, M., Shindo, H., Onaya, T., Sasaki, H., Nishimura, H., Chin, M., Mitsuhashi, H., 1989. The existence of aldose reductase inhibitors in some kampo medicines (oriental herb prescriptions). *Planta Med.* 55: 22–26.

Aitani, M., Kimura, H., Abiru, Y., Soyama, H., Murakami, H., Zhang, H.L., Sugishita, T., Konishi, Y., 2003. Effect of an extract from evening-primrose seeds on postprandial blood glucose level and its active components. *J. Jpn. Soc. Food Sci. Technol.* 50: 180–187.

Akhtar, M.S., Iqbal, J., 1991. Evaluation of the hypoglycaemic effect of *Achyranthes aspera* in normal and alloxan-diabetic rabbits. *J. Ethnopharmacol.* 31: 49–57.

Akhtar, M.S., Khan, M.A., Malik, M.T., 2002. Hypoglycaemic activity of *Alpinia galangal* rhizome and its extracts in rabbits. *Fitoterapia* 73: 623–628.

Akhtar, M.S., Khan, Q.M., Khaliq, T., 1984. Effects of *Euphorbia prostrata* and *Fumaria parviflora* in normoglycemic and alloxan-treated hyperglycaemic rabbits. *Planta Med.* 50: 138–142.

Alarcon–Aguilar, F.J., Roman–Ramos, R., Flores–Saenz, J.L., Aguirre–Garcia, F., 2002. Investigation on the hypoglycaemic effects of extracts of four Mexican medicinal plants in normal and alloxan-diabetic mice. *Phytother. Res.* 16: 383–386.

Alarcon–Aguilar, F.J., Roman–Ramos, R., Perez–Gutierrez, S., Aguilar–Contreras, A., Contreras–Weber, C.C., Flores–Saenz, J.L., 1998. Study of the antihyperglycemic effect of plants used as antidiabetics. *J. Ethnopharmacol.* 61: 101–110.

Al-Ghaithi, F., El-Ridi, M.R., Adeghate, E., Amiri, M.H., 2004. Biochemical effects of *Citrullus colocynthis* in normal and diabetic rats. *Molecular Cell. Biochem.* 261: 143–149.

Al-Habori, M., Raman, A., 1998. Antidiabetic and hypocholesterolaemic effects of fenugreek. *Phytother. Res.* 12: 233–242.

Ali, B.H., 1997. The effect on plasma glucose, insulin and glucagon levels of treatment of diabetic rats with the medicinal plant *Rhazya stricta* and with glibenclamide, alone and in combination. *J. Pharm. Pharmacol.* 49: 1003–1007.

Ali, M.M., Abd El Kader, M.A., 2004. The influence of naringin on the oxidative state of rats with streptozotocin-induced acute hyperglycaemia. *Zeitschrift Fur Natureforschung* C-A *J. Biosc.* 59: 726–733.

Ali, B.H., Blunden, G., 2003. Pharmacological and toxicological properties of *Nigella sativa*. *Phytother. Res.* 17: 299–305.

Ali, M.S., Jahangir, M., µl Hussan, S.S., Choudhary, M.I., 2002. Inhibition of α-glucosidase by oleanolic acid and its synthetic derivatives. *Phytochemistry* 60: 295–299.

Amalraj, T., Ignacimuthu, S., 1998. Evaluation of the hypoglycaemic effect of *Memecylon umbellatum* in normal and alloxan diabetic mice. *J. Ethnopharmacol.* 62: 247–250.

Amer, M., El-Habibi, El-S., El-Gendy, A., 2004. Effects of *Trifolium alexandrinum* extracts on streptozotocin-induced diabetes in male rats. *Ann. Nutr. Metab.* 48: 343–347.

An, T.Y., Hu, L.H., Chen, Z.L., Li, J., Shen, Q., 2003. Anti-diabetes agents — I: Tetralone derivative from *Juglans regia*. *Chin. Chem. Lett*. 14: 489–490.

Anand, K.K., Singh, B., Chand, D., Chandan, B.K., Gupta, V.N., 1989. Effect of *Zizyphus sativa* leaves in normal and alloxan-diabetic rats. *J. Ethnopharmagol*. 27: 121–127.

Anjaneyulu, M., Chopra, K., 2004. Quercetin, an anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats. *Clin. Exp. Pharmacol. Physiol*. 31: 244–248.

Anjaneyulu, M., Chopra, K., 2003. Quercetin, a bioflavonoid, attenuates thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Progress in Neuro-Psychopharmcology & Biological Psychiatry* 27: 1001–1005.

Asano, N., Nash, R.J., Molyneux, R.J., Fleet, G.W.J., 2000. Sugar-mimic glycosidase inhibitors: natural occurrence, biological activity and prospects for therapeutic application. *Tetrahedron: Asymmetry* 11: 1645–1680.

Asthana, R.K., Sharma, N.K., Kulshreshtha, D.K., Chatterjee, S.K., 1991. A xanthone from *Swertia chirayita*. *Phytochemistry* 30: 1037–1039.

Aswal, B.S., Bhakani, D.S., Goel, A.K., Mehrotra, B.N., 1984a. Screening of Indian plants for biological activity. Part X. *Indian J. Exp. Biol*. 22: 312–332.

Aswal, B.S., Bhakani, D.S., Goel, A.K., Mehrotra, B.N., 1984b. Screening of Indian plants for biological activity. Part XI. *Indian J. Exp. Biol*. 22: 487–504.

Atta, A.H., Alkofahi, A., 1998. Antinociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts. *J. Ethnopharmacol*. 60: 117–124.

Attele, A.S., Zhou, Y-P., Xie, J.T., Wu, J.A., Zhang, L., Dey, L., Pugh, W., Rue, P.A., Polonsky, K.S., Yuan, C.S., 2002. Antidiabetic effects of *Panaz ginseng* berry extract and the identification of an effective component. *Diabetes* 51: 1851–1858.

Babu, P.S., Prince, P.S.M., 2004. Antihyperglycaemic and antioxidant effect of hyponidd, an ayurvedic herbomineral formulation in streptozotocin-induced diabetic rats. *J. Pharm. Pharmacol*. 56: 1435–1442.

Bae, E.A., Han, M.J., Lee, K.T., Choi, J.W., Park, H.J., Kim, D.H., 1999. Metabolism of 6″-*O*-xylosyltectoridin and tectoridin by human intestinal bacteria and their hypoglycemic and *in vitro* cytotoxic activities. *Biological Pharmaceutical Bull*. 22: 1314–1318.

Bailey, C.J., Day, C., 1989. Traditional plant medicines as treatments for diabetes. *Diabetes Care* 12: 553–564.

Basnet, P., Kadota, S., Pandey, R.R., Takahashi, T., Kojima, Y., Shimizu, M., Takata, Y., Kobayashi, M., Namba, T., 1995. Screening of traditional medicines for their hypoglycaemic activity in streptozotocin (STZ)-induced diabetic rats and a detailed study on *Psidium guajava*. *Wakan Iyakugaku Zasshi* 12: 109–117.

Basnet, P., Kadota, S., Terashima, S., Shimizu, M., Namba, T., 1993. Two new 2-arylbenzofuran derivatives from hypoglycaemic activity-bearing fractions of *Morus insignis*. *Chemical Pharmaceutical Bull*. 41: 1238–1243.

Beppu, H., Nagamuru, Y., Fujita, K., 1993. Hypoglycemic and antidiabetic effects in mice of *Aloe arborescens* Miller var *natalensis* Berger. *Phytother. Res*. 7: S37–S42.

Bever, O., 1980. Review of hypoglycemic plants (Africa (W)). *J. Ethnopharmacol*. 2: 119–127.

Bhakuni, D.S., Goel, A.K., Jain, S., Mehrotra, B.N., Patnaik, G.K., Prakash, V., 1988. Screening of Indian plants for biological activity: Part XIII. *Indian J. Exp. Biol*. 26: 883–904.

Boby, R.G., Leelamma, S., 2003. Blackgram fiber (*Phaseolus mungo*): mechanism of hypoglycaemic action. *Plant Foods Hum. Nutr*. 58: 7–13.

Candan, F., Sokman, A., 2004. Effects of *Rhus coriaria* L. (Anacardiaceae) on lipid peroxidation and free radical scavenging activity. *Phytother. Res*. 18: 84–86.

Chase, M.W., 2005. Relationships between the families of flowering plants. In *Plant Diversity and Evolution: Genotypic and Phenotypic Variation in Higher Plants*. 7–23. (Ed., Henry, R.J.) CAB International, London.

Chau, C.F., Cheung, P.C.K., Wong, Y.S., 1998. Hypocholesterolemic effects of protein concentrates from three Chinese indigenous legume seeds. *J. Agric. Food Chemistry* 46: 3698–3701.

Chaudhur, R.K., Ghosal, S., 1971. Studies on chemical constituents of Centianaceae. 1. Xanthones of *Canscora decussata* Schult. *Phytochemistry* 10: 2425–2432.

Chen, Q.M., Xie, M.Z., 1986. Studies on the hypoglycaemic effect of *Coptis chinensis* and berberine. *Acta Pharmaceutica Sinica* 21: 401–406.

Chen, W., Lui, F., Yu, M.H., Zhu, Q. Y., Zhu, X.X., 2001. *Astragalus* polysaccharides prevention of type 1 diabetes in nonobese diabetic mice. *J. Fudan Univ.* (med. sci. ed.) 28: 57–60.

Choi, S.B., Park, S., 2002. A steroidal glycoside from *Polygonatum odoratum (*Mill.) Druce. improves insulin resistance but does not alter insulin secretion in 90% pancreatectomized rats. *Biosci. Biotechnol. Biochemistry* 66: 2036–2043.

Choi, J., Shin, M.H., Park, K.Y., Lee, K.T., Jung, H.J., Lee, M.S., Park, H.J., 2004. Effect of kaikasaponin III obtained from *Pueraria thunberrgiana* flowers on serum and hepatic lipid peroxides and tissue factor activity in the streptozotocin-induced diabetic rat. *J. Medicinal Food* 7: 31–37.

Chung, C.K., Jung, N.E., 2003. Ethanol fraction of *Aralia elata* Seeman enhances antioxidant activity and lowers serum lipids in rats when administered with benzo (alpha) pyrene. *Biological Pharmaceutical Bull.* 26: 1502–1504.

Dall'Agnol, R., von Poser, G.L., 2000. The use of complex polysaccharides in the management of metabolic diseases: the case of *Solanum lycocarpum* fruits. *J. Ethnopharmacol.* 71: 337–341.

Darias, V., Bravo, L., Rabanal, R., Mateo, C.S., Luis, R.M.G., Perez, A.M.H., 1989. New contributions to the ethnopharmacological study of the Canary Islands. *J. Ethnopharmacol.* 25: 77–92.

Das, A.K., Mandal, S.C., Banerjee, S.K., Sinha, S., Saha, B.P., Pal, M., 2001. Studies on the hypoglycaemic acivity of *Punica granatum* seed in streptozotocin induced diabetic rats. *Phytother. Res.* 15: 628–629.

De Tommasi, N., Desimone, F., Cirino, G., Cicala, C., Pizza, C., 1991. Hypoglycemic effects of sesquiterpene glycosides and polyhydroxylated triterpeniods of *Eriobotrya japonica*. *Planta Med.* 57: 414–416.

Dhar, M.L., Dhar, M.M., Dhawan, B.N., Mehrotra, B.N., Ray, C., 1968. Screening of Indian plants for biological activity: Part I. *Indian J. Exp. Biol.* 6: 232–247.

Dhawan, B.N., Dubey, M.P., Mehrotra, B.N., Rastogi, R.P., Tandon, J.S., 1980. Screening of Indian plants for biological activity: Part IX. *Indian J. Exp. Biol.* 18: 594–606.

Diallo, D., Sanogo, R., Yasambou, H., Traore, A., Coulibaly, K., Maiga, A., 2004. Study of the compounds of *Ziziphus mauritiana* Lam. (Rhamnaceae) leaves, used traditionally in the treatment of diabetes in Mali. *Comptes Rendus Chimie* 7: 1073–1080.

Diatewa, M., Samba, C.B., Assah, T.C.H., Abena, A.A., 2004. Hypoglycemic and antihyperglycemic effects of diethyl ether fraction isolated from the aqueous extract of the leaves of *Cogniauxia podoleana* Baillon in normal and alloxan-induced diabetic rats. *J. Ethnopharmacol.* 92: 229–232.

Eddouks, M., Lemhadri, A., Michel, J.B., 2004. Caraway and caper: potential antihyperglycaemic plants in diabetic rats. *J. Ethnopharmacol.* 94: 143–148.

El-Fiky, F.K., Abou–Karam, M.A., Afify, E.A., 1996. Effect of *Luffa aegyptiaca* (seeds) and *Carissa edulis* (leaves) extracts on blood glucose level of norml and streptozotocin diabetic rats. *J. Ethnopharmacol.* 50: 43–47.

El Hilaly, J., Lyoussi, B., 2002. Hypoglycaemic effect of the lyophilised aqueous extract of *Ajuga iva* in normal and streptozotocin diabetic rats. *J. Ethnopharmacol.* 80: 109–113.

Elder, C., 2004. Ayurveda for diabetes mellitus: a review of the biomedical literature. *Alternative Ther. Health Med.* 10: 44–50.

Elsaadany, S.S., Abdelrahim, E.A., Wasif, M.M., 1986. Biochemical action of *Balanites aegyptiaca* fruits as a possible hypoglycaemic agent. *Food Chem.* 19: 307–315.

Enigbokan, M.A., Felder, T.B., Thompson, J.O., Kuti, J.O., Ekpenyong, K.I., 1996. Hypoglycaemic effects of *Opuntia ficus-indica* Mill., *Opuntia lindheimei* Englem and *Opuntia robusta* Wendl. in streptozotocin-reduced diabetic rats. *Phytother. Res.* 10: 379–382.

Enomoto, S., Okada, Y., Guvenc, A., Erdurak, C.S., Coskun, M., Okuyama, T., 2004. Inhibitory effect of traditional Turkish folk medicines on aldose reductase (AR) and hematological activity, and on AR inhibitory activity of quercetin-3-*O*-methyl ether isolated from *Cistus laurifolius* L. *Biological Pharmaceutical Bull.* 27: 1140–1143.

Esmaeili, M.A., Yazdanparast, R., 2004. Hypoglycaemic effect of *Teucrium polium*: studies with rat pancreatic islets. *J. Enthopharmacol.* 95: 27–30.

Fort, D.M., Rao, K., Jolad, S.D., Luo, J., Carlson, T.J., King, S.R., 2000. Antihyperglycemic activity of *Teramnus labialis* (Fabaceae). *Phytomedicine* 6: 465–467.

Francis, J.A., Jayaprakasam, B., Olson, L.K., Nair, M.G., 2004. Insulin secretagogues from *Moringa oleifera* with cyclooxygenase enzyme and lipid peroxidation inhibitory activities. *Helvetica Chim. Acta* 87: 317–326.

Frias, A.C.D., Sgarbieri, V.C., 1998. Guar gum effects on food intake, blood serum lipids and glucose levels of Wister rats. *Plant Foods Hum. Nutr.* 53: 15–28.

Fuentes, O., Arancibia–Avila, P., Alarcon, J., 2004. Hypoglycemic activity of *Bauhinia candicans* in diabetic induced rabbits. *Fitoterapia* 75: 527–532.

Gallagher, A.M., Flatt, P.R., Duffy, G., Abdel–Wahab, Y.H.A., 2003. The effects of traditional antidiabetic plants on *in vitro* glucose diffusion. *Nutr. Res*. 23: 413–424.

Gamez, M.J., Jimenez, J., Risco, S., Zarzuelo, A., 1987. Hypoglycemic activity in various species of the Genus *Lavandula*. 1. *Lavandula stoechas* L. and *Lavendula multifida* L. *Pharmazie* 42: 706–707.

Garcia, F., 1944. Some clinical tests on plant extracts. *Philippine J. Sci*. 76: 3–19.

Garcia López, P.M., de la Mora, P.G., Wysocka, W., Maiztegui, B., Alzugaray, M.E., Del Zotto, H., Borelli, M.I., 2004. Quinolizidine alkaloids isolated from *Lupinus* species enhance insulin secretion. *Eur. J. Pharmacol*. 504: 139–142.

Gholap, S., Kar, A., 2004. Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration. *Pharmazie* 59: 876–878.

Gong, Y.H., Jiiang, J.X., Li, Z., Zhu, L.H., Zhang, Z.Z., 1991. Hypoglycemic effect of sanchinoside C1 in alloxan-diabetic mice. *Acta Pharmaceutica Sinica* 26: 81–85.

Gray, A.M., Abdel–Wahab, Y.H.A., Flatt, P.R., 2000. The traditional plant treatment, *Sambucus nigra* (elder), exhibits insulin-like and insulin-releasing actions *in vitro*. *J. Nutr.* 130: 15–20.

Grover, J.K., Yadav, S., Vats, V., 2002. Medicinal plants of India with anti-diabetic potential. *J. Ethnopharmacol*. 81: 81–100.

Gupta, M.P., Solis, N.G., Avella, M.E., Sanchez, C., 1984. Hypoglycemic activity of *Neurolaena lobata* (L.) R. Br., *J. Ethnopharmacol*. 10: 323–327.

Grubben, G.J.H., Denton, O.A., 2004. *Plant Resources of Tropical Africa 2: Vegetables*. Backhuys Publishers, Wageningen, The Netherlands.

Handa, S.S., Chawla, A.S., Maninder, A.S.C., 1989. Hypoglycaemic plants — a review. *Fitoterapia* LX: 195–224.

Hao, Z.Q., Hang, B. Q., Wang, Y., 1992. Study on anti-hyperglycemic effect of *Ligustrum lucidum* Ait. *Chin. J. Chin. Materia Med*. 17: 429–431.

Heacock, P.M., Hertzler, S.R., Williams, J.A., Wolf, B.W., 2005. Effects of a medical food containing an herbal alpha-glucosidase inhibitor on postprandial glycemia and insulinemia in healthy adults. *J. Am. Dietetic Assoc*. 105: 65–71.

Herrera–Arellano, A., Aguilar–Santamaria, L., Garcia–Hernandez, B., Nicasio–Torres, P., Tortoriello, J., 2004. Clinical trial of *Cecropia obtusifolia* and *Marrubium vulgare* leaf extracts on blood glucose and serum lipids in type 2 diabetics. *Phytomedicine* 11: 561–566.

Hikino, H., Yoshizawa, M., Suzuki, Y., Oshima, Y., Konno, C. 1989. Antidiabetes drugs. 29. Isolation and hypoglycemic activity of trichosans A, B, C, D and E: glycans of *Trichosanthes kirilowii* roots. *Planta Med*. 55: 349–350.

Hikino, H., Takalashi, M., Oshima, Y., Konna, C., 1988. Anti-diabetes drugs. 28. Isolation and hypoglycemic activity of oryzabrans A, B, C and D, glycans of *Oryza sativa* bran. *Planta Med*. 54: 1–3.

Hikino, H., Konno, C., Takahashi, M., Murakami, M., Kato, Y., Karikura, M., Hayashi, T., 1986. Antidiabetes drugs. 21. Isolation and hypoglycaemic activity of dioscorans A, B, C, D, E, and F; glycans of *Dioscorea japonica* rhizophors. *Planta Med*. 52: 168–171.

Hikino, H., Mizuno, T., Oshima, Y., Konno, C., 1985. Antidiabetes drugs. 4. Isolation and hypoglycemic activity of moran A, a glycoprotein of *Morus alba* root barks. *Planta Med*. 51: 59–160.

Hintz, K.K., Ren, J., 2004. Phytoestrogenic isoflavones daidzein and genistein reduce glucose-toxicity-induced cardiac contractile dysfunction in ventricular myocytes. *Endocrine Res*. 30: 215–223.

Hnatyszyn, O., Mino, J., Ferraro, G., Acevedo, C., 2002. The hypoglycemic effect of *Phyllanthus sellowianus* fractions in streptozotocin-induced diabetic mice. *Phytomedicine* 9: 556–559.

Hosseinzadeh, H., Ramezani, M., Danaei, A.R., 2002. Antihyperglycaemic effect and acute toxicity of *Securigera securidaca* L. seed extracts in mice. *Phytother. Res*. 16: 745–747.

Hsu, F.L., Liu, I.M., Kuo, D.H., Chen, W.C., Su, H.C., Cheng, J.T., 2003. Antihyperglycemic effect of puerarin in streptozotocin-induced diabetic rats. *J. Nat. Prod*. 66: 788–792.

Hsu, F.L., Lai, C.W., Cheng, J.T., 1997. Antihyperglycemic effects of paeoniflorin and 8-debenzoylpaeoniflorin, glucosides from the root of *Paeonia lactiflora*. *Planta Med*. 63: 323–325.

Hundal, R.S., Inzucchi, S.E., 2003. Metformin. New understandings, new uses. *Drugs* 63: 1879–1894.

Husen, R., Pihie, A.H.L., Nallappan, M., 2004. Screening for antihyperglcaemic activity in several local herbs of Malaysia. *J. Ethnopharmacol*. 95: 205–208.

Hussain, Z., Waheed, A., Qureshi, R.A., Burdi, D.K., Verspohl, E.J, Khan, N., Hasan, M., 2004. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. *Phytother. Res*. 18.: 73–77.

Hwang, J.K., Kong, T.W., Baek, N.I., Pyun, Y.R., 2000. Alpha-glycosidase inhibitory activity of hexagalloyl-glucose from the galls of *Quercus infectoria*. *Planta Med*. 66: 273–274.

Ibrahim, N., El-Eraqy, W., 1996. Protein content and amino acid composition of *Nelumbo nucifera* seeds and its evaluation as hypoglycemic agent. *Egyptian J. Pharmaceutical Sci*. 37: 635–641.

Ichiki, H., Miura, T., Kubo, M., Ishihara, E., Komatsu, Y., Tanigawa, K., Okada, M., 1998. New antidiabetic compounds, mangiferin and its glucoside. *Biological Pharmaceutical Bull*. 21: 1389–1390.

Ivorra, M.D., Paya, M., Villar, A., 1989a. A review of natural products and plants as potential antidiabetic drugs. *J. Ethnopharmacol*. 27: 243–275.

Ivorra, M.D., Paya, M., Villar, A., 1989b. Effect of tormentic acid on insulin-secretion in isolated rat islets of langerhans. *Phytother. Res*. 3: 145–147.

Jamaluddin, F., Mohamed, S., Lajis, M.N., 1995. Hypoglycemic effect of stigmast-4-en-3-one, from *Parkia speciosa* empty pods. *Food Chem*. 54: 9–13.

Jang, Y.J., Kim, J.K., Lee, M.S., Ham, I.H., Whang, W.K., Kim, K.H., Kim, H.J., 2001. Hypoglycemic and hypolilidemic effects of crude saponin fractions from *Panax ginseng* and *Gynostemma pentaphyllum*. *Yakhak Hoechi* 45: 545–556.

Jayaker, B., Suresh, B., 2003. Antihyperglycemic and hypoglycemic effect of *Aporosa lindleyana* in normal and alloxan induced diabetic rats. *J. Ethnopharmacol*. 84: 247–249.

Jeppesen, P.B., Gregersen, S., Alstrup, K.K., Hermansen, K., 2002. Stevioside induces antihyperglycaemic, insulinotropic and glucagonostatic effects *in vivo*: studies in the diabetic Goto–Kakizaki (GK) rats. *Phytomedicine* 9: 9–14.

Jorge, A.P., Horst, H., de Sousa, E., Pizzolatti, M.G., Silva, F.R.M.B., 2004. Insulinomimetic effects of kaempferitrin on glycaemia and on ^{14}C-glucose uptake in rat soleus muscle. *Chemico-Biological Interactions* 149: 89–96.

Jung, S.H., Lee, Y.S., Lee, S., Lim, S., Kim, Y.S., Shin, K.H., 2002. Isoflavonoids from the rhizomes of *Belamcanda chinensis* and their effects on aldose reductase and sorbitol accumulation in streptozotocin induced diabetic rat tissues. *Arch. Pharmacal Res*. 25: 306–312.

Kako, M., Miura, T., Nishiyama, Y., Ichimaru, M., Moriyasu, M., Kato, A., 1997. Hypoglycemic activity of some triterpenoid glycosides. *J. Nat. Prod*. 60: 604–605.

Kamalakkannan, N., Prince, P.S.M., 2004. Antidiabetic and anti-oxidant activity of *Aegle marmelos* extract in streptozotocin-induced diabetic rats. *Pharmacueutical Biol*. 42: 125–130.

Kamtchouing, P., Sokeng, S.D., Moundipa, P.F., Watcho, P., Jatso, H.B., Lontsi, D., 1998. Protective role of *Anacardium occidentale* extract against streptozotocin-induced diabetes in rats. *J. Ethnopharmacol*. 62: 95–99.

Kanth V.R., Diwan, P.V., 1999. Analgesic, antiinflammatory and hypoglycaemic activities of *Sida cordifolia*. *Phytother. Res*. 13: 75–77.

Kar, A., Choudhary, B.K., Bandyopadhyay, N.G., 2003. Comparative evaluation of hypoglycemic activity of some Indian medicinal plants in alloxan diabetic rats. *J. Ethnopharmacol*. 84: 105–108.

Kaur, N., Gupta, A.K., 2002. Applications of insulin and oligofructose in health and nutrition. *J. Biosci*. 27: 703–714.

Kesari, A.N., Gupta, R.K., Watal, G., 2005. Hypoglycemic effects of *Murraya koenigii* on normal and alloxan-diabetic rabbits. *J. Ethnopharmacol*. 97: 247–251.

Kim, Y.M., Wang, M.H., Rhee, H.I., 2004. A novel α-glucosidase inhibitor from pine bark. *Carbohydr. Res*. 339: 715–717.

Kim, J.S., Kwon, C.S., Son, K.H., 2000. Inhibition of α-glucosidase and amylase by luteolin, a flavonoid. *Biosci. Biotechnol. Biochem*. 64: 2458–2461.

Kim, S.G., Kim, Y.M., Khil, L.Y., Jeon, S.D., So, D.S., Moon, C.H., Moon, C.K., 1998. Brazilin inhibits activities of protein kinase C and insulin receptor serine kinase in rat liver. *Arch. Pharmacal Res*. 21: 140–146.

Kim, Y.M., Kim, S.G., Khil, L.Y., Moon, C.K., 1995. Brazilin stimulates the glucose-transport in 3T3-LI cells. *Planta Med*. 61: 297–301.

Kitamura, H., Mori, Y., Matsumiya, S., Uchiyama, M., Ikeda, Y., 1997. Effect of ginseng on diabetic nephropathy in WBN/Kob rats. *Diabetes Frontier* 8: 388–389.

Kobayashi, T., Song, Q-H, Hong, T., Kitamura, H., Cyong, J-C., 2002. Preventative effects of the flowers of *Inula britannica* on autoimmune diabetes: a possible mechanism of action. *J. Ethnopharmacol*. 81: 317–320.

Komaki, E., Yamaguchi, S., Maru, I., Kinoshita, M., Kakehi, K., Ohta, Y., Tsukada, Y., 2003. Identification of anti-α-amylase components from olive leaf extracts. *Food Sci. Technol*. Res. 9: 35–39.

Kong, W.J., Wei, J., Abidi, P., Lin, M.H., Inaba, S., Li, C., Wang, Y.L., Wang, Z.Z., Si, S.Y., Pan, H.N., Wang, S.K., Wu, J.D., Wang, Y., Li, Z.R., Liu, J.W., Jiang, J.D., 2004. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat. Med*. 10: 1344–1351.

Konno, C., Murayama, M., Sugiyama, K., Arai, M., Murakami, M., Takahashi, M., Hikino, H. 1985a. Antidiabetes drugs. 5. Isolation and hypoglycemic activity of aconitans A, B, C and D, glycans of *Aconitum carmichaeli* roots. *Planta Med*. 51: 160–161.

Konno, C., Mizuno, T., Hikino, H., 1985b. Isolation and hypoglycemic activity of lithospermans A, B and C, glycans of *Lithospermum erythrorhizon* roots. *Planta Med*. 51: 157–158.

Konno, C., Suzuki, Y., Oishi, K., Munakata, E., Hikino, H., 1985c. Isolation and hypoglycemic activity of atractans A, B and C, glycans of *Atractylodes japonica* rhizomes. *Planta Med*. 51: 102–103.

Korec, R., Sensch, K.H., Zoukas, T., 2000. Effects of the neoflavonoid coutareagenin, one of the antidiabetic active substances of *Hintonia latiflora*, on streptozotocin-induced diabetes mellitus in rats. *Arzneimittel Forschung Drug Res*. 50: 122–128.

Kubo, H., Kobayashi, J., Higashiyama, K., Kamei, J., Fujii, Y., Ohmiya, S., 2000. The hypoglycemic effect of (7*R**,9*aS**)-7-phenyl-octahydroquinolizin-2-one in mice. *Biological Pharmaceutical Bull*. 23: 1114–1117.

Kubo, M., Matsuda, H., Tokuoka, K., Kobayashi, Y., Ma, S.P., Tanaka, T., 1994. Methanolic extract and the alkaloidal components from *Corydalis* tuber on *in vitro* aldose reductase activity. *Biological Pharmaceutical Bull*. 17: 458–459.

Kumari, K., Mathew, B.C., Augusti, K.T., 1995. Antidiabetic and hypolipidemic effects of *S*-methyl cysteine sulfoxide isolated from *Allium cepa* Linn. *Indian J. Biochemistry Biophys*. 32: 49–54.

Kuznetsova, L.A., Plesneva, S.A., Shpakov, A.O., Bondareva, V.M., Pertseva, M.N., 2004. *J. Evol. Biochemistry Physiol*. 40: 420–431.

Kwon, C.S., Son, K.H., Kim, J.S., 2004. Effect of *Lonicera japonica* flower on body weight gain and glucose tolerance in rodents. *Food Sci. Biotechnol*. 13: 768–771.

Labbé, I.T., 1936. The vegetable insulinoides and their therapeutic indications. *Can. Med. Assoc. J*. 34: 141–144.

Ladeji, O., Omekarah, I., Solomon, M., 2003. Hypoglycemic properties of aqueous bark extract of *Ceiba pentandra* in streptozotocin-induced diabetic rats. *J. Ethnopharmacol*. 84: 139–142.

Lang, J., Cao, H., Wei, A., 1998. Comparative study on effect of *Panax notoginseng* and ticlid in treating early diabetic nephropathy. *Chin. J. Integrated Traditional West. Med*. 18: 727–729.

Latha, M., Pari, L., Sandhya, S.B., Bhonde, R., 2004. Insulin-secretagogue activity and cytoprotective role of the traditional antidiabetic plant *Scoparia dulcis* (sweet broomweed). *Life Sci*. 75: 2003–2014.

Laurens, A., Mosser, J., Giono–Barber, P., Sylla, O., Giono–Barber, H., 1985. Aldose reductase inhibitory activity of extracts of the leaves of *Poupartia birrea* (Hochst) Aubr. *Ann. Pharmaceutiques Francaises* 43: 23–26.

Laurenz, J., Collier, C.C., Kuti, J.O., 2003. Hypoglycemic effect of *Opuntia lindheimeri* Englem. in a diabetic pig model. *Phytother. Res*. 17: 26–29.

Lee, H.A., Sim, H.S., Choi, K.L., Lee, H.B., 1998. Hypoglycemic action of red ginseng components (II): investgation of the effect of fat soluble fraction from red ginseng on enzymes related to glucose metabolism in cultured rat hepatocytes. *J. Ginseng Res*. 22: 51–59.

Lee, H.S., 2002. Inhibitory activity of *Cinnamomum cassia* bark-derived component against rat lens aldose reductase. *J. Pharm. Pharmaceutical Sci*. 5: 226–230.

Lee, K.T., Sohn, I.C., Kim, D.H., Choi, J.W., Kwon, S.H., Park, H.J., 2000. Hypoglycemic and hypolipidemic effects of tectorigenin and kaikasaponin III in the streptozotocin-induced diabetic rat and their antioxidant activity *in vitro*. *Arch. Pharmacal Res*. 23: 461–466.

Lemhadri, A., Zeggwagh, N.A., Maghrani, M., Jouad, H., Michel, J.B., Eddouks, M., 2004a. Hypoglycaemic effect of *Calamintha officinalis* Moench. in normal and streptozotocin-induced diabetic rats. *J. Pharm. Pharmacol*. 56: 795–799.

Lemhadri, A., Zeggwagh, N.-A., Maghrani, M., Jouad, H., Eddouks, M., 2004b. Antihyperglycemic activity of the aqueous extract of *Origanum vulgare* growing wild in Tafilalet region. *J. Ethnopharmacol*. 92: 251–256.

Lemus, I., Garcia, R., Delvillar, E., Knop, G., 1999. Hypoglycaemic activity of four plants used in Chilean popular medicine. *Phytother. Res*. 13: 91–94.

Leng, S.H., Lu, F.E., Xu, L.J., 2004. Therapeutic effects of berberine in impaired glucose tolerance rats and its influence on insulin secretion. *Acta Pharmacologica Sinica* 25: 496–502.

Lewis, W.H., 1977. *Medical Botany*, Wiley, New York.

Li, W.L., Zheng, H.C., Bukuru, J., De Kimpe, N., 2004. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. *J. Ethnopharmacol*. 92: 1–21.

Li, W.L., Wu, J.L., Ren, B.R., Guo, R.L., Zhou, A.l., Zheng, H.C., 2002. Pharmacological experiments of five Chinese traditional medicinal plants on lowering blood glucose level in mice. *J. Plant Resour. Environ.* 11: 19–32.

Liang, X.C., Hagino, N., Guo, S.S., Tsutsumi, T., Kobayashi, S., 2002. Therapeutic efficacy of *Stephania tetrandra* S. Moore for treatment of neovascularization of retinal capillary (retinopathy) in diabetes — *in vitro* study. *Phytomedicine* 9: 377–384.

Lieberman, I., Lentz, D.P., Trucco, G.A., Seow, W.K., Thong, Y.H., 1992. Prevention by tetrandrine of spontaneous development of diabetes mellitus in BB rats. *Diabetes* 41: 616–619.

Lin, G., Xu, X.D., Liu, D., Ju, J.H., Yang, J.S., 2000. Study on chemical constituents of *Aralia decaisneana. Chin. Pharmaceutical J*. 35: 289–300.

Lopez Garcia, R.E., Martin Herrera, D., Darias, V., Rabanal, R.M., 1996. Study of the hypoglycaemic, diuretic and cardiovascular activity of *Cedronella canariensis* var *canariensis* (L) W&B. *Phytother. Res*. 10: 541–543.

Ludvik, B., Neuffer, B., Pacini, G., 2004. Efficacy of *Ipomoea batatas* (Caiapo) on diabetes control on type 2 diabetic subjects treated with diet. *Diabetes Care* 27: 436–440.

Luo, Q., Cai, Y.Z., Yan, J., Sun, M., Corke, H., 2004. Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from *Lycium barbarum*. *Life Sci*. 76: 137–149.

Luo, Q., Li, J.W., Zhang, S.W., 1997. Effect of *Lycium barbarum* polysaccharides-X on reducing blood glucose in diabetic rabbits. *J. Trophol*. 19: 173–177.

Lust, J., 1986. *The Herb Book*, Bantam Books, London.

Maiti, R., Jana, D., Das, U.K., Ghosh, D., 2004. Antidiabetic effect of aqueous extract of seed of *Tamarindus indica* in streptozotocin-induced diabetic rats. *J. Ethnopharmacol*. 92: 85–91.

Malalavidhane, S., Wickramasinghe, S.M.D.N., Jansz, E.R., 2001. An aqueous extract of the green leafy vegetable *Ipomoea aquatica* is as effective as the oral hypoglycaemic drug tolbutamide in reducing the blood sugar levels of Wistar rats. *Phytother. Res*. 15: 635–637.

Mansour, H.A., Newairy, A.S.A., Yousef, M.I., Sheweita, S.A., 2002. Biochemical study on the effects of some Egyptian herbs in alloxan-induced diabetic rats. *Toxicology* 170: 221–228.

Marles, R.J., Farnsworth, N.R., 1995. Antidiabetic plants and their active constituents. *Phytomedicine* 2: 137–189.

Maroo, J., Vasu, V.T., Aalinkel, R., Gupta, S., 2002. Glucose lowering effect of aqueous extract of *Enicostemma littorale* Blume in diabetes: a possible mechanism of action. *J. Ethnopharmacol*. 81: 317–320.

Marquis, V.O., Adanlawo, T.A., Olaniyi, A.A., 1977. Effect of foetidin from *Momordica foetida* on blood-glucose level of albino-rats. *Planta Med*. 31: 366–374.

Masso, J.L., Adzet, T., 1976. Hypoglycemic activity of *Centaurea aspera* L. *Revista Espanola De Fisiologia* 32: 313–316.

Mathuram, L.N., Samanna, H.C., Ramaswamy, V.M., Natarajan, R.,1981. Studies on the hypoglycemic effects of *Strychnos potatorum* and *Acacia arabica* on alloxan diabetes in rabbits. *Cheiron* 10: 1–5.

Matsuda, H., Li, Y., Yamahara, J., Yoshikawa, M., 1999. Inhibition of gastric emptying by triterpene saponin, momordin Ic, in mice: roles of blood glucose, capsaicin-sensitive sensory nerves, and central nervous system. *J. Pharmacol. Exp. Therapeutics* 289: 729–734.

Matsuda, H., Li, Y.H., Murakami, T., Matsumura, N., Yamahara, J., Yoshikawa, M., 1998a. Antidiabetic principles of natural medicines. III. Structure-related inhibitory activity and action mode of oleanolic acid glycosides on hypoglycemic activity. *Chemical Pharmaceutical Bull*. 46: 1399–1403.

Matsuda, H., Murakami, T., Li, Y.H., Yamahara, J., Yoshikawa, M., 1998b. Mode of action of escins Ia and IIa and *E*,*Z*-senegin II on glucose absorption in gastrointestinal tract. *Bioorganic Medicinal Chem*. 6: 1019–1023.

Matsui, T., Kobayashi, M., Hayashida, S., Matsumoto, K., 2002. Luteolin, a flavone, does not suppress postprandial glucose absorption through an inhibition of α-glucosidase action. *Biosc. Biotechnol. Biochem*. 66: 689–692.

Mishkinsky, J., Menczel, E., Sulman, F.G., 1966. Hypoglycemic effect of *Poterium spinosum* L. (Rosaceae). *Arch. Int. Pharmaccodynamie Ther.* 161: 306–313.

Miura, T., Kato, A., 1995. The difference in hypoglycemic action between *Polygonati rhizoma* and *Polygonati officinalis* rhizoma. *Biological Pharmaceutical Bull*. 18: 1605–1606.

Miyatake, K., Kensho, G., Fujimoto, T., Noguchi, E., Shinohara, M., Takenaka, S., Taira, T., Upadhaya, S.P., Ichimoto, I., Nakano, Y. 1994. Effect of conduritol A, a polyol form *Gymnema sylvestre*, on the development of diabetic cataracts in streptozotocin-treated rats and on aldose reductase. *Biosci. Biotechnol. Biochem*. 58: 756–757.

Moharram, F.A., Marzouk, M.S., El-Toumy, S.A.A., Ahmed A.A.E., Aboutabl, E.A., 2003. Polyphenols of *Melaleuca quinquenervia* leaves — pharmacological studies of grandinin. *Phytother. Res*. 17: 767–773.

Moon, C.K., Lee, S.H., Lee, M.O., Kim, S.G., 1993. Effects of brazilin on glucose-oxidation, lipogenesis and therein involved enzymes in adipose tissues from diabetic kk-mice. *Life Sci*. 53: 1291–1297.

Moon, C.K., Yun, Y.P., Lee, J.H., Wagner, H., Shin, Y.S., 1985. Inhibition of lens-aldose reductase activity by brazilin and haematoxylin. *Planta Med*. 51: 66–67.

Morell, M.K., Konik–Rose, C., Ahmed, R., Li, Z.Y., Rahman, S., 2004. Synthesis of resistant starches in plants. *J. AOAC Int*. 87: 740–748.

Morota, T., Takeda, H., Sasaki, H., Sato, S., 1990. Aldose reductase inhibitors containing phenols of *Caesalpinia sappan*. Japan Kokai Tokkyo Koho (patent), p. 7. Patent number: JP 02264718.

Moshi, M.J., Mbwambo, Z.H., 2002. Experience of Tanzanian traditional healers in the management of non-insulin dependent diabetes mellitus. *Pharmaceutical Biol*. 40: 552–560.

Moshi, M.J., Lutale, J.J.K., Rimoy, G.H., Abbas, G., Josiah, R.M., Swai, A.B.M., 2001. The effect of *Phyllanthus amarus* aqueous extract on blood glucose in non-insulin dependent diabetic patients. *Phytother. Res*. 15: 577–580.

Moskalenko, S.A., 1987. Slavic ethnomedicine in the Soviet Far East. Part 1: Herbal remedies among Russians/Ukrainians in the Sukhodol Valley, Primorye. *J. Ethnopharmacol*. 21: 231–251.

Mossa, J.S., El-Denshary, E.S.M., Hindawi, R., Ageel, A.M., 1988. The hypoglycemic effect of sadin. *Int. J. Crude Drug Res*. 26: 81–87.

Mukherjee, P.K., Pal, S.K., Saha, K., Saha, B.P., 1995. Hypoglycemic activity of *Nelumbo nucifera* Gaertn (Fam Nymphaeaceae) rhizome (methanolic extract) in streptozotocin-induced diabetic rats. *Phytother. Res*. 9: 522–524.

Murakami, T., Matsuda, H., Inadzuki, M., Hirano, K., Yoshikawa, M., 1999. Medicinal foodstuffs. XVI. Sugar beet. (3): Absolute stereostructures of betavulgarosides II and IV, hypoglycemic saponins having a unique substituent, from the roots of *Beta vulgaris* L. *Chemical Pharmaceutical Bull*. 47: 1717–1724.

Nagappa, A.N., Thakurdesai, P.A., Rao, N.V., Singh, J., 2003. Antidiabetic activity of *Terminalia catappa* Lin fruits. *J. Ethnopharmacol*. 88: 45–50.

Nagaraja, N., Rao, K.N., 1989. Plants used in India against diabetes. *Ancient Sci. Life* 9: 31–35.

Nagarajan, S., Jain, H.C., Aulakh, G.S., 1982. Indigenous plants used in the control of diabetes. In *Cultivation and Utilisation of Medicinal Plants* (Eds. Atal, C.K., Kapur, B.M.) 584–604. Regional Research Laboratory, Council of Scientific and Industrial Research, Jammu–Tawi, India.

Nakagawa, K., Kishida, H., Arai, N., Nishiyami, T., Mae, T., 2004. Licorice flavonoids suppress abdominal fat accumulation and increase in blood glucose level in obese diabetic KK-A (y) mice. *Biological Pharmaceutical Bull*. 27: 1775–1778.

Nakajima, M., Cooney, M.J., Tu, A.H., Chang, K.Y., Cao, J.T., Ando, A., An, G.J., Melia, M., de Juan, E., 2001. Normalization of retinal vascular permeability in experimental diabetes with genistein. *Invest. Ophthalmol. Visual Sci*. 42: 2110–2114.

Narayanan, C.R., Joshi, D.D., Mujumdar, A.M., Dhekne, V.V., 1987. Pinitol — a new antidiabetic compound from the leaves of *Bougainvilla spectabilis*. *Curr. Sci.* 56: 139–141.

Neame, P.B., Pillay, V.K., 1964. Spontaneous hypoglycaemia, hepatic and renal necrosis following the intake of herbal medicines. *S. Afr. Med. J.* 38: 729–732.

Nicola, W.G., Ibrahim, K.M., Mikhail, T.H., Girgis, R.B., Khadr, M.E., 1996. Role of the hypoglycemic plant extract *Cleome droserifolia* in improving glucose and lipid metabolism and its relation to insulin resistance in fatty liver. *Boll. Chim. Farmaceutico* 135: 507–517.

Nishimura, H., Kubo, M., Takeda, H., Chin, M., 1992. Flavone *C*-glycosides for treatment of diseased associated with diabetes. Japan Kokai Tokkyo Koho (patent), p. 7. Patent number JP 04059788.

Nishimura, H., Morota, T., Yamaguchi, T., Chin, M., 1990a. Extraction of phenethyl alcohol derivatives as aldose reductase inhibitors for treatment of diabetes-related diseases. Japan Kokai Tokkyo Koho (patent), p. 13. Patent number JP 02036189.

Nishimura, H., Morota, T., Yamaguchi, T., Chin, M., 1990b. Isolation of iridoids as aldose reductase inhibitors from *Rehmannia glutinosa*. Japan Kokai Tokkyo Koho (patent), p. 9. Patent number JP 02096587.

Niyonzima, G., Laekeman, G., Witvrouw, M., Van Poel, B., Pieters, L., Paper, D., De Clercq, E., Franz, G., Vlietinck, A.J., 1999. Hypoglycemic, anticomplement and anti-HIV activities of *Spathodea campanulata* stem bark. *Phytomedicine* 6: 45–49.

Nkengfack, A.E., Azebaze, A.G.B., Waffo, A.K., Fomum, Z.T., Meyer, M., van Heerden, F.R., 2001. *Erythrina* studies part 37 — cytotoxic isoflavones from *Erythrina indica*. *Phytochemistry* 58: 1113–1120.

Nojima, H., Kimura, I., Chen, F.J., Sugihara, Y., Haruno, M., Kato, A., Asano, N., 1998. Antihyperglycemic effects of N-containing sugars from *Xanthocercis zambesiaca*, *Morus bombycis*, *Aglaonema treubii,* and *Castanospermum australe* in streptozotocin-diabetic mice. *J. Nat. Prod.* 61: 397–400.

Noor, H., Hammonds, P., Sutton, R., Ashcroft, S.J.H., 1989. The hypoglycaemic and insulin activity of *Tinospora crispa*: studies with human and rat islets and HIT- T15 B cells. *Diabetologia* 32: 354–359.

Norberg, A., Hoa, N.K., Liepinsh, E., Van Phan, D., Thuan, N.D., Jornvall, H., Sillard, R., Ostenson, C.G., 2004. A novel insulin-releasing substance, phanoside, from the plant *Gynostemma pentaphyllum*. *J. Biochem. Chem.* 279: 41361–41367.

Ogata, T., Li, L., Yamada, S., Yamamoto, Y., Tanaka, Y., Takei, I., Umezawa, K., Kojima, R., 2004. Promoton of β-cell differentiation by conophylline in fetal and neonatal rat pancreas. *Diabetes* 53: 2596–2602.

Ojewole, J.A.O., 2003. Hypoglycemic effect of *Sclerocarya birrea* ((A. Rich.) Hochst.) (Anacardiaceae) stem-bark aqueous extract in rats. *Phytomedicine* 10: 675–681.

Ojewole, J.A.O., Adewunmi, C.O., 2004. Anti-inflammtory and hypoglycaemic effects of *Tetrapleura tertapetra* (Taub) [Fabaceae] fruit aqueous extract in rats. *J. Ethnopharmacol.* 95: 177–182.

Olajide, O.A., Awe, S.O., Makinde, J.M., Morebise, O., 1999. Evaluation of the anti-diabetic property of *Morinda lucida* leaves in streptozotocin-diabetic rats. *J. Pharm. Pharmacol.* 51: 1321–1324.

Onal, S., Timur, S., Okutuca, B., Zihnioglu, F., 2005. Inhibition of α-glucosidase by aqueous extracts of some potent antidiabetic medicinal herbs. *Prep. Biochem. Biotechnol.* 35: 29–36.

Osadebe, P.O., Okide, G.B., Akabogu, I.C., 2004. Study on anti-diabetic activities of crude methanolic extracts of *Loranthus microrathus* (Linn.) sourced from five different host plants. *J. Ethnopharmacol.* 95: 133–138.

Oshima, Y., Sato, K., Hikino, H., 1987. Isolation and hypoglycemic activity of quinquefolans A, B and C, glycans of *Panax quinquefolium* roots. *J. Nat. Prod.* 50: 188–190.

Oshio, H., Inouye, H., 1982. Iridoid glycosides of *Rehmannia glutinosa*. *Phytochemistry* 2: 133–138.

Ozsoy–Sacan, O., Karabulut–Bulan, O., Bolkent, S., Yanardag, R., Ozgey, Y., 2004. Effects of chard (*Beta vulgaris* L. var *cicla*) on the liver of the diabetic rats: a morphological and biochemical study. *Biosci. Biotechnol. Biochem.* 68: 1640–1648.

Palanichamy, S., Nagarajan, S., Devasagayam, M., 1988. Effect of *Cassia alata* leaf extraxt on hyperglycemic rats. *J. Ethnopharmacol.* 22: 81–90.

Pan, G.Y., Huang, Z.J., Wang, G.J., Fawcett, J.P., Liu, X.D., Zhao, X.C., Sun, J.G., Xie, Y.Y., 2003. The antihyperglycaemic activity of berberine arises from a decrease of glucose absorption. *Planta Med.* 69: 632–636.

Pan, J., Liu, G., Liu, H., Qiu, Z., Chen, L., 1988. Effects of *Artemisia capillaris* on blood glucose and lipid in mice. *Zhong Yao Cai*. 21: 408–411.

Pari, L., Satheesh, M.A., 2004. Antidiabetic activity of *Boerhaavia diffusa* L. effect on hepatic key enzymes in experimental diabetes. *J. Ethnopharmacol.* 91: 109–113.

Pari, L., Venkateswaran, S., 2002. Hypoglycaemic activity of *Scoparia dulcis* L. extract in alloxan induced hyperglycaemic rats. *Phytother. Res*. 16: 662–664.

Pari, L., Umamaheswari, J., 2000. Antihyperglycaemic activity of *Musa sapientum* flowers: effect on lipid peroxidation in alloxan-diabetic rats. *Phytother. Res*. 14: 136–138.

Park, J.K., Cho, H.J., Lim, Y., Cho, Y.H., Lee, C.H., 2002. Hypocholestrolemic effect of CJ90002 in hamsters: a potent inhibitor for squalene synthase from *Paeonia moutan*. *J. Microbiol. Biotechnol*. 12: 222–227.

Patumraj, S., Tewit, S., Amatyakul, S., Jariyapongskul, A., Maneesri, S., Kasantikul, V., Shepro, D., 2000. Comparative effects of garlic and aspirin on diabetic cardiovascular complications. *Drug Delivery* 2: 91–96.

Perez, G.R.R., Vargas, S.R., 2002. Triterpenes from *Agarista mexicana* as potential antidiabetic agents. *Phytother. Res*. 16: 55–58.

Perez, R.M., Ramirez, E., Vargas, R., 2001. Effect of *Cirsium pascuarense* on blood glucose levels of normoglycaemic and alloxan-diabetic mice. *Phytother. Res*. 15: 552–554.

Perez, C., Ramon Canal., J., Enrique Campillo, J., Romero, A., Dolares Torres, M., 1999. Hypotriglyceridaemic activity of *Ficus carica* leaves in experimental hypertriglyceridaemic rats. *Phytother. Res*. 13: 188–191.

Perez, R.M., Zavala, M.A., Perez, S., Perez, C., 1998a. Antidiabetic effect of compounds isolated from plants. *Phytomedicine* 5: 55–75.

Perez, R.M, Perez, C., Perez, S., Zavala, M.A. 1998b. Effect of triterpenoids of *Bouvardia terniflora* on blood sugar levels of normal and alloxan diabetic mice. *Phytomedicine* 5: 475–478.

Perez, R.M., Perez, S., Zavala, M.A., Perez, S.C., 1996. Effect of *Agarista mexicana* and *Verbesina persicifolia* on blood glucose level of normoglycaemic and alloxan-diabetic mice and rats. *Phytother. Res*. 10: 351–353.

Perez, S., Perez, R.M., Perez, C., Vargas, R., 1992. Hypoglycemic effect of *Acrocomia mexicana* Karw. *Phyton-Int. J. Exp. Bot*. 53: 39–42.

Perfumi, M., Arnold, N., Tacconi, R., 1991. Hypoglycemic activity of *Salvia fructicosa* Mill from Cyprus. *J. Ethnopharmacol*. 34: 135–140.

Petlevski, R., Hadzija M., Slijepcevic, M., Juretic, D., 2001. Effect of "antidiabetes" herbal preparation on serum glucose and fructosamine in NOD mice. *J. Ethnopharmacol*. 75: 181–184.

Pick, M.E., Hawrysh, Z.J., Gee, M.I., Toth, E., Garg, M.L., Hardin, R.T., 1996. Oat bran concentrate bread products improve long-term control of diabetes: a pilot study. *J. Am. Dietetic Assoc*. 96: 1254–1261.

Prakasam, A., Sethupathy, S., Pugalendi, K.V., 2003. Erythrocyte redox status in streptozotocin diabetic rats: effect of *Casearia esculenta* root extract. *Pharmazie* 58: 920–924.

Premalatha, B., Sujatha, V., Sachdanandam, P., 1997. Modulating effect of *Semecarpus anacardium* Linn. nut extract on glucose metabolising enzymes in afltoxin BI-induced experimental hepatocellular carcinoma. *Pharmacological Res*. 36: 187–192.

Puri, D., 2001. The insulinotropic activity of a Nepalese medicinal plant *Biophytum sensitivum*: preliminary experimental study. *J. Ethnopharmacol*. 78: 89–93.

Puri, D., 2003. Hypocholesterolemic effect of *Biophytum sensitivum* leaf water extract. *Pharmaceutical Biol*. 41: 253–258.

Rajan, S., Sethuraman, M., Mukherjee, P.K., 2002. Ethnobiology of the Nilgiri Hills, India. *Phytother. Res*. 16: 98–116.

Rajasekaran, S., Sivagnanam, K., Ravi, K., Subramanian, S., 2004. Hypoglycemic effect of *Aloe vera* gel on streptozotocin-induced diabetes in experimental rats. *J. Med. Food* 7: 61–66.

Ramdath, D.D., Isaacs, R.L.C., Teelucksingh, S., Wolever, T.M.S., 2004. Glycaemic index of selected staples commonly eaten in the Caribbean and the effects of boiling vs. crushing. *Br. J. Nutr*. 91: 971–977.

Rao, B.K., Rao, C.A., 2001. Hypoglycemic and antihyperglycemic activity of *Syzgium alternifolium* (Wt.) Walp. seed extracts in normal and diabetic rats. *Phytomedicine* 8: 88–93.

Rao, R.B., Murugesan, T., Sinha, S., Saha, B.P., Pal, M., Mandal, S.C., 2002. Glucose lowering efficacy of *Ficus racemosa* bark extract in normal and alloxan diabetic rats. *Phytother. Res*. 16: 590–592.

Rastogi, R.P., Dhawan, B.N., 1982. Research on medicinal plants at the Central Drug Research Institute, Lucknow, India. *Indian J. Med. Res*. 76 Suppl: 27–45.

Rathi, S.S., Grover, J.K., Vats, V., 2002. The effect of *Momordica charantia* and *Mucuna pruriens* in experimental diabetes and their effect on key metabolic enzymes involved in carbohydrate metabolism. *Phytother. Res*. 16: 236–243.

Ravi, K., Rajasekaren, S., Subramanian, S., 2003. Hypoglycemic effect of *Eugenia jambolana* seed kernels on streptozotocin-induced diabetes in rats. *Pharmaceutical Biol*. 41: 598–603.

Reher, G., Slijepcevi, M., Kraus, L., 1991. Hypoglycemic activity of triterpenes and tannins from *Sarcopoterium spinosum* and two *Sanguisorba* species. *Planta Med*. 57: Suppl. 2: A57–A58.

Rodriguez, J.C., Loyola, J., Schmedahirschmann, G., 1992. Hypoglycemic activity of *Hexachlamys edulis* (Yvahai) extract in rats. *Phytother. Res*. 6: 47–49.

Roman Ramos, R., Alarcon–Aguilar, F., Lara–Lemus, A., Flores–Saenz, J.L., 1992. Hypoglycemic effect of plants used in Mexico as antidiabetics. *Arch. Med. Res*. 23: 59–64.

Russo, E.M.K., Reichelt, A.A.J., Desa, J.R., Furlanetto, R.P., Moises, R.C.S., Kasamatsu, T.S., Chacra, A.R., 1990. Clinical trial of *Myrcia uniflora* and *Bauhinia forficata* leaf extracts in normal and diabetic-patients. *Brazilian J. Med. Biological Res*. 23: 11–20.

Sabu, M.C., Kuttan, R., 2003. Antioxidant activity of Indian herbal drugs in rats with alloxan-induced diabetes. *Pharmaceutical Biol*. 41: 500–505.

Sabu, M.C., Kuttan, R., 2002. Antidiabetic activity of medicinal plants and its relationship with their antioxidant property. *J. Ethnopharmacol*. 81: 155–160.

Sachdewa, A., Khemani, L.D., 2003. Effect of *Hibiscus rosa sinensis* Linn. ethanol flower extract on blood glucose and lipid profile in streptozotocin induced diabetes in rats. *J. Ethnopharmacol*. 89: 61–66.

Saif–Ali, R., Al-Qirbi, A., Al-Geiry, A., Al-Habori, M., 2003. Effect of *Catha edulis* on plasma glucose and C-peptide in both type 2 diabetics and nondiabetics. *J. Ethnopharmacol*. 86: 45–49.

Sauvaire, Y., Petit, P., Broca, C., Manteghetti, M., Baissac, Y., Fernandez–Alvarez, J., Gross, R., Roye, M., Leconte, A., Gomis, R., Ribes, G. 1998. 4-Hydroxyisoleucine: a novel amino acid potentiator of insulin secretion. *Diabetes* 47: 206–210.

Sawada, S., Takeda, Y., Tashiro, M., 2002. Primary structures of α- and β-subunits of α-amylase inhibitors from seeds of three cultivars of *Phaseolus* beans. *J. Protein Chem*. 21: 9–17.

Shang, M.F., 2000. Status of the development of antidiabetic TCM in China. *Chin. J. Traditional Chin. Med. Inf*. 7: 78–81.

Shani, J., Ahronson, Z., Sulman, F.G., Mertz, W., Frenkel, G., Kraicer, P.F., 1972. Potentiation of insulin action by ashes of A*triplex halimus*. *Acta Diabetologica Latina* 9: 814–814.

Shapiro, K., Gong, W.C., 2002. Natural products used for diabetes. *J. Am. Pharmaceutical Assoc*. 42: 217–226.

Sharma, S.R., Dwivedi, S.K., Swarup, D., 1997. Hypoglycemic, antihyperglycemic and hypolipidemic activities of *Caesalpinia bonducella* seeds in rats. *J. Ethnopharmacol*. 58: 39–44.

Sheela, C.G., Kumud, K., Augusti, K.T., 1995. Antidiabetic effects of onion and garlic sulfoxide amino acids in rats. *Planta Med*. 61: 356–357.

Shen, Z.F., Xie, M.Z., 1985. Hypoglycemic effect of the combined use of puerarin and aspirin in mice. *Acta Pharmaceutica Sinica* 20: 863–865.

Sheweita, S.A., Newairy, A.A., Mansour, H.A., Yousef, M.I., 2002. Effect of some hypoglycaemic herbs on the activity of phase 1 and 2 drug-metabolizing enzymes in alloxan-induced diabetic rats. *Toxicology* 174: 131–139.

Shi, J., Arunasalam, K., Yeung, D., Kakuda, Y., Mittel, G., Jiang, Y.M., 2004. Saponins from edible legumes: chemistry, processing, and health benefits. *J. Med. Food* 7: 67–78.

Shim, Y.J., Doo, H.K., Ahn, S.Y., Kim, Y.S., Seong, J.K., Park, I.S., Min, B.H., 2003. Inhibitory effect of aqueous extract from the gall of Rhus chinensis on alpha-glucosidase activity and postprandial blood glucose. *J. Ethnopharmacol*. 85: 283–287.

Shirwaikar, A., Rajendran, K., Dinesh Kumar, C., Bodla, R., 2004. Antidiabetic activity of aqueous leaf extract of *Annona squamosa* in streptozotocin-nicotinamide type 2 diabetic rats. *J. Ethnopharmacol*. 91: 171–175.

Shukla, K., Narain, J.P., Puri, P., Gupta, A., Bijlani, R.L., Mahapatra, S.C., Karmarkar, M.G., 1991. Glycemic response to maize, bajra and barley. *Indian J. Physiol. Pharmacol*. 35: 249–254.

Silva, R.M., Santos, F.A., Rao, V.S.N., Maciel, M.A., Pinto, A.C., 2001. Blood glucose — and triglyceride — lowering effect of transdehydrocrotonin, a diterpene from *Croton cajucara* Benth. in rats. *Diabetes Obesity Metab.* 3: 452–456.

Simmonds, M.S.J., Kite, G.C., Porter, E.A., 1999. Taxonomic distribution of iminosugars in plants and their biological activities. In *Iminosugars as Glycosidase Inhibitors*. (Ed., Sturtz, A.E.) Wiley–VCH, Weinheim, Germany, 8–30.

Singh, K.N., Chandra, V., 1977. Hypoglycaemic and hypocholesterolaemic effects of proteins of *Acacia milanoxylon* and *Bauhinia retusa* wild leguminous seeds in young albino rats. *J. Indian Med. Assoc.* 68: 201–203.

Singh, K.N., Mittel, R.K., Barthwal, K.C., 1976. Hypoglycemic activity of *Acacia catechu*, *Acacia suma,* and A*lbizzia oderatissima* seed diets in normal albino rats. *Indian J. Res.* 64: 754–757.

Sittie, A.A., Nyarko, A.K., 1998. *Indigofera arrecta*: Safety evaluation of an antidiabetic plant extract in non-diabetic human volunteers. *Phytother. Res.* 12: 52–54.

Soffar, S.A., Metwali, D.M., Abdel–Aziz, S.S., el-Wakil, H.S, Saad, G.A., 2001. Evaluation of the effect of a plant alkaloid (berberine derived from *Berberis aristata*) on *Trichomonas vaginalis in vitro*. *J. Egypt Soc. Parasitol.* 31: 893–904.

Stanely Mainzen Prince, P., Menon, V.P., 2003. Hypoglycemic and hypolipidemic action of alcohol extracts of *Tinospora cordifolia* roots in chemical induced diabetes in rats. *Phytother. Res.* 17: 410–413.

Streeter, J.G., 2001. Simple partial purification of D-pinitol from soybean leaves. *Crop Sci.* 41: 1985–1987.

Sui, D.Y., Lu, Z.Z., Li, S.H., Cai, Y., 1994. Hypoglycemic effect of saponin isolated from leaves of *Acanthopanax senticosus* (Rupr. et Maxin.) Harms. Chin. *J. Chin. Materia Med.* 19: 683–685, 703.

Sussman, L.K., 1980. Herbal medicine on Mauritius. *J. Ethnopharmacol.* 2: 254–278.

Swanston–Flatt, S.K., Day, C., Flatt, P.R., Gould, B.J., Bailey, C.J., 1989. Glycemic effects of traditional European plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. *Diabetes Res.* 10: 69–73.

Takahashi, M., Konno, C., Hikino, H., 1986. Antidiabetes drugs. 16. Isolation and hypoglycemic activity of coixans A, B and C, glycans of *Coix lachryma-jobi* var *ma-yeun* seeds. *Planta Med.* 52: 64–65.

Takahashi, M., Konno, C., Hikino, H., 1985. Antidiabetes drugs. 10. Isolation and hypoglycemic activity of saccharans A, B, C, D, E and F, glycans of *Saccharum officinarum* stalks. *Planta Med.* 51: 258–260.

Takatsuna, H., Umezawa, K., 2004. Screening of bioactive metabolites for pancreatic regeneration chemotherapy. *Biomed. Pharmacol.* 58: 610–613.

Takeuchi, H., Mooi, L.Y., Inagaki, Y., He, P.M., 2001. Hypoglycemic effect of a hot-water extract from defatted sesame (*Sesamum indicum* L.) seed on the blood glucose level in genetically diabetic KK-A(y) mice. *Biosci. Biotechnol. Biochem.* 65: 2318–2321.

Tezuka, Y., Stampoulis, P., Banskota, A.H., Awale, S., Tran, K.Q., Saiki, I., Kadota, S., 2000. Constituents of the Vietnamese medicinal plant *Orthosiphon stamineus*. *Chemical Pharmaceutical Bull.* 48: 1711–1719.

Tolan, I., Ragoobirsingh, D., St A Morrison, E.Y.S.A., 2001. The effect of capsaicin on blood glucose plasma insulin levels and insulin binding in dog models. *Phytother. Res.* 15: 391–394.

Tomoda, M., Shimizu, N., Gonda, R., Kanari, M., Yamada, H., Hikino, H., 1990. Anticomplementary and hypoglycemic activities of the glycans from the seeds of *Malva verticillata*. *Planta Med.* 56: 168–170.

Tomoda, M., Shimizu, N., Oshima, Y., Takahashi, M., Murakami, M., Hikino, H., 1987. Glucomannans active in normal mice. *Planta Med.* 53: 8–12.

Tormo, M.A., Gil–Exojo, I., de Tejada, A.R., Campillo, J.E., 2004. Hypoglycaemic and anorexigenic activities of an α-amylase inhibitor from white kidney beans (*Phaseolus vulgaris*) in Wister rats. *Br. J. Nutr.* 92: 785–790.

Trinidad, T.P., Valdez, D.H., Loyola, A.S., Mallillin, A.C., Askali, F.C., Castillo, J.C., Masa, D.B., 2003. Glycemic index of different coconut (*Cocos nucifera*) — flour products in normal and diabetic subjects. *Br. J. Nutr.* 90: 551–556.

Trovato, A., Galati, E.M., Rossitto, A., Monforte, M.T., d'Aquino, A., Forestieri, A.M., 1998. Hypoglycemic effects of *Salvadora persica* L. in the rat. *Phytomedicine* 5: 129–132.

Tunali, T., Yarat, A., Yanardag, R., Ozcelik, F., Ozsoy, O., Ergenekon, G., Emekli, N., 1999. Effect of parsley (*Petroselinum crispum*) on the skin of STZ induced diabetic rats. *Phytother. Res.* 13: 138–141.

Umezawa, K., Hiroki, A., Kawakami, M., Naka, H., Takei, I., Ogata, T., Kojima, I., Koyano, T., Kowithayakorn, T., Pang, H.S., Kam, T.S., 2003. Induction of insulin production in rat pancreatic acinar carcinoma cells by conophylline. *Biomed. Pharmacother.* 57: 341–350.

Venkatesh, S., Reddy, G.D., Reddy, Y.S.R., Sathyavathy, D., Reddy, B.M., 2004. Effect of *Helicteres isora* root extracts on glucose tolerance in glucose-induced hyperglycaemic rats. *Fitoterapia* 75: 364–367.

Venkateswaran, S., Pari, L., 2002. Effect of *Coccinia indica* on blood glucose, insulin, and hepatic key enzymes in experimental diabetes. *Pharmaceutical Biol.* 40: 165–170.

Venkateswarlu, V., Kokate, C.K., Rambhau, D., Veersham, C., 1993. Antidiabetic activity of roots of *Salacia macrosperma*. *Planta Med*. 59: 391–393.

Vessal, M., Hernmati, M., Vasei, M., 2003. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comp. Biochem. Physiol. C-Toxicol. Pharmacol*. 135: 357–364.

Waltner–Law, M.E., Wang, X.H.L, Law, B.K., Hall, R.K., Nawano, M., Granner, D.K., 2002. Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. *J. Biological Chem*. 277: 34933–34940.

Wang, L., Li, S.L., Wang, L., 2000. Progress on the study of polysaccharides and glucosides of hypoglycaemic plants. *Chin. Med. Mater*. 23: 575–577.

Wang, L., Dong, J., Jiang, L.Z., Zhang, C.J., Hu, S.X., Xie, P.L., Li, W.B., Deng, X.D., 1999. The effects of LBP-D, hypoglycemic agents alone or in combination, on blood glucose and immune functions in alloxan-induced diabetes mice. *J. Yunnan Univ.* (nat. sci. ed.) 21: 186–188.

Wang, Y., Zhu, Z., Wang, C., Yang, J., 1998. Determination of oleanolic acid and total saponins in *Aralia* L. *Chin. J. Chin. Materia Med*. 23: 518–521, 574.

Wijaya, E., Wu, Z.M., Ng, F., 1995. Effect of Slimax, a Chinese herbal mixture, on obesity. International *J. Pharmacognosy* 33: 41–46.

Wild, S., Roglic, G., Green, A., Sicree, R., King, H., 2004. Global prevalence of diabetes. Estimates for the year 2000 and projections 2030. *Diabetes Care* 27: 1047–1053.

Winkelman, M., 1989. Ethnobotanic treatment of diabetes in Baja California North/Narte. *Med. Anthropol.* 11: 255–268.

Wollersheim, H., Netten, P.M., Lutterman, J.A., Lenders, J.W.M., 1989. Ephedrine improves microcirculation in the diabetic neuropathic foot. *Angiology* 40: 1030–1034.

Won, H.S., Lee, J., Khil, L.Y., Chae, S.H., Ahn, M.Y., Lee, B.H., Chung, J.H., Kim, Y.C., Moon, C.K., 2004. Mechanism of action of brazilin on gluconeogenesis in isolated rat hepatocytes. *Planta Med*. 70: 740–744.

Xiu, L.M., Miura, A.B., Yamamoto, K., Kobayashi, T., Song, Q.H., Kitamura, H., Cyong, J.C., 2001. Pancreatic islet regeneration by ephedrine in mice with streptozotocin-induced diabetes. *Am. J. Chin. Med*. 29: 493–500.

Yamahara, J., Mibu, H., Sawada, T., Fujimura, H., Takino, S., Yoshikawa, M., Kilagawa, I., 1981. Biologically active principles of crude drugs. *Yokurigaku Zasshi* 101: 86–90.

Yamashita, T., Yasuda, K., Kizu, H., Kameda, Y., Watson, A.A., Nash, R.J., Fleet, G.W.J., Asano, N., 2002. New polyhydroxylated pyrrolidine, piperidine, and pyrrolizidine alkaloids from *Scilla sibirica*. *J. Nat. Prod*. 65: 1875–1881.

Yang, Y.Y., Gao, S., Wang, H.P., Chen, S., Ma, L.X., 2001. Studies on the effect of konjak oligosaccharides on blood sugar and serum cholestrol in the diabetic mice. *J. Hubei Univ.* (nat. sci. ed.) 23: 277–279.

Yaniv, Z., Dafni, A., Friedman, J., Palevitch, D., 1987. Plants used for the treatment of diabetes in Israel. *J. Ethnopharmacol*. 19: 145–151.

Yao, Z.P., Chen, J.X., Li, F.R., 2000. A survey of *Euonyrnus alatus* (Thunb.) Sieb. on its chemistry, pharmacology and clinic. *Chin. J. Inf. Traditional Chin. Med*. 7: 31–33.

Yasuda, K., Kizu, H., Yamashita, T., Kameda, Y., Kato, A., Nash, R.J., Fleet, G.W.J., Molyneux, R.J., Asano, N., 2002. New sugar-mimic alkaloids from the pods of *Angylocalyx pynaertii*. *J. Nat. Prod*. 65: 198–202.

Yeh, G.Y., Eisenberg, D.N., Kaptchuk, T.J., Phillips, R.S., 2003. Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care* 26: 1277–1294.

Yin, J., Hu, R.M., Chen, M.D., Tang, J.F., Li, F.Y., Yang, Y., Chen, J.L., 2002. Effects of berberine on glucose metabolism *in vitro*. *Metab. Clin. Exp*. 51: 1439–1443.

Yokozawa, T., Nakagawa, T., 2004. Inhibitory effects of Luobuma tea and its components against glucose-mediated protein damage. *Food Chemical Toxicol*. 42: 975–981.

Yokozawa, T., Kim, H.Y., Cho, E.J., Choi, J.S., Chung, H.Y., 2002. Antioxidant effects of isorhamnetin 3,7-di-*O*-β-D-glucopyranoside isolated from mustard leaf (*Brassica juncea*) in rats with streptozotocin-induced diabetes. *J. Agric. Food Chem*. 50: 5490–5495.

Yoshikawa, M., Murakami, T., Inaduki, M., Hirano, K., Yamahara, J., Matsuda, H., 1997a. Absolute stereostructures of betavulgarosides III and IV, inhibitors of glucose absorption, from the roots of *Beta vulgaris* L (sugar beet). *Chemical Pharmaceutical Bull*. 45: 561–563.

Yoshikawa, M., Murakami, T., Kadoya, M., Li, Y.H., Murakami, N., Yamahara, J., Matsuda, H., 1997b. Medicinal foodstuffs. 9. The inhibitors of glucose absorption from the leaves of *Gymnema sylvestre* R. Br. (Asclepiadaceae): structures of gymnemosides a and b. *Chemical Pharmaceutical Bull*. 45: 1671–1676.

Yoshimura, H., Sugawara, K., Saito, M., Saito, S., Murakami, S., Miyata, N., Kawashima, A., Morimoto, S., Gao, N., Zhang, X.G., Yang, J.S., 2003. *In vitro* TGF-1 antagonistic activity of ursolic and oleanolic acids isolated from *Clerodendranthus spicatus*. *Planta Med*. 69: 673–675.

You, L., Wang, G., 2000. 65 Chinese traditional and herbal medicines with effect to blood glucose. *Chin*. *J*. *Inf*. *Traditional Chin*. *Med*. 7: 32–34.

Zhang, R.X., Zhou, J.H., Ha, Z.P., Zhang, Y.X., Gu, G.M., 2004b. Hypoglycemic effect of Rehmannia glutinosa ogigosaccharide in hyperglycemic and alloxan-induced diabetic rats and is mechanism. *J*. *Ethnopharmacology* 90: 39–43.

Zhang, Y.J., Jayaprakasam, B., Seeram, N.P., Olson, L.K., DeWitt, D., Nair, M.G., 2004. Insulin secretion and cyclooxygenase enzyme inhibition by Cabernet Sauvignon grape skin compounds. *J*. *Agric*. *Food Chem*. 52: 228–233.

Zhang, Z.Y., Ye, H.Y., Yu, M.H., You, L., Yan, Y.Q., Yang, X.F., 2001. Effects of *Astragalus* polysaccharide on the mycocardial ultrastructure of diabetic rats. *J*. *Fudan Univ. (*med. sci. ed.) 28: 476–478.

3 Preclinical and Clinical Methods for Evaluating Antidiabetic Activity of Plants

Caroline Day and Clifford J. Bailey

CONTENTS

INTRODUCTION

More than 1000 plants have been described as efficacious in the treatment of diabetes mellitus (Bailey & Day 1989; Day 1998, 2000; Swanston–Flatt et al. 1990a, b). However, many of these descriptions are anecdotal accounts of traditional usage, and fewer than half of these plants or plant extracts have received a thorough medical or scientific evaluation of their purported benefits. This chapter reviews the preclinical *in vivo* methods and clinical procedures used to investigate the antidiabetic activity of plants and plant-derived extracts, including a consideration of the ethical issues affecting use of traditional plant treatments for diabetes.

ANIMAL MODELS

Animal models have been used extensively to investigate the *in vivo* efficacy, mode of action and side effects of antidiabetic plants and their active principles. Due to the heterogeneity of diabetic

conditions in man, no single animal model is entirely representative of a particular type of human diabetes. Thus, many different animal models have been used, each displaying a different selection of features seen in human diabetic states (Bailey & Flatt 2003). Normal nondiabetic animals and animals with impaired glucose tolerance and insulin resistance (but not overt diabetes) have also been used to demonstrate hypoglycemic activity and to investigate the mode of action of antidiabetic plant materials (Bailey & Flatt 1990).

It is noteworthy that agents that show a blood glucose-lowering effect in animals are not necessarily effective in man and vice-versa. This may be due at least in part to differences in hepatic metabolism, where the metabolites are the active compounds. Considerable variations in sensitivity to the same agent can also occur between species due to different rates of absorption, metabolism, and elimination. The most widely used animal models are small rodents, which are less expensive to maintain than larger animals and generally show a more rapid onset of their diabetic condition consistent with their short lifespan. Moreover, a greater variety of mutations leading to diabetes has been observed in rodents, and these have been characterized in more detail than those in other animal groups (Bailey & Flatt 2003).

INSULIN-DEPENDENT MODELS

To date, no evidence that any natural plant material can serve as a complete substitute for insulin has been validated. Several plant products have been reported to mimic the effects of insulin partially or enhance the effects of very low endogenous insulin concentrations, but none has sustained life in the total absence of insulin. Nevertheless, animal models of insulin-dependent diabetes provide a valuable insight into the efficacy of potential adjuncts to insulin therapy in severely hypoinsulinemic states. The main insulin-dependent models are:

- Spontaneous syndromes (e.g., BB rat, NOD mouse, LEW.1AR1/Ztm-iddm rat)
- Experimentally induced (e.g., chemically, with alloxan or streptozotocin or surgically by near-total pancreatectomy)

These incur extensive or complete loss of pancreatic β-cells, and the consequent lack of insulin causes extreme hyperglycemia with glycosuria, polyuria, polydipsia, hyperphagia, and weight loss. If untreated, these forms of diabetes culminate in fatal hyperosmolar ketoacidosis.

Spontaneous and Transgenic Models

The three established spontaneous rodent syndromes of insulin-dependent diabetes are: the biobreeding (BB) rat, the LEW.1AR1/Ztm-iddm rat, and the nonobese diabetic (NOD) mouse. These syndromes show many similarities with the autoimmune development of human type 1 diabetes. Each model carries an inherited susceptibility to diabetes involving defects of the immune system associated with several genes of the major histocompatibility complex (MHC) and probably other genes that are not linked to the MHC (Lally & Bone 2003; Lenzen et al. 2001). Unidentified events trigger abnormal activity of cellular and humoral components of the immune system causing insulitis, β-cell destruction, and a dependence on exogenous insulin to sustain life.

Although insulin-dependent diabetes is well recognized in many other animals, such as hamsters, guinea pigs, dogs, cats, and monkeys, these animals have received less attention as models for the testing of potential new therapies. Models of transgenic overexpression of cytokines and viral antigens that cause insulitis and insulin-dependent diabetes have also received little use in the testing of new therapies (Lally & Bone 2003). Other transgenics such as knockouts of the genes for glucokinase and the insulin receptor produce fatal diabetic ketoacidosis in early neonatal life (Patti & Kahn 1997) and are unsuitable for testing new therapies.

Experimentally Induced Models

The most common experimentally induced models of insulin-dependent diabetes involve administration of chemicals that selectively destroy pancreatic β-cells — notably, alloxan and streptozotocin (Cooperstein & Watkins 1981; Bailey & Flatt 1990). A single large dose of alloxan (e.g., ≥40 mg/kg intravenously to a fasted adult rat, or a higher dose to a fed rat or by the intraperitoneal route) usually produces a severe insulinopenic diabetes, although partial recovery may gradually occur thereafter. A single large dose of streptozotocin (e.g., ≥35 mg/kg intravenously to a fasted adult rat or ≥65 mg/kg to a fed rat or by the intraperitoneal route) also produces a severe insulinopenic diabetes that is generally more permanent than that produced by alloxan. It is emphasized that some studies have employed dosages of these agents that do not achieve or maintain a completely insulin-dependent diabetic state.

Thus, interventions that might superficially appear to replace insulin may only partially mimic or enhance insulin action (Bailey & Flatt 1990). Indeed, regeneration of islet tissue can occur naturally in the long term, and this could be erroneously attributed to administration of a test substance if the experiments are not adequately controlled. Surgical pancreatectomy, which is rarely total, is open to the same problems.

Streptozotocin (STZ) produces a more specific and controllable destruction of islet β-cells than alloxan and is now the most widely used model of insulin-dependent diabetes for testing new therapies. STZ-induced diabetes in rodents has been used to investigate the properties of many traditional antidiabetic plants and their active principles; several of these have been shown to delay the onset or reduce the severity of the diabetic condition (Swanston–Flatt et al. 1990a, b).

NON-INSULIN-DEPENDENT MODELS

An extensive range of spontaneous and experimentally induced non-insulin-dependent animal models of diabetes has been described in the literature (Bailey & Flatt 2003). These models vary greatly in their etiology, pathogenesis, and natural history. Some animals may progress to a state of severe hyperglycemia, which can eventually deteriorate into an insulin-requiring state, although these animals do not require insulin for most of their lifespan. The majority of models that do not require insulin exhibit the moderate hyperglycemia frequently associated with overweight or obesity and insulin resistance.

Spontaneous and Transgenic Models

The genetic defects responsible for some spontaneous non-insulin-dependent diabetic models have recently been identified, and environmental factors contributing to these diabetic syndromes are now established. Table 3.1 and Table 3.2 list the main spontaneous non-insulin-dependent models and summarize their key features. Table 3.3 lists spontaneous models of impaired glucose tolerance that do not usually develop overt diabetes. Detailed descriptions of these and other models are available elsewhere (Bailey & Flatt 1990, 2003; Shafrir 1992; Brindley & Russell 2002); here, the focus will be on the models that have been used in studies of antidiabetic plants and their principles.

The diabetic C57BL/KsJ *db*/*db* mouse provides many similarities with the natural history of human type 2 diabetes. An initial period of hyperphagia, obesity, and hyperinsulinemia gives rise to insulin resistance and hyperglycemia. Beta-cell hyperplasia facilitates greater compensatory hyperinsulinemia until the capacity for continued β-cell division is "exhausted." Thereafter, gradual β-cell degeneration leads to a decline in insulin concentrations and a marked escalation of the hyperglycemia, which may eventually result in an insulin-requiring diabetic state.

The *db*/*db* syndrome is brought about by a mutation of the leptin receptor. (Leptin is a peptide hormone derived from adipose tissue. It acts centrally to induce satiety and promote thermogenesis). Although hyperphagia due to a leptin receptor mutation is rarely the cause of human type 2 diabetes,

TABLE 3.1
Animal Models of Severely Hyperglycemic Non-Insulin-Dependent Diabetes

Animal	Inheritance	Environmental Influence	Body Weight	Food Intake	Glycemia	Insulinemia	Insulin Action	β-Cell Population
Chinese hamster, *Cricetulus griseus*	P	?	+[b]/N	+[b]	+/+ +	+[b]/N/–[ac]	N/–	+[b]/–
Diabetes mouse (*db*) C57BL/KsJ	AR	?	+ +	+ +	+ +	+ +[b]/N	– –	+/–[c]
Djungarian hamster, *Phodopus sungorus*	P	HED/RE	N/+	N/+	+/+ +	+/+ +	–	+
Egyptian sand rat, *Psammomys obesus*	?	HED/RE	+	+	+/+ +	+/N–[d]	–	N/+
New Zealand white rabbit (NZW)	?	?	N	N/+	+ +	–/– –	?	N
South African hamster, *Mystromys albicaudatus*	P	?	N	+	+/+ +	?	?	–
Spiny mouse, *Acomys cahirinus*	?	HED/RE	+	+	N/+/+ +	+[b]/N/–[c]	–	+

Notes: + + = severe increase; + = moderate increase; N = normal; – = moderate decrease; – – = severe decrease; ? = uncertain or not reported; AR = autosomal recessive; P = polygenic; HED = high-energy diet; RE = reduced exercise.

[a] Some aging animals may require insulin.
[b] Occurs during early development.
[c] Occurs in some aging animals.
[d] In severely diabetic animals.

the rapid progression of obesity and insulin resistance to hyperinsulinemic diabetes and then to hypoinsulinemic diabetes renders the *db*/*db* mouse one of the most representative and convenient models available.

Another valuable spontaneous syndrome is that of the sand rat (*Psammomys obesus*). In the wild, these animals actively forage for a meager diet. Constrained under laboratory conditions with free access to an energy-rich diet, they become hyperphagic, obese, and hyperinsulinemic and develop insulin resistance and hyperglycemia. In later life, some of these animals incur β-cell failure with severe hyperglycemia. Rhesus monkeys (*Macaca mulatta*) maintained in captivity with limited space and unrestricted availability to an energy-rich diet are also prone to become obese and develop diabetes. Although this closely reflects human type 2 diabetes, primate models have received very limited use due to expense and the relatively long time period for their diabetes to develop.

The *ob*/*ob* mouse lacks biologically active leptin due to a mutation in the leptin gene. This model develops severe insulin resistance and marked hyperinsulinemia with gross obesity, extensive β-cell hyperplasia, and mild to moderate hyperglycemia. The *ob*/*ob* mouse provides an especially challenging test for any potential treatment against insulin resistance. The Zucker fatty (*fa*/*fa*) rat, which results from a mutation in the leptin receptor, is also used as a model of insulin resistance. However, the *fa*/*fa* rat is more likely to exhibit impaired glucose tolerance than overt diabetes. Cross-breeding of rats carrying the *fa* mutation has produced other insulin-resistant models that develop overt diabetes, such as the Zucker diabetic fatty (ZDF) rat and the Wistar Kyoto (WKY) fatty rat.

In recent years, diabetic transgenic mice have been produced by overexpression or knockout of selected genes affecting β-cell function and insulin action (Patti & Kahn 1997; Bailey & Flatt

TABLE 3.2
Animal Models of Moderately Hyperglycemic Non-Insulin-Dependent Diabetes

Animal	Inheritance	Environmental Influence	Body Weight	Food Intake	Glycemia	Insulinemia	Insulin Action	β-Cell Population
Goto–Kakizaki rat (GK)	?	?	N	?	+	N/–	?	N/–
Japanese KK mouse	P?	HED	+[e]	+[e]	+[e]	+[e]	–[e]	+
Male Wistar Kyoto fatty rat (WKY)	?	HCD	+	?	+	+	–	?
Male Zucker diabetic fatty rat (ZDF)	AR(LRM)	?	+	+	+/+ +	+/N/–	–/– –	?
New Zealand obese mouse (NZO)	P	?	+ +	+[b]	+	+[e]	–	+ +
Obese mouse (*ob*), C57BL/6J, V stock, Aston	AR(LM)	?	+ +[e]	+ +[be]	+[e]	+ +[e]	– –[e]	+ +
Paul Bailey black mouse (PBB/Ld)	P?	?	+ +	+	+	+	–?	+?
Rhesus monkey, *Macaca malatta*	?	?	+	+	+	+/–[acd]	–?	?
Selectively inbred Cohen diabetic rat	?	HCD	N	N?	+	+[b]/N/–[c]	–	?
Spontaneous hypertensive/NIH corpulent rat (SHR/N-cp)	AR(LRM)	?	+ +	+	+	+ +	–	N/+
Wellesley hybrid mouse	P?	?	+	+	+	+ +	– –	+ +
Yellow obese mouse (A^y, A^{vy}, A^{iy})	AD(APM)	?	+ +	+	N/+	+	–	+

Notes: + + = severe increase; + = moderate increase; N = normal; – = moderate decrease; – – = severe decrease; ? = uncertain or not reported; AR = autosomal recessive; AD = autosomal dominant; P = polygenic; HED = high-energy diet; RE = reduced exercise; HCD = high-carbohydrate diet; LRM = leptin receptor mutation; LM = leptin mutation; APM = agouti protein mutation.

[a] Some aging animals may require insulin.

[b] Occurs during early development.

[c] Occurs in some aging animals.

[d] In severely diabetic animals.

[e] Regresses toward normal in aging animals.

2003). Those showing a sustained period of non-insulin-dependent diabetes are listed in Table 3.4, but none has yet been used to investigate traditional antidiabetic plants.

Experimentally Induced Models

Non-insulin-dependent forms of diabetes are produced by low-dose or neonatal administration of alloxan or STZ (Bailey & Flatt 2002). For example, a single intravenous or intraperitoneal injection of STZ at a dose of 25 to 30 mg/kg to a fasted adult rat will usually produce a sustained mild to moderate state of hyperglycemia. A single intravenous or intraperitoneal injection of STZ at a dose of 50 to 100 mg/kg to a nonfasted rat during the first week of life produces a transient hyperglycemia in the neonate. This is followed by several weeks of normoglycemia that give way to a sustained

TABLE 3.3
Animal Models of Impaired Glucose Tolerance and Borderline Non-Insulin-Dependent Diabetes

Animal	Inheritance	Environmental Influence	Body Weight	Food Intake	Glycemia	Insulinemia	Insulin Action	β-Cell Population
Aging laboratory rats and mice	?	?HED/RE	N/+	N	N[a]	N/+	–	N/+
Bureau of Home Economics (BHE) rat	?	HSD	+	N	N[a]	+	–	?
Fatty Zucker rat (*fa*)	AR(LRM)	?	+ +	+	N[a]	+/+ +	–/– –	+/+ +
Nonobese, non-insulin-dependent diabetic mouse (NON)	?	?	N	?	N[a]/+	–	?	?
Yucatan miniature swine	?	?	N	?	N[a]/+	N/+	N/–	N

Notes: + + = severe increase; + = moderate increase; N = normal; – = moderate decrease; – – = severe decrease; ? = uncertain or not reported; AR = autosomal recessive; AD = autosomal dominant; P = polygenic; HED = high-energy diet; RE = reduced exercise; HSD = high-sucrose diet; LRM = leptin receptor mutation.

[a] Basal glycemia may be within the normal range but glucose tolerance is impaired.

TABLE 3.4
Transgenic Mice that Show a Sustained Period of Non-Insulin-Dependent Diabetes

Primary alteration of α-cell function	
HNF–1α –/–	Hepatic nuclear factor –1 knockout
Kir6.2–/– β-cell	Kir6.2 channel knockout in β-cell
IR–/– β-cell	Insulin receptor knockout in β-cell
Primary alteration of insulin action	
IR–/– liver	Insulin receptor knockout in liver
IRS–2–/–	Insulin receptor substrate –2 knockout
GLUT–4+/–	Glucose transporter–4 heterozygous knockout

mild to moderate hyperglycemia in later life. Sub-total (>95%) pancreatectomy and surgical or chemical lesioning of the hypothalamus also produce non-insulin-dependent diabetes but are not routinely used to test new therapies. Diets massively enriched with fats or fructose and the administration of glucocorticoids are often used to produce non-insulin-dependent diabetes, although these have not generally been used to investigate antidiabetic plants.

MODELS OF DIABETIC COMPLICATIONS

Microvascular (retinopathy and nephropathy) and neuropathic disorders that typically develop with chronic diabetic hyperglycemia in human diabetes are uncommon in rodent models of diabetes (Bailey & Flatt 2003). This probably reflects the relatively short life span of rodents compared with the protracted period of hyperglycemia required for development of these complications.

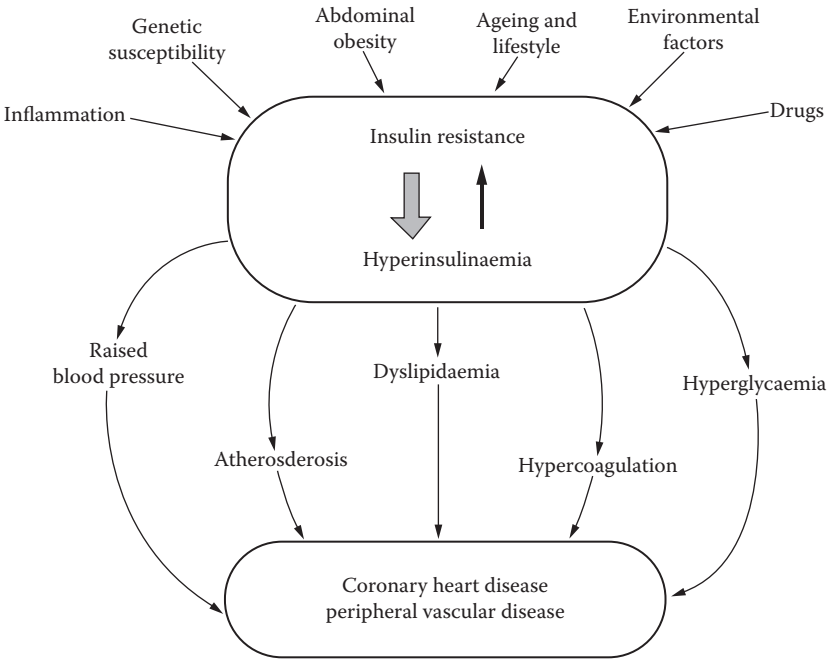

FIGURE 3.1 A schematic representation of the insulin resistance syndrome (also termed metabolic syndrome, dysmetabolic syndrome, Reaven's syndrome, or syndrome X). Insulin resistance with or without compensatory hyperinsulinemia is associated with a clustering of risk factors for premature coronary heart disease.

Nevertheless, ageing diabetic rodents, particularly those with severe hyperglycemia, sometimes exhibit thickening of glomerular capillary basement membranes and increased loss of urinary albumin. Cataracts and impaired conduction by peripheral nerves are also evident in some models, but classical proliferative retinopathy and autonomic neuropathy have not been observed (Bailey & Flatt 2003).

Macrovascular complications are particularly prevalent in human type 2 diabetes, forming an inevitable consequence of the so-called insulin resistance syndrome (also termed metabolic syndrome or syndrome X). The syndrome represents a clustering of cardiovascular risk factors; each factor is associated to some extent with insulin resistance or compensatory hyperinsulinemia (Figure 3.1). In addition to hyperglycemia, non-insulin-dependent diabetes is often associated with overweight or obesity. Many patients with the syndrome also have one or more of raised blood pressure, dyslipidemia (raised triglyceride and low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol), increased risk factors for coagulation, inflammatory markers, and evidence of atherosclerosis (Isoma et al. 2001).

A useful model of the insulin-resistance syndrome is the spontaneously hypertensive rat (SHR). This carries the *cp* (corpulent) mutation of the leptin receptor and, in conjunction with a genetic susceptibility for hypertension, produces a syndrome of obesity and insulin resistance. Some strains also develop hyperlipidemia, non-insulin-dependent diabetes, atherosclerosis, and ischaemic heart disease (Brindley & Russell 2002).

Selecting an Appropriate Model to Test Plant Materials

The guidelines that apply to preclinical testing of a new chemical entity (NCE) do not necessarily apply to a traditional plant treatment. For example, the plant may be a normal dietary ingredient traditionally taken as a raw or cooked part of the whole plant (e.g., leaf or root) or as an unrefined extract (e.g., simple decoction or infusion). If the purpose of testing is to assess claimed antidiabetic

efficacy of the plant as a normal dietary adjunct, a comprehensive program of tests designed for an NCE would not be appropriate. If it is proposed to consume inordinately large quantities of an unrefined extract, chronic toxicity assessments are indicated. Standard preclinical tests should be anticipated for a highly refined extract or novel isolated principle if this is proposed for clinical investigation and possible therapeutic use as a conventional medicine. Although toxicity tests are customarily undertaken in normal, nondiabetic animals, efficacy studies are most usefully undertaken in models that most closely represent the clinical target population.

The heterogeneity of human types of diabetes and the lack of exact replicas among nonprimate animals often require efficacy studies in more than one model, especially to investigate mode of action. Accounts of the traditional use of an antidiabetic plant in type 1 or type 2 diabetic patients provide an indication of the type of model (e.g., insulin dependent or non-insulin dependent) that might be suitable for initial investigation of hypoglycemic activity. As noted previously, experimentally induced models of insulin-dependent diabetes are often not completely devoid of endogenous insulin. This is an important consideration when claims of an insulin substitute are being investigated.

To test the efficacy of antidiabetic plants using STZ-induced or alloxan-induced diabetes in rodents, a convenient procedure is to commence plant therapy within a few days of STZ/alloxan administration before hyperglycemia becomes severe. Efficacy can then be judged by a slower progression and less severe hyperglycemia. If the study is continued until a parallel placebo (untreated) group develops ketoacidosis and requires insulin, this suggests antidiabetic activity in an insulin-dependent state. However, it is possible that the therapeutic intervention has prevented complete β-cell destruction. This can be seen if insulin concentrations are measured and animals survive when the intervention is discontinued. Because some natural regeneration of islets can occur from islet remnants, long-term survival cannot be exclusively attributed to the therapeutic intervention.

An alternative protocol to test efficacy in an insulin-dependent state is to introduce plant therapy to spontaneously or experimentally induced models that have already developed severe hyperglycemia and are controlled by exogenous insulin injections. When plant treatment is introduced and the dosage titrated up, evidence of reduced hyperglycemia or a reduction of insulin dosage without deterioration of glycemic control can be used as indices of efficacy.

The selection of non-insulin-dependent models to assess efficacy of antidiabetic plants can also provide important information about mechanism of action. Human type 2 diabetes arises through the combined impact of insulin resistance and β-cell dysfunction, and it is advantageous if a model designed to test efficacy exhibits both of these pathogenic features. Therapies that ameliorate obesity and dyslipidemia offer secondary benefits to improve glycemic control; therefore, models that incorporate these features can often yield additional relevant information. Thus, the diabetic *db*/*db* mouse and male ZDF rat provide very useful models. It is noteworthy that a plant treatment may have no efficacy if the model in which it is tested lacks the particular pathogenic feature (e.g., insulin resistance, β-cell dysfunction, obesity, dyslipidemia) against which the treatment exerts its main effect. Consequently, it may be necessary to conduct studies in several animal models to establish efficacy as well as to determine mode of action.

TESTS FOR ANTIDIABETIC ACTIVITY

For initial efficacy testing of antidiabetic activity, it is advisable to replicate the traditional method of preparation of the plant closely because activity may be altered by minor deviations. Most traditional antidiabetic plant materials are taken orally, so initial tests with unrefined plant materials or plant extracts usually involve oral administration in the diet. Oral gavage may be necessary if the smell or taste of the plant creates an aversion to feeding or drinking. Monitoring of feeding, drinking, general behavior, and standard parameters of glucose homeostasis (detailed later) in as

much detail as possible is recommended. Isolation of active hypoglycemic fractions and principles and their effects in animal models of diabetes are reviewed in detail in other chapters of this volume.

It is generally inappropriate to administer a crude plant extract by a parenteral route due to the risk of a local adverse reaction or more disseminated toxicity from a high concentration of the antidiabetic principle or other components of the extract. Even highly purified extracts may have adverse effects if administered intravenously, but adverse effects may not occur after oral administration. Thus, the enteral route of administration provides a natural barrier against unnecessary toxicity and facilitates initial dose-ranging studies. Some plant extracts may be modified chemically as they pass along the alimentary tract; thus, enteral and parenteral administration may give rise to a different profile of effects.

With this caution in mind, it can still be useful to compare the pharmacodynamic effects of purified extracts administered by different routes. For example, comparing the effects of enteral vs. parenteral administration in the fed and fasted state might indicate the importance of the intestine as a site of action of an isolated principle to inhibit intestinal digestion and/or nutrient absorption. Comparing different intravenous administration sites, such as peripheral vs. hepatic portal injection, could indicate the relative importance of the liver as a site of action.

The efficacy of antidiabetic plant materials can vary with time; this is customarily investigated through a sequence of acute, subchronic, and chronic studies. The typical measures of glucose homeostasis to be undertaken usually include basal (fasting) or random blood/plasma glucose and insulin concentrations and oral (or intravenous or intraperitoneal) glucose tolerance tests. Although experimental protocols to investigate mode of action are beyond the scope of this chapter, it is relevant to note that measures of β-cell function (e.g., insulin secretion in response to a range of secretagogues), insulin action (e.g., whole-body glucose disposal), glucose handling by key gluco-regulatory tissues (e.g., muscle and liver), and intestinal glucose absorption are likely to yield valuable information.

An appreciation of the mode of action of an antidiabetic plant material indicates the types of diabetes against which the material is most likely to be effective. For example, plant materials that slow intestinal glucose absorption are most effective in the prandial and early postprandial periods and can be used as dietary adjuncts to all types of diabetes. Knowledge of the mode of action also indicates the risk of "over-lowering" blood glucose. Substances that stimulate insulin secretion at low glucose concentrations, strongly inhibit hepatic glucose output, or block counter-regulatory mechanisms to raise blood glucose can induce overt hypoglycemia and are often referred to as "hypoglycemic." Substances that enhance or partially mimic insulin action or reduce intestinal glucose absorption are not likely to lower glucose to the extent of hypoglycemia and are considered to be "antihyperglycemic." Indicators of long-term glycemic control such as glycated hemoglobin and fructosamine have received relatively little use during chronic studies in animal models. Most studies of antidiabetic plants have preceded the availability of these assays for small sample volumes, and further standardization of the assays may be required for application to blood samples from animals.

CLINICAL EVALUATION OF ANTIDIABETIC PLANTS

Unlike conventional medicines, traditional plant therapies do not have an established procedure for clinical evaluation of efficacy and safety. Conventional agents follow a sequential process, starting with a new chemical entity (NCE) (Table 3.5). Preclinical stages involve animal studies to characterize biological properties and clinical potential. Application is then made for clinical testing as an investigational new drug (IND). Chemical tests start cautiously in healthy volunteers (phase 1), followed by small trials in patients (phase 2). If an agent is appropriately efficacious and uncomplicated, extensive trials are performed in larger groups of patients (phase 3). With satisfactory indices of efficacy and safety, a new drug application (NDA) is made to market the agent as a drug.

TABLE 3.5
Stages in the Development of a New Drug

Preclinical Stages
New chemical entity (NCE)
• Identification, extraction/synthesis, and patenting of compounds
• Screening for biological activity *in vitro* and *in vivo* in animals
• Preclinical development
• Pharmacology, mode of action, pharmacodynamics (activity, safety, tolerance), pharmacokinetics (bioavailability, distribution, metabolism, elimination), and toxicity in animals
Clinical Stages
Investigational new drug (IND) application: permission to begin clinical studies
Phase 1:
• First administration to small numbers of healthy human volunteers. Dose ranging, pharmacodynamics, pharmacokinetics and drug interactions
Phase 2:
• First trials in small numbers of patients. Dose ranging, efficacy, further pharmacodynamics and pharmacokinetics
Phase 3:
• Trials in larger numbers of patients. Multicenter trials, comparative trials with other treatments, efficacy, further pharmacodynamics
New drug application (NDA): permission to market as a drug
Phase 4:
• Use in medical practice. Further evaluation similar to phase 3, postmarketing surveillance, adverse drug reactions, use in special subgroups (e.g., elderly people)

Note: Bold type indicates the approval stages required by the U.S. Food and Drug Administration (FDA).

Data from all studies are critically assessed by the sponsor and regulatory authority; if approved for marketing, further studies and a period of extended scrutiny usually follow (phase 4).

If a discrete compound is isolated from a traditional plant treatment, it enters the conventional testing process described previously. However, unrefined extracts and whole-plant therapies that are already in use have seldom received detailed phase 1 through 4 clinical trials because their use predates current legislation. Many commercial antidiabetic plant therapies are made available as dietary adjuncts, supplements, or other "over the counter" (OTC) categories that do not carry specific medicinal claims. Herbal preparations can also be made privately by practitioners and patients outside conventional pharmaceutical legislation.

The requirements for evaluation of conventional medicines are described in detail by regulatory agencies such as the American Food and Drug Administration (FDA) (https://www.fda.gov) and the European Agency for the Evaluation of Medicinal Products (EMEA) (http://www.endora.org/emea.html). However, it is not entirely clear how to interpret these requirements for herbal preparations, although in principle all medicines should conform to the same general standards. In this regard, substantial variability exists between countries, and the EMEA is reviewing procedures for herbal medicinal products. New EMEA regulations for herbal medicinal products are scheduled for introduction in October 2005.

Most of the published clinical studies into the efficacy of antidiabetic plant materials have not been undertaken to comply with licensing requirements for registration purposes. They commonly involve unblinded protocols with small numbers of patients; the diabetic status is often poorly defined and many studies last for less than 6 months. The endpoints of these studies are typically standard measures of glycemic control, notably basal or random plasma glucose concentrations and an oral glucose tolerance test. The majority of studies predate the availability of glycated hemoglobin (HbA1c) or fructosamine as longer term indices of glycemic control. Relatively few

studies with plant extracts have measured insulin concentrations, and complex procedures to investigate mode of action such as the euglycemic–hyperinsulinemic clamp technique and the minimal-model intravenous glucose tolerance test have rarely been undertaken (Bergman et al. 1979; Ferrannini & DeFronzo 1997).

Phase 1 Trial Designs

Current concepts for the design and conduct of phase 1 and 2 studies of antidiabetic therapies are concisely explained by Bratty and Kelly (1997). Most clinical studies to assess the efficacy of traditional antidiabetic plants will not, by nature of their previous use, constitute first exposure in humans (equivalent to phase 1). However, newly isolated principles that have shown antidiabetic activity in preclinical studies and been granted IND status will be treated as first exposure in humans.

An initial dose-ranging study is required, probably using an acute single-dose design starting at about 1/100 of the no-effect dose in the most sensitive animal species studied during preclinical experimentation. The duration of repeat-dose studies with slowly acting agents and the parameters to be monitored are subject to clinical discretion, but blood glucose will be closely followed, together with vital signs and standard blood chemistry. Stepwise dose escalation studies are then undertaken, and it is often practical to measure pharmacokinetics at the same time. It must be appreciated that antidiabetic principles do not necessarily show basal blood glucose-lowering activity in normal (nondiabetic) individuals and may not show a significant effect on a glucose tolerance test or meal tolerance test. Therefore, higher doses are best examined on one or two patients before proceeding to larger groups, and other pharmacodynamic parameters may be more instructive for determination of the upper dose level.

Phase 2 Trial Designs

Small studies to test and quantify efficacy (similar to phase 2) are preferably double blinded or at least single blinded, provided a dose range has been established. It is often difficult to blind the use of materials with a distinctive taste or smell, and patients who participate in studies with raw plants and unrefined extracts are often already familiar with the material under investigation. Recruitment to initial trials of this nature is customarily restricted to type 2 patients, although adjunctive (but not alternative) therapy with insulin can be studied in adults using different protocols. Diet-treated type 2 patients with unsatisfactory but stable glycemic control (e.g., HbA1c in the range 7.5 to 10%; fasting plasma glucose in the range 7.5 to 13 mmol/L) are usually included if they have no complications or other medical conditions. Normal liver, kidney, and heart function are important. When patients have previously received antidiabetic drug therapy, a short (e.g., 2 weeks) washout period may suffice, but this can create interpretation difficulties for chronic studies using HbA1c as an endpoint.

After a brief baseline (pretreatment) period, a randomized, blinded, placebo-controlled design is usually acceptable for acute and short-term studies. However, chronic studies may now be encouraged to adopt an active treatment arm as control using a recognized conventional agent because an extended period of poor control without active treatment is not considered acceptable. If possible, at least two doses of the test agent are included in the design (Figure 3.2). In chronic studies, the daily dosage will be titrated up at weekly (or, exceptionally, monthly) intervals in accordance with the level of glycemic control. This can be based on fasting plasma glucose and patient self-monitoring of blood glucose until a preset level of control (e.g., fasting plasma glucose < 6 mmol/L) is achieved.

In chronic studies, HbA1c is now the preferred endpoint measure of efficacy, although a selection of other indices of metabolic control can be included as endpoints, and endpoints other than HbA1c will be required for short-term studies. The most common parameters selected are 24-h glucose profile and tests of insulin secretion, insulin sensitivity, and glucose handling by muscle,

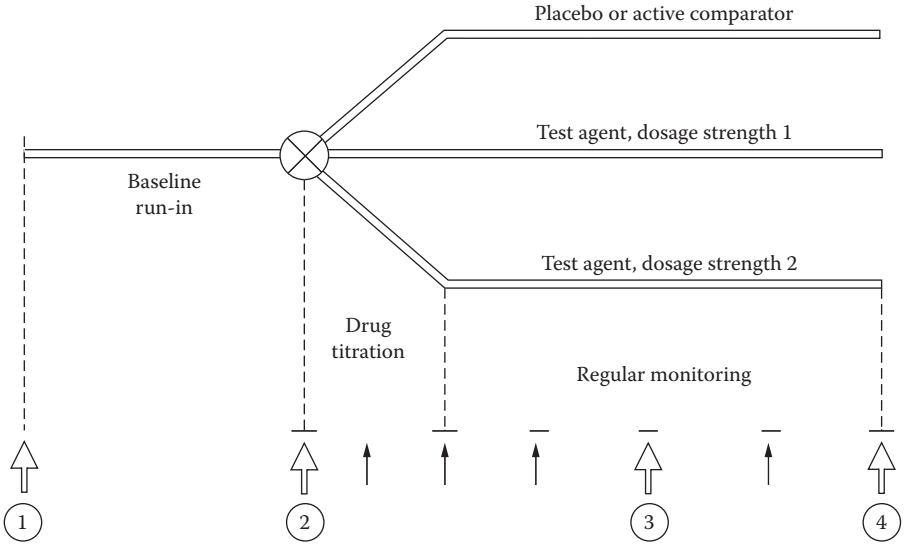

FIGURE 3.2 Minimalistic design for a clinical trial to assess the efficacy and adverse events of a potential antidiabetic material. Large arrow = main assessment; small arrow = other assessment; 1 = recruitment assessment; 2 = randomization assessment; 3 = intermediate assessment; 4 = endpoint assessment.

liver, and fat. A comprehensive review of these procedures is beyond the scope of this chapter, so the reader is directed to other sources (Bratty & Kelly 1997; Ferranniini & DeFronzo 1997; Walker et al. 1997; Bergman et al. 1979).

Safety monitoring throughout all studies should be as thorough as possible. With plant materials and many plant chemicals (e.g., alkaloids, flavonoids, and glucosides) that feature frequently as putative antidiabetic agents, it is important to exclude adverse effects by measuring standard indices of liver and renal function (Longmore et al. 2001).

Phase 3 Trial Designs

Extensive trials equivalent to phase 3 regulatory trials have not been reported for raw antidiabetic plant materials or unrefined extracts. Isolated and chemically characterized compounds from plants and synthetic analogues investigated as potential new antidiabetic therapies would be expected to require the same phase 3 evaluation as that for conventional medicinal agents. However, in several situations, the design and management of large-scale trials would differ for individual natural chemicals, mixtures of these chemicals, or unrefined plant materials.

One such situation would be that in which the proposed usage is not primarily based on a medicinal claim and use will be recommended in quantities that are not exceptionally beyond those anticipated during normal dietary consumption of the material. Here, the requirements for OTC products are applicable, and definitive evidence of medicinal benefit is not necessarily required. Dietary supplement status would be a potential positioning of such material. Nevertheless, some evidence of efficacy commensurate with the claims made on the packaging should be incumbent upon the sponsor, and satisfactory evidence of safety should be established. Large-scale trials to provide this information are difficult to organize in a blinded manner with unrefined materials, as discussed for phase 2 trials. The boundaries between a natural health product and a medicine are often unclear. Categorization is somewhat arbitrary and may reflect the claims made on the packaging and the recommended dosage rather than the testing procedure and the evidence base.

For compounds evaluated in phase 3 trials, the sponsors and the recruited patients should comply with revised versions of the 1964 Declaration of Helsinki or appropriate alternatives

(Stockhausen 2000). All trials should also comply with local ethical committee requirements and other criteria defined by regulatory agencies (see http://www.fda.gov and http://www.endora.org/emea.html). The preferred design and organization of trials for regulatory purposes can vary between agencies, and consultation with the agency is always advisable. The principles underlying phase 3 trials are essentially the same as those for phase 2, but involve larger numbers of patients to reflect the target populations for the agent and the manner in which it would be used for normal medicinal purposes.

For antidiabetic agents, trials are likely to last 4 to 12 months (6 months is frequently chosen) and power calculations will be used to determine numbers required based on the predefined endpoints. Type 2 diabetic patients recruited for these trials are customarily inadequately controlled by diet alone and without significant complications. Subgroups comprising patients with particular characteristics (e.g., young or elderly patients and patients with clearly defined accompanying conditions such as hepatic or renal insufficiency) may be included with appropriate clinical discretion. Thorough baseline evaluation is essential. A typical trial will be fully randomized, double blinded, and placebo controlled, or it will include arms with conventional comparator agents (the latter is increasingly preferred given the known risks of poor glycemic control).

Most large trials are multicenter and often multinational and therefore dictate a detailed unambiguous protocol with predetermined instructions for all reasonably anticipated events. Independent safety monitoring is usually included in these trials. It is usually cost effective to include more than one dosage form of the test agent, although most designs will titrate up the dosage until a particular level of glycemic control is achieved (e.g., fasting plasma glucose < 6 mmol/L). Because diabetic patients are often receiving other medications, it is important to minimize and keep full account of changes to any medications and intercurrent conditions that could influence diabetic control.

Frequent monitoring of glycemic control and other indices of metabolic status (e.g., plasma lipids) and standard clinical parameters are customarily incorporated into phase 3 trials. Patient self-monitoring of blood glucose is valuable for drug titration, and laboratory measurements of fasting plasma glucose and HbA1c are used for main assessments. The primary endpoint is usually based on HbA1c, with supplementary information from a glucose tolerance test or meal tolerance test. Secondary endpoints will include other metabolic indices and standard clinical parameters, many of which are routinely required by the regulatory agencies. Comprehensive recordings of adverse events will include symptoms of hypoglycemia.

To finalize the labeling and gain approval for marketing, the risk–benefit analysis must be favorable for the patient groups involved. This is interpreted in somewhat different ways by different agencies, but the underlying principles are consistent. For an antidiabetic agent in which long-term use is envisaged, safety is paramount. Efficacy of the new agent is preferably better than or comparable to existing agents. If a new agent offers a novel mode of action or other benefits that can be used to advantage when existing agents are contraindicated or no longer effective, efficacy may be interpreted more liberally. Likewise, it is advantageous if a new agent can be used in an additive capacity with existing agents.

Trials that recruit patients already receiving active oral therapy may incorporate a prior washout period, although this creates the same problems of interpretation discussed for phase 2 trials. Alternatively, patients can be switched to the test agent and/or receive the test agent as additive therapy while the placebo arm continues to receive the original therapy alone. Trials with insulin-treated patients raise special difficulties. Very rigorous glucose monitoring is essential. Introduction and titration of the test agent may require adjustment to the insulin dosage, which can be used as a measure of efficacy. More detailed consideration of these types of trials is beyond the scope of this chapter.

ETHICAL ISSUES

Recent decades have seen a resurgence of interest in traditional plant treatments in general and an obsession with so-called evidence-based medicine. Applying the latter to the former creates some interesting potential ethical controversies. By custom and practice, traditional herbal medicines have not received the same rigorous scrutiny for efficacy and safety demanded of conventional medicines. Moreover, in most countries, traditional practitioners receive training and carry responsibilities different from those for practitioners of conventional medicine, and restrictions on the availability of herbal and conventional medicinal products are different (Watt & Wood 1988).

Most conventional medicines have a recognized literature of scientific and clinical studies, a national or international approvals procedure for registration and accepted prescribing indication, quality control over the formulation, and a system for safety monitoring. In contrast, the use of traditional plant treatments relies strongly on anecdotal and folklore accounts, few such treatments are officially approved or registered, prescribing indications are often highly subjective, product quality is difficult to substantiate, and *ad hoc* unsupervised use can compromise safety awareness. Despite these limitations, the accumulated wisdom and experience gained from centuries of use have refined the preparation and application of many traditional plant medicines and identified clinical signs and symptoms for indication and safety precautions to be respected (British Herbal Medicine Association, 1979).

Deprived settlements, particularly in rural communities of many developing countries, rely on traditional herbal medicines as the main (and sometimes the only) source of medication, and humanitarian issues take precedence (Ajgaonkar 1979; Farnsworth & Segelman 1971). Indeed, about half of the world's population uses mainly traditional medicines. When traditional and conventional medicines coexist, and can be afforded by the patient, the type of practitioner selected will largely determine the type of medicine. Whether traditional plant treatments of unproven efficacy should be used in preference to conventional treatments of known efficacy remains a dilemma for the patient. In principle, it should be incumbent upon the practitioner to give adequate and balanced information, although it is doubtful whether either type of practitioner would have a sufficiently diverse knowledge base (Watt & Wood, 1988).

Inevitably, some patients will consult with conventional and "alternative" practitioners and may take conventional and traditional medicines at the same time. Moreover, because traditional medicines are often taken without consultation, it should be appreciated that interactions between these medicines can occur. For example, the blood glucose-lowering effects of *Momordica charantia* (karela) are additive to that of sulphonylureas (Aslam & Stockley 1979) and can precipitate episodes of hypoglycemia. Some plants still carry a mystique that may owe more to reputation and placebo effect than medicinal benefit. Thus, practitioners must take care to avoid patient preference overriding clinical judgment. When a patient is severely hyperglycemic and unresponsive to any single or combined oral therapies — conventional or traditional — the probable need for insulin therapy should not be overlooked or avoided. Poor glycemic control hastens the onset and aggravates the severity of diabetic complications (Stratton et al. 2000).

Detailed evaluation of the effectiveness and mode of action of antidiabetic plant therapies is given in other chapters. Direct clinical comparisons (head-to-head trials) of conventional and traditional antidiabetic therapies have not been reported, leaving comparative estimates of efficacy tentative and open to conjecture (Bailey & Day 1989; Day 1998). In addition to their use in the treatment of diabetes, herbal therapies may also be used as adjuncts to conventional therapy to relieve ancillary symptoms; for example, the calming reputation of chamomile tea might assist an anxious patient (Konig et al. 1998).

Because some herbal practitioners do not reveal the components of their medicines, it is not possible to make an objective assessment of potential safety hazards. Fungi such as *Amanita phalloides* are hepatoxic (Kronberger 1964) and aqueous extracts of some antidiabetic *Momordica*

species have been reported to cause hepatic portal inflammation and testicular lesions (Dixit et al. 1978).

With regard to intellectual property rights, it could be argued that herbal medical information, whether derived from native peoples or herbal practitioners, could be worthy of patentable status if it can be justified by appropriate criteria. Usage of rare traditional plants might create ecological problems and encourage use of already endangered species. Indeed, as natural habitats disappear and communities adopt new ways of life, knowledge of traditional medicines is more likely to be lost (Day & Bailey 1988).

CONCLUSION

At present, the rigorous procedures for evaluation of conventional antidiabetic medicines have rarely been applied to the testing of raw plant materials and the unrefined principles used as traditional treatments for diabetes. The same general preclinical and clinical approaches have been applied to the investigation of antidiabetic plant materials, but the less intensive evaluation of plant medicines precludes accurate comparison between conventional and traditional antidiabetic therapies.

REFERENCES

Ajgaonkar SS (1970). Herbal drugs in the treatment of diabetes. *Int Fed Bull* 23: 10–17.

Aslam M and Stockley IH (1979). Interaction between curry ingredient (karela) and drug chlorpropamide. *Lancet* i: 607.

Bailey CJ and Day C (1989). Traditional plant medicines as treatments for diabetes. *Diabetes Care* 12: 553–564.

Bailey CJ and Flatt PR (1990). Models for testing new hypoglycemic drugs. In Bailey CJ, Flatt PR (Eds), *New Antidiabetic Drugs*, London, Smith–Gordon, 65–82.

Bailey CJ and Flatt PR (2003). Animal syndromes of non-insulin-dependent diabetes mellitus. In Pickup JC, Williams G (Eds), *Textbook of Diabetes*, 3rd ed, Oxford, Blackwell Science, 25.1–25.30.

Bergman RN, Ider YZ, Bourden CR and Cobelli C (1979). Quantitative estimation of insulin sensitivity. *Am J Physiol* 236: E667–E677.

Bratty JR and Kelly F (1997). Development of antidiabetic therapy, phases I and II. In O'Grady J, Joubert PH (Eds), *Handbook of Phase I/II Clinical Drug Trials*, Boca Raton, FL, CRC Press, 475–481.

Brindley DN and Russell TC (2002). Animal models of insulin resistance and cardiovascular disease: some therapeutic approaches using the JCR:LA-cp rat. *Diabetes Obesity Metab* 4: 1–10.

British Herbal Medicine Association (1979). *British Herbal Pharmacopoeia*. Keighley, U.K., British Herbal Medicine Association.

Cooperstein SJ and Watkins D (1981). Action of toxic drugs on islet cells. In Cooperstein SJ, Watkins D (Eds), *The Islets of Langerhans*, New York, Academic Press, 387–425.

Day C (1998). Traditional plant treatments for diabetes mellitus: pharmaceutical foods. *Br J Nutr* 80: 5–6.

Day C (2000). Traditional plant treatments for diabetes mellitus. *Acta Chim Therap* 26: 131–150.

Day C and Bailey CJ (1988). Hypoglycemic agents from traditional plant treatments for diabetes. *Int Ind Biotechnol* 8: 5–9.

Dixit VP, Khanna P and Bhargava SK (1978) Effects of *Momordica charantia* fruit extract on the testicular function of dog. *Planta Med* 34: 280–286.

Farnsworth NR and Segelman AB (1971). Hypoglycaemic plants. *Tile Till* 57: 53–55.

Ferrannini E and DeFronzo RA (1997). Insulin actions *in vivo*: glucose metabolism. In Alberti KGMM, Zimmet P, DeFronzo RA, Keen H (Eds), *International Textbook of Diabetes Mellitus*, 2nd ed, John Wiley, Chichester, 505–530.

Isoma B, Almgren P, Tuomi T and Groop L (2001). Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24: 683–689.

Konig GM, Wright AD, Keller WJ, Judd RL, Bates S and Day C (1998). Hypoglycemic activity of an HMG-containing flavonoid glucoside, chamaemoloside, form *Chamaemelum nobile*. *Planta Med* 64: 612–614.

Kronberger K (1964). Pilze und diabetes. *Ber Naturwiss Ges Bayreuth* 11: 231–235.

Lally F and Bone AJ (2003). Animal models of type 1 diabetes. In Pickup JC, Williams G (Eds), *Textbook of Diabetes*, 3rd ed, Oxford, Blackwell Science, 19.1–19.17.

Lenzen S, Tiedge M, Elsne M, Lortz S, Weiss H, Jorns A, Kloppel G, Wedekind D, Prokop CM and Hedrich HJ (2001). The LEW.1AR1/Ztm.iddm rat: a new model of spontaneous insulin-dependent diabetes mellitus. *Diabetologia* 44: 1189–1196.

Longmore M, Wilkinson I and Torok E (2001). *Oxford Handbook of Clinical Medicine*, 5th ed, Oxford University Press, Oxford, 857 pp.

Patti ME and Kahn CR (1997). Transgenic animal models: insights into the pathophysiology of NIDDM. *Diabetes Rev* 5: 149–164.

Shafrir E (1992). Animal models of non-insulin-dependent diabetes. *Diabetes Metab Rev* 8: 179–208.

Stockhausen K (2000). The declaration of Helsinki: revising ethical research guidelines for the 21st century. *Med J Austral* 172: 252–253.

Stratton IM, Adler IA, Andrew H, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC and Holman RR, on behalf of the UK prospective Diabetes Study (2000). Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Br Med J* 321: 405–412.

Swanston–Flatt SK, Day C, Bailey CJ and Flatt PR (1990a). Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. *Diabetologia* 33: 462–464.

Swanston–Flatt SK, Day C, Flatt PR and Bailey CJ, (1990b). Evaluation of the antihyperglycaemic properties of traditional plant treatments for diabetes in streptozotocin-diabetic and *db*/*d*b mice. In Shafir E (Ed), *Frontiers in Diabetes Research. Lessons from Animal Diabetes III*, London, Smith–Gordon, 286–293.

Walker M, Fulcher GR and Alberti KGMM (1997). The assessment of insulin action *in vivo*. In Alberti KGMM, Zimmet P, DeFronzo RA, Keen H (Eds), *International Textbook of Diabetes Mellitus*, 2nd ed, John Wiley, Chichester, 595–610.

Watt J and Wood C (Eds) (1998). *Talking Health: Conventional and Complementary Approaches*, London, Royal Society of Medicine.

4 *In Vitro* Models for Assessing Antidiabetic Activity

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CONTENTS

INTRODUCTION

Antidiabetic effects of plants can be assessed clinically in humans, *in vivo* using animal models or *in vitro* using a variety of test systems. Each level of testing has its advantages and limitations. Human studies are ultimately necessary because the product is tested by the intended route in the eventual beneficiary of an effective treatment. However, in many cases it is neither feasible nor ethical to conduct initial trials in humans because little is known about the safety or efficacy of the herb or even of a suitable dose or method of preparation. It is therefore appropriate to conduct studies in animals prior to administering the herb to humans.

Preliminary testing of a herb in an animal model can give valuable information on the type of extract to be made, a suitable dose, likely toxic effects, and, of course, efficacy. This information can then be translated to human studies, although species differences and ethical considerations may be limiting factors. Animal and human studies are essential to determine the ultimate safety and efficacy of a herb or its components when used clinically. However, they provide limited information on the mechanism of action of a particular therapeutic agent. Methods for studying antidiabetic herbs in clinical and preclinical animal models are described in Chapter 3 of this book.

In vitro tests can play an important role in the evaluation of antidiabetic or other medicinal plants, as initial screening tools or as follow-up to human or animal studies. Biological material used in these includes, in increasing order of simplicity, perfused whole organs, isolated tissues,

cells in primary or immortal culture, subcellular membranes or purified receptors, and enzymes. *In vitro* assays are typically based on a specific biological process relevant to the disease and its treatment. The advantages of *in vitro* assays in ethnobotanical research and general drug discovery programs are as follows:

- Mechanism of action — *in vitro* models are based on a fairly specific process — e.g., activity of a particular enzyme, binding to a particular receptor, or effects on a particular metabolic reaction within a given cell type or organ. They are of considerable value in identifying the mechanism of action of a therapeutic agent.
- Amount of material needed — *in vitro* tests require far less test material than clinical and animal studies do. This is of particular relevance to natural products, which may be hard to obtain for reasons of conservation or low abundance.
- Lower cost — in the vast majority of cases, *in vitro* assays are more economical (per sample tested) than tests using animals or humans as subjects.
- Reduced use of animals — *in vitro* tests provide an alternative to animal testing for many aspects of an investigation. Organs or tissues derived from one or a few animals can be used to test many replicates or many samples, whereas for *in vivo* studies, several individual animals would be required per sample or dose. Immortalized cell lines, although originally derived from animals or humans, do away completely with the repeated need for animal tissue in assays.
- Reduced variability — cells from a single cell line or tissues derived from one animal have the advantage of genetic homogeneity, resulting in minimum inherent variability. Thus, comparison of data between treatments or with control conditions is less complex than using animal or human subjects in which genotypic or phenotypic variations between individuals can complicate the interpretation of results and increase the number of replicates required.
- Automation and fast throughput — *in vitro* assays can be adapted to rapid or high-throughput formats using automation for liquid handling and end-point measurements. This makes them essential to high-throughput screening programs such as those employed by drug discovery programs in the pharmaceutical industry and academia.
- Bioassay-guided fractionation of plant extracts — there is a dearth of information on the active components of many plant materials known to be useful for diabetes. This is largely due to practical difficulties and high cost of coupling the fractionation of an active extract to biological testing using an animal model — often the first model in which activity was seen. *In vitro* assays, by virtue of their more rapid output, lower cost, and need for less material, are an ideal means of following the active components during a fractionation process. The end result is one or more components with defined biological activity. These components may then be isolated in larger quantities and tested *in vivo* to confirm their effects.

In vitro tests do, however, have several limitations that must be considered when interpreting data. These issues are particularly important in the context of their use with plant extracts, which are complex mixtures of chemicals:

- Narrow mechanism — mechanism-based *in vitro* tests can be useful when screening samples to detect agents with a specific biological activity. However, they are less useful when trying to determine whether a particular plant extract is useful for a certain disease. The plant may be an effective treatment, but work by a different mechanism from that represented in the assay; an antidiabetic plant could work by one of a number of useful mechanisms (see later). Indeed, the heterogeneous nature of plant material may result in a variety of effects relevant to the disease as observed for fenugreek (Al-Habori and

Raman, 1998) and *Momordica charantia* (Raman and Lau, 1996). This would be missed using a bioassay based on a single mechanism. A plant's efficacy in diabetes, or lack of it, cannot therefore be determined by a single *in vitro* assay.

- Bioavailability — *in vitro* tests take no account of the bioavailability of the test materials. A substance may have an effect when added directly to the *in vitro* test system, but if given orally to humans or animals, it may not be absorbed into the blood stream or it may be rapidly degraded by first-pass hepatic metabolism. There is also no guarantee that it will reach its ultimate site of action in the cell at an effective concentration. An *in vitro* "hit" may therefore be irrelevant *in vivo*.
- Metabolism — samples used in *in vitro* tests do not undergo any metabolism (unless metabolized by the test tissue), whereas the components of a herbal remedy may well undergo metabolism in the body. The activity of a traditional herb may be due to metabolites formed *in vivo* rather than compounds originally present in the plant extract. Active compounds of this sort would be missed *in vitro* but not *in vivo*.
- Effective concentration — a compound may be seen to be effective at a particular concentration range *in vitro*. However, it is important to consider how relevant that concentration is to the *in vivo* situation.
- Artifacts —a number of naturally occurring substances can interfere with *in vitro* tests, giving false positives or negatives. Polyphenolics are ubiquitous in nature and found in many plant extracts. They have a tendency to bind protein and this can result in nonspecific biological effects *in vitro* that can mask the activity or inactivity of the other compounds present. Saponins can disrupt cell membranes, causing cell death or leaking of constituents. This should be considered in cell-based assays, e.g., those involving insulin secretion from cells. Plant extracts can contain significant amounts of glucose and other monosaccharides, which could interfere with assays involving measurements of glucose uptake, metabolism, or release by digestion. Means of detecting, removing, and accounting for these interfering compounds are discussed in the section on "practical considerations."

RATIONALE BEHIND THE *IN VITRO* MODELS USED IN DIABETES RESEARCH

A range of *in vitro* models is available to study potential antidiabetic activity in plant extracts. They are based on the primary need to control hyperglycemia in diabetes and the various means of achieving this goal. *In vitro* models may be used to screen randomly or ethnobotanically selected materials for a specific activity that would result in the lowering of blood glucose levels. Alternatively, the models may be used to determine the mechanism of action of a plant extract with traditional use and/or human or *in vivo* data to support an antidiabetic effect.

It is relevant, in the context of *in vitro* tests for antidiabetic activity, to examine the source and fate of glucose in the body in the normal and diabetic states. Glucose is derived primarily from the digestion of dietary carbohydrates in the gastrointestinal tract, from which it is absorbed into the blood by passive and active mechanisms. In the fed state, a rise in blood glucose normally stimulates insulin secretion from the pancreas. This hormone initiates glucose uptake into specific target tissues, primarily liver, muscle, and fat cells (adipocytes). It promotes glucose oxidation and glycogen deposition in liver and muscle and the incorporation of glucose (as glycerol) into triglycerides in adipocytes. These combined activities have the effect of lowering elevated plasma glucose resulting from the intake of a meal. In the fasted state, glucose and insulin levels decrease. Glucose is then mobilized from glycogen stores in the liver (glycogenolysis).

Another important source of glucose in the fasted state is gluconeogenesis — the *de novo* formation of glucose from smaller, nonsugar, precursor molecules. This occurs in the liver and, to

a lesser extent, kidneys and is under the control of glucagon, a counter-hormone whose levels rise as those of insulin fall, and vice versa. When glucagon levels are high and those of insulin are low, gluconeogenesis and glycogenolysis are stimulated and glucose enters the bloodstream.

In diabetes, insulin is absent (type I diabetes) or insufficient (type II diabetes). In type II diabetes, insulin target tissues are generally less responsive to insulin (insulin resistant) than normal. The fine balance between glucose uptake into target organs and release of hepatic glucose is impaired, resulting in abnormally high fasting glucose levels as well as poor glucose tolerance following a meal.

From the foregoing, the following mechanisms have been proposed for an agent that would lower or control plasma glucose levels:

- Inhibition of carbohydrate-digesting enzymes, reducing the amount or rate of glucose release from the diet
- Impairment of glucose uptake from the small intestine
- Stimulation of insulin secretion from β-cells of the pancreas
- Insulinomimetic or insulin-sensitizing activity at insulin target tissues, i.e., liver, skeletal muscle, or adipocytes
- Antagonism of glucagon activity

Further discussion and examples of studies using the preceding models follow in the next section of this chapter. The reader is also directed to a review by Verspohl (2002) that summarizes numerous *in vivo* and *in vitro* test methods for the evaluation of antidiabetic activity.

MODELS TO STUDY INHIBITION OF CARBOHYDRATE-DIGESTING ENZYMES

The main sources of glucose in the human diet are the polysaccharide starch and the disaccharides sucrose and lactose. Starch in meals is initially broken down to oligosaccharides by the enzyme α-amylase present in saliva and pancreatic juice. The pancreatic form released into the small intestine is several times more powerful than the salivary enzyme, and contact with these enzymes results in almost total conversion of starch to the disaccharide maltose and other very small glucose oligomers before it leaves the duodenum (Guyton and Hall, 2000). Alpha-glucosidase is a collective term referring to membrane-bound enzymes of the small intestinal villi involved in the breakdown of α-linkages of oligosaccharides and disaccharides into glucose. These enzymes include maltase, isomaltase, sucrase, lactase, trehalase, and α-dextrinase.

The final products of carbohydrate digestion are the monosaccharides glucose, fructose, and galactose. Normally, monosaccharides released by digestion are rapidly absorbed in the first half of the small intestine. However, in the presence of the inhibitors, digestion occurs throughout the small intestine, resulting in slower absorption of monosaccharides and blunting of the postprandial glucose rise (Rhabasa–Lhoret and Chiasson, 2004). A search for compounds that can inhibit α-amylases or intestinal α-glucosidases is therefore regarded as one of the therapeutic approaches for developing novel antidiabetic agents. Acarbose is an example of a drug used in diabetic therapy that acts by this mechanism (Lebovitz, 1992).

Salivary and pancreatic α-amylases are available commercially; porcine pancreatic α-amylase is an economical source. Assay of enzyme activity involves incubating the enzyme with starch as substrate, resulting in the release of the reducing disaccharide maltose (Bernfeld, 1955). Maltose is quantified by addition of 3,5-dinitrosalicylic acid, which is reduced to 3-amino-5-nitrosalicylic acid, a reddish product detectable at 540 nm. Maltose is quantified by reference to a standard curve. In the presence of an α-amylase inhibitor, the amount of maltose released will be reduced. On a practical note, the natural presence of reducing sugars in plant extracts under investigation can

result in artificially high absorbance readings. Their contribution should be evaluated by including suitable controls (starch plus plant extract, but no enzyme). Methods may also be employed to remove these sugars prior to testing (see the section on practical considerations). Inhibition of α-amylase has been shown for extracts of the antidiabetic plants *Murraya koenigi*, *Cyperus rotundus* (Bawden et al., 2002, 2003), and *Phyllanthus amarus* (Ali et al., 2003). Two glucosides of leuteolin have been identified as α-amylase inhibitors in *Olea europaea* L (olive) leaves (Komaki et al., 2003).

The inhibitory effect of plant extracts on α-glucosidases is assessed *in vitro* by determining a decrease in the amount of glucose liberated from molecules of substrate after incubation with the enzyme. Glucose can be determined colorimetrically using the glucose oxidase method (Bergmeyer and Bernt, 1963). Alpha-glucosidase enzyme used in these studies can be prepared from rat small intestine brush border membrane (Kessler et al., 1978). Rat intestinal acetone powder is also available commercially and α-glucosidases can be partially purified and used in free solution or immobilized onto a gel support to mimic their membrane-bound state *in vivo* (Oki et al., 2000). For faster analysis, a continuous method for enzyme assay has been developed (Matsumoto et al., 2003) in which immobilized α-glucosidase is coupled on-line to an immobilized glucose oxidase reactor using a multichannel stopped flow system.

The choice of substrate applied depends on the enzyme of interest; if the activity of sucrase is to be determined, sucrose will be used as the substrate, whereas maltose and isomaltose would be used to determine maltase and isomaltase respectively. Alternatively, a pseudodisaccharide, p-nitrophenyl-α-D-glucopyranoside, can be used and the amount of p-nitrophenol released measured at 400 nm (Matsui et al., 2001a, b). In this case, it is not possible to target a particular α-glucosidase.

Abesundara et al. (2004) describe the use of immobilized α-glucosidase to screen the inhibitory activity of various Sri Lankan plant extracts on maltase and sucrase. The methanol extract of *Cassia auriculata* was inhibitory to maltase *in vitro* and improved hyperglycemia following maltose administration to rats *in vivo*. Other studies have resulted in the isolation of a number of α-glucosidase inhibitors from traditional antidiabetic plants, including kotalanol from *Salacia reticulata* with a potent inhibitory effect on sucrase and maltase (Yoshikawa et al., 1998a), myrciacitrin, myciaphenone, myricitrin, desmanthin-I, and guaijaverin from *Myrcia multiflora* (Yoshikawa et al., 1998b). Others include 1-deoxynojirimycin, α-homonojirimycin, and 7-O-β-*D*-glucopyroanosyl-α-homonojirimycin from *Commelina communis* (Kim et al., 1999). Anthocyanins have also been reported to be inhibitors of α-glucosidase (Matsui et al., 2001a, b).

Matsui et al. (1996) have examined the inhibitory activity of various foodstuffs in order to identify those that might be useful for inclusion in a diabetic diet. *Salacia oblonga* extracts have been shown to contain the *in vitro* α-glucosidase inhibitors salacinol and kotalonol (Matsuda et al., 1998); a recent study in healthy adults (Heacock et al., 2005) showed significant reduction of postprandial plasma glucose, serum insulin and increased breath hydrogen after ingestion of 1000 mg of *Salacia oblonga* extract. The increase in breath hydrogen is attributable to a mechanism involving inhibition of α-glucosidase.

MODELS TO STUDY INHIBITION OF INTESTINAL GLUCOSE UPTAKE

Models developed for studying intestinal absorption can be arranged into two main groups: models prepared from whole small intestine and those prepared from isolated cells or cellular components.

Everted segments or everted sacs are simplified systems regularly used for studying intestinal absorption. These are prepared from whole small intestine everted onto a glass rod with the mucosal (inner) surface in the bathing solution. The substance whose absorption is to be studied is added to the bathing solution along with potential modifiers of absorption (Wood and Lawrence, 1991). The amount absorbed into the sacs is quantified by means of radiolabeled substrate, colorimetric methods, or high-performance liquid chromatography. The inverted gut has been used to study the

effect of antidiabetic plant extracts (e.g., *Momordica charantia*) on intestinal glucose absorption (Meir and Yaniv, 1985). Perl and Hikino (1989) used the model to study the effect of a number of plant-derived glycans, including ganoderan A and B, aconitan A, and lithosperman A. Glucose-evoked transmural potential difference, rather than glucose concentrations per se, has been used to study inhibition of glucose transport into everted ileal fragments by extracts of *Gymnema inodorum* (Shimizu et al., 2001) and *Gymnema sylvestre* (Yoshikawa et al., 1997).

The major drawback of the everted gut model is related to the short-term viability (maximum viability 3 hours) of the tissues (Wood and Lawrence, 1991). Additionally, this system alone cannot provide conclusive information on the mechanism by which absorption is reduced. Gallagher et al. (2003) describe a simple model measuring glucose diffusion through a semipermeable membrane to investigate mechanical effects of plant extracts on glucose absorption. However, more complex biological systems (i.e., isolated membrane preparations from enterocytes) have been developed to study mechanisms of absorption at the glucose transporter level. These models include brush border membrane vesicles (BBMV) prepared from apical membrane and vesicles prepared from basolateral membrane (BLMV). Knowledge of intestinal amino-acid and sugar transport have greatly expanded owing to these models (Audus et al., 1990).

Glucose transport into BBMV is by the sodium-dependent glucose transporter (SGLT1), whereas that into BLMV is due to GLUT 2 transporters (Thorens, 1996). Evidence from rat models suggests that expression of both of these transporters is raised in the diabetic state (Fedorak et al., 1987, 1991; Burant et al., 1994). Effects on these two transport systems can be studied separately and uncomplicated by glucose metabolism using these vesicles. Vesicles are incubated with ^{3}H-D-glucose and are rapid filtered through a cellulose acetate/nitrate membrane after set time intervals over a period of about 1 minute. The vesicles are retained on the filter and glucose transported into them can be quantified by counting the radioactivity. The time points are used to construct a glucose uptake profile and the inhibition at peak uptake can be measured (Vedavanam et al., 1999).

The BBMV model has been used to study the effects on intestinal glucose absorption of fenugreek extracts (Al-Habori et al., 2001), extracts of *Momordica charantia* (Lau et al., 1996), and soya phytochemical extract (Vedavanam et al., 1999) and for general screening of plant extracts (Srijayanta et al., 1998). Green tea polyphenols have also been shown to inhibit SGLT1 in BBMV (Kobayashi et al., 2000).

Over the last two decades, techniques to culture mature enterocyte monolayers as cell culture models for drug absorption have been extensively developed in an attempt to overcome the problems of rapid degradation of animal tissues and the variations due to differences between species and animals that usually occur when intestinal tissues and isolated membrane preparations are used. However, the attempt has met with little success (Hilgers et al., 1990). It has been reported that, when intestinal epithelial cells were cultured as a monolayer, they underwent transformation to a cell type different from the initial cells (Audus et al., 1990).

To date, the use of cell monolayers in intestinal absorption studies has exploited cells derived from human colon carcinoma cells (e.g., Caco-2, HT-29, SW 116, LS 174T, SW 480) (Audus et al., 1990). Among these, the Caco-2 cell line established by Fogh et al. (1977) is the most widely used for intestinal transport and function studies (Artursson, 1990; Hilgers et al., 1990). Despite its colonic origin, Caco-2 cells have been reported to undergo spontaneous enterocytic differentiation in culture (Audus et al., 1990). The cells have been reported to have morphological (polarized and columnar cells and the presence of microvilli) and biochemical properties (the distribution of brush border enzymes) that are much more intestinal than colonic (Hilgers et al., 1990). Caco-2 cells have been used to study the transport of various substances, including natural products such as flavonoids (Li et al., 2003). In the field of antidiabetic plants, the cells were used to investigate the effects of galegine isolated from *Galega officinalis* (Neef et al., 1996) and baicalein, a flavone from *Scutellaria baicalensis* (Nishioka et al., 1998), on intestinal glucose absorption.

HT-29 cells that also originate from colon cell lines have been reported to have a lower degree of enterocytic differentiation compared to Caco-2 cells (Audus et al., 1990). However, HT-29-H

cells, a subclone of HT-29 (Phillips et al., 1988), can secrete mucin molecules and produce a mucus gel layer similar to that present on the human intestinal epithelium. This layer is thought to be a rate-limiting barrier to absorption of molecules across the intestine (Wikman et al., 1993) and absorption studies using these cells may therefore be closer to the *in vivo* situation.

MODELS TO STUDY INSULIN SECRETION FROM β-CELLS OF THE PANCREAS

A number of *in vitro* models have been developed for studying the pancreatic secretion of insulin. These include the perfused pancreas, intact isolated islets, purified β-cells, and insulin-secreting cell lines. Insulin released is measured by radioimmunoassay (using ^{125}I-labeled insulin) or enzyme-linked immunoassay (Ruitton–Uglienco, 1981). Perfused pancreas, isolated islets, and purified β-cells are all prepared from freshly sacrificed animals (usually rats or mice). Isolation of the islets of Langerhans involves collagenase digestion and purification from exocrine tissues. Islet isolation from rodents yields a maximum of several hundreds of islets (Poitout et al., 1996). The following are examples of studies in the area of natural products that have employed the use of isolated islets.

Farzami et al. (2003) examined the insulin secretagogue activity of *Urtica dioica* leaf extract in perifused islets of Langerhans. Using static incubations, pancreatic islets isolated from rats were used by Suzuki and Hikino (1989a) to study the effects of panaxan B, a glycan from *Panax ginseng*, on insulin secretion. Ahmad et al. (1991a, b) used islets prepared from rats to study the effects of *Pterocarpus marsupium* extract and constituents on insulin secretion and the accumulated level of cAMP. Rat islets were used in a study by Hii and Howell (1984, 1985) to study the effects of catechin, chrysin, epicatechin, naringenin, and quercetin on Ca^{2+} handling in these cells — an effect related to insulin secretion.

Although a significant number of islets can be obtained from large-animal pancreata, isolation and purfication techniques are time consuming and require experienced staff (Poitout et al., 1996). The techniques to purify primary β-cells are equally complicated and require special techniques such as fluorescence-activated cells sorting to differentiate between β-cells and other cells of the islets of Langerhans (Poitout et al., 1996). In addition, primary β-cells do not proliferate in culture and are difficult to maintain for a long period of time without special techniques. These factors limit the use of intact islets or primary β-cells in rapid throughput experiments.

A number of insulin-secreting cell lines has been developed in an attempt to establish cell lines that retain the characteristic features of β-cells. The cell lines are transformed using different techniques such as irradiation, viral tranformation, and transgenic technology (Poitout et al., 1996). They may therefore be different from primary β-cells in terms of their behavior and responsiveness to insulin secretagogues (for a review, see Poitout et al., 1996; Persaud, 1999). The most widely used β-cell lines are RINm5F, HIT-T15, βTC, MIN6, INS-1, and BRIN-BD11 cells (Poitout et al., 1996). Their application in the natural products area is increasing. The advantage of cell lines is that they can be used in rapid-throughput experiments and are much less labor intensive and conservative of resources than the use of isolated islets. This therefore minimizes the number of animals used in an experiment. However, because these cells are a transformation of pancreatic β-cells, some characteristic features of β-cells may not be faithfully represented by the cell lines (Persaud, 1999).

Examples of studies include the use of HIT-TI5 cells to study the effect of *Tinospora crispa* extract on insulin secretion (Noor et al., 1989). BRIN-BD11 cells have been used in a number of studies; examples are investigations on the effect of *Coriandrum sativum* and *Viscum album* (Gray and Flatt, 1999a, b) and *Medicago sativum* (Gray and Flatt, 1997).

In measuring insulin secretion in any of the preceding models — islets or cell lines — two practical factors need to be considered. First, any increase in the permeability of cell membranes (e.g., by contact with saponins) will result in a release of insulin by nonspecific mechanisms. This

has been observed in studies testing *Gymnema sylvestre* extract in rat islets and several pancreatic cell lines (Persaud et al., 1999). It is important to examine for this effect when assessing insulin release data. Integrity of the cell membrane can be assessed by trypan blue uptake (only damaged cells take up the dye) as described in Persaud et al. (1999) or by measuring the release of lactate dehydrogenase (LDH), which only takes place from damaged cells (Srijayanta et al., 1999). The effect of the secretion inhibitor diazoxide can also be examined because it would be ineffective in cases of insulin release due to cell damage (e.g., see papers by Gray and Flatt).

Another factor to consider is that glucose, which can be present in polar plant extracts, can act as a stimulant to insulin secretion. It is important to remove glucose from extracts before testing them. This is discussed in more detail under the section on practical considerations. RINm5F cells, which are unresponsive to glucose but respond to glycerol as nutrient secretagogue (Persaud, 1999), may be useful for screening glucose-containing plant extracts.

Apart from measurement of insulin secretion per se, other properties related to diabetes may be measured. Rotshteyn and Zito (2004) have adapted the use of HIT-T15 cells to screen herbal extracts specifically for sulfonylurea-like activity. In their experiments, they isolated the microsomal cell membrane of HIT-T15 cells by ultracentrifugation and then carried out competitive binding studies with ^{3}H-glibenclamide (a sulfonylurea drug). Sitaswad et al. (2000) studied the effect of *Momordica charantia* juice on lipid peroxidation and intracellular DNA damage in isolated islets and RIN cells following treatment with streptozotocin *in vitro*.

MODELS BASED ON THE LIVER AS AN INSULIN TARGET TISSUE

The liver is a key organ in the control of plasma glucose levels (Kurukulasuriya et al., 2003). Insulin stimulates several activities in the liver that help to lower plasma glucose levels (Guyton and Hall, 1997), including glucose uptake by activating glucokinase enzyme, glucose breakdown by activating glycolytic enzymes, and glycogen synthesis by activating glycogen synthase. Concurrently, glycogenolysis and gluconeogenesis are inhibited. These processes occur under the influence of elevated insulin and depressed glucagon levels. In the fasted state, however, glucose for systemic use is released from the liver (but not muscle) by glycogenolysis and by hepatic and renal gluconeogenesis. This process is stimulated by low-insulin and high-glucagon levels.

From this, it is clear that insulinomimetics, insulin-sensitizing agents, and glucagon antagonists (see later) would be of therapeutic use against hyperglycemia in diabetes. Kurukulasuriya et al. (2003) have reviewed the enzymes involved in gluconeogenesis and glycogenolysis that could form suitable targets for antidiabetic drug therapy. These include glycogen phosphorylase, glycogen synthase kinase 3, glucose-6-phosphatase, fructose-1,6-bisphosphatase, and phosphoenolpyruvate carboxykinase (PEPCK). Glucokinase is an important insulin-sensitive enzyme that phosphorylates glucose as it enters the hepatocyte and produces glucose-6-phosphate, a substrate for glycogenesis and glycolysis.

The effect of natural products on insulin-sensitive processes can be measured using a number of *in vitro* hepatic models. Insulinomimetic and insulin-sensitizing activity can be distinguished by examining the effect of a test substance in the presence or absence of insulin and comparing its effects to that of insulin alone in the test model. Systems developed thus far mostly use tissues taken from rodents. These models are (Agius, 1987):

- Perfused liver
- Liver slices or homogenates
- Hepatocyte suspensions
- Hepatocyte monolayer cultures
- Hepatocytes in co-culture with epithelial cells
- Periportal and perivenous hepatocyte suspensions or cultures

The use of crude liver preparations such as slices or homogenates is always hampered by limitations of substrate and oxygen diffusion (Agius, 1987). The perfused liver is the system most closely representing physiological conditions. However, the use of perfused liver is limited by short-term viability and limited availability of tissues from a single preparation. Its use has therefore been replaced with isolated primary hepatocytes maintained in suspension or culture. In 1969, Berry and Friend (1969) developed techniques for isolation of high yields of viable parenchymal hepatocytes using a two-step collagenase perfusion method. Although these cells have been widely used over a number of years to study glucose handling, their disadvantage is that they are in a catabolic state of protein and glycogen turnover and have short-term viability (Agius, 1987). These developments led to the development of monolayer cultures of hepatocytes.

By means of suitable culturing as monolayers, isolated hepatocytes can recover from the catabolic state and can be maintained for several days for long-term studies. This system has been widely used in a number of studies on the extrapancreatic actions of antidiabetic drugs — e.g., gliquidone (Rinninger et al., 1984) and glyburide (Fleig et al., 1984) — and studies on the glycogen synthesis pathway (Newgard et al., 1983; Bismut and Plas, 1989). The drawback of monolayer culture of hepatocytes is that the cells tend gradually to lose some characteristic functions of the liver (e.g., loss of glycogen content, albumin production, gluconeogenesis, and ketogenesis) during culture.

The most frequently measured parameter of insulin's effects on the liver is glycogen synthesis. A number of methods have been developed to measure glycogen production in hepatocytes. These differ in terms of the techniques used to extract glycogen from the cells and the methods used to quantify the extracted glycogen. Cells are first solubilized or disrupted to release glycogen, using strong alkali (Good et al., 1933), perchloric acid (Salhanick et al., 1989), sonication (Vu et al., 1998), or freeze-thawing (Vu et al., 1998). Glycogen is then precipitated using 66% ethanol (Fleig et al., 1984; Solling and Esmann, 1975).

One method of quantifying the precipitated glycogen is to measure the amount of radiolabeled glucose incorporated from the original incubation medium. D-[U-^{14}C]-glucose can be used; however, if tritiated glucose is preferred, it is important that D-[3-^{3}H]glucose and not D-[6-^{3}H]glucose be used because the hydrogen in position 6 could be partially lost during conversion of glucose to glycogen by indirect pathways (Tosh et al., 1994). A colorimetric method can also be used to quantify glycogen in which glucose is liberated from glycogen using the enzyme α-amyloglucosidase (Plomp et al., 1990; Vu et al., 1998). The glucose liberated is measured using enzymes such as glucokinase/glucose-6-phosphate dehydrogenase (Fleig et al., 1985) or glucose oxidase (Bergmeyer and Bernt, 1963). Gomez–Lechon et al. (1996) have developed a method for measuring glycogen in 96-well plate cell cultures.

Rather than measuring hepatic glycogen, Al-Habori et al. (2001) measured the amount of glycogen phosphorylase-a activity in hepatocytes treated with fenugreek extracts. Post-treatment, the enzyme is released by cell lysis and incubated with ^{14}C-glucose-1-phosphate, and the amount of labeled glycogen formed is measured by precipitation on filter paper using aqueous ethanol. Valentova et al. (2004) have measured the effects of *Smallanthus sonchifolius* leaf extracts on gluconeogenesis and glycogenolysis in rat hepatocyte suspensions. For these two processes, primary hepatocytes were obtained from fasted and fed rats, respectively. Glucose released into the medium was measured using a glucose oxidase method following centrifugation of the suspension.

An alternative to the addition of test compounds to hepatocytes is to measure the activity of various relevant enzymes' *in vitro* in hepatic tissue obtained from animals treated with the plant extract *in vivo*. Shibib et al. (1993) showed, for example, that pretreatment of diabetic rats with *Momordica charantia* or *Coccinia indica* resulted in depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of the liver and shunt enzyme glucose-6-phosphate dehydrogenase. Suzuki and Hikino (1989b) have similarly measured the levels of key enzymes of glucose metabolism in the livers of mice treated *in vivo* with *Panax ginseng*-derived panaxan A and B. These enzymes, including glucokinase, can be

measured using standard methods reported in the literature or available from commercial enzyme suppliers.

More recently, hepatoma cell lines from the rat (e.g., FTO-2B and H4IIE) and humans (HepG2 and Hep3B) have been established as an alternative to the use of primary hepatocytes. They have been widely used to investigate the effect of conventional antidiabetic drugs and hormones on liver metabolism. For example, H4IIE cells were used to study the effect of metformin on glycogen synthesis (Purello et al., 1988), the inhibitory effect of tolbutamide on PEPCK (Agius et al., 1990), and the effect of insulin on glycogen synthase activity (Okubo et al., 1993). HepG2 cells were used to study the effect of troglitazone on glycogen synthesis and gluconeogenesis (Day, 1999). Valera and Bosch (1994) have developed transfected cell lines from FTO-2B and H4IIE cells (FTOGK and H4GK, respectively), which express glucokinase. These new cells are able to take up glucose more efficiently and accumulate high levels of glycogen. Valentova et al. (2004) have used Fao cells (a derivative of H4IIEC3 cells) to show that *Smallanthus sonchifolius* leaf extracts have similar effects to insulin on cytochrome P450 (CYP) mRNA levels.

MODELS BASED ON ADIPOCYTES AS AN INSULIN TARGET TISSUE

Adipocytes are an important tissue sensitive to insulin, where it causes glucose uptake and its incorporation into fat as glycerol, and inhibits the hydrolysis (lipolysis) of triglycerides. Glucose uptake into adipocytes is controlled by GLUT4 glucose transporters. Adipocytes are present in various parts of the body where fat is stored. However, primary adipocytes for experimental work are usually isolated from the epididymal adipose tissue (fat pads) of aged rats. Glucose uptake and oxidation, lipogenesis (formation of lipids), and inhibition of lipolysis (breakdown of lipids) are three effects of insulin that can be observed in this tissue. The relevant methodology has been described by Edens et al. (2002), who studied the effect of yeast extract on the transport and incorporation into lipids of D-[U-^{14}C] glucose. Lipolysis was measured using an enzymatic fluorescence method to assay glycerol in the cell culture medium. Broadhurst et al. (2000) screened a range of medicinal plants in a similar adipocyte assay, this time measuring the release of $^{14}CO_2$ from [U-^{14}C] glucose as a measure of glucose metabolism using a method originally described by Anderson et al. (1978).

Adipocytes isolated from rat epididymal adipose tissue have been used to study the effect of *Ganoderma lucidum* extract on adrenaline-induced lipolysis and lipogenesis from glucose (Kimura et al., 1988) and the effect of ganoderan B isolated from *Ganoderma lucidum* (Hikino et al 1989a) and aconitan A isolated from *Aconitan carmichaeli* (Hikino et al., 1989b) on the binding of insulin to adipocytes. Extracts of *Momordica charantia* seeds and fruit have been shown to stimulate lipogenesis (Ng et al., 1986) and inhibit hormone-induced lipolysis in adipocytes (Wong et al., 1985).

The mouse-derived 3T3-L1 fibroblast cell line provides an alternative to the use of freshly isolated primary adipocytes. The cells are commercially available in preadipocyte form and can be induced to differentiate into adipocytes by the inclusion of a glucocorticoid, insulin, and an agent that elevates intracellular cAMP (e.g., isobutylmethylxanthine) in the culture medium (Ntambi and Kim, 2000). The differentiation process, as well as glucose uptake, lipogenesis, and inhibition of lipolysis in differentiated cells, are all insulin-like effects that can be assessed in this cell line. Liu et al. (2001) have shown, for example, that an extract of *Lagerstroemia speciosa* stimulates glucose uptake (measured as 2-deoxy-D-[^{3}H] glucose), but does not induce adipocyte differentiation or potentiate the effects of insulin in 3T3-L1 cells. This suggests a non-insulinomimetic action of the plant, which may nevertheless be useful in controlling hyperglycemia.

By contrast, the compound shikonin, originally isolated from the Chinese medicinal plant *Lithospermum erythrorhizon*, was found to stimulate basal glucose uptake and potentiate insulin-stimulated glucose uptake in these cells (Kamei et al., 2002). However, further studies using specific inhibitors of insulin's signal transduction pathway showed that shikonin's activity is not mediated

via the insulin receptor/PI3K pathway but via a distinct tyrosine kinase-dependent route (Kamei et al., 2002). *Cryptolepis sanguinolenta* and the antihyperglycemic alkaloid cryptolepine were found to increase glucose uptake in 3T3-L1 cells (Luo et al., 1998).

Yoshikawa et al. (2002) report the use of an alternative commercially available rat preadipocyte cell line in which differentiation to adipocytes can be induced by dexamethasone and insulin. The differentiated cells were used to evaluate the effects of *Salacia reticulata* and some of its isolated components on lipolysis by measuring the triglyceride content of the cells.

Kanai et al. (1993) report the insertion of GLUT4 cDNA (GLUT4myc) into 3T3-L1 adipocytes. These and similarly transfected Chinese hamster ovary fibroblasts were used to study insulin-induced translocation of GLUT4 transporters to the cell surface (Kanai et al., 1993; Kamei et al., 2002).

MODELS BASED ON MUSCLE AS AN INSULIN TARGET TISSUE

The uptake and utilization of glucose into muscle is under influence of insulin, which provides other *in vitro* methods to evaluate antidiabetic plants. As with fat cells, the GLUT4 glucose transporter is translocated to the cell surface in response to insulin (Tremblay et al., 2003).

Abdominal muscle taken from mice has been used to study the effect of a number of plant extracts, including *Medicago sativa* (Gray and Flatt, 1997), *Agrimony eupatoria* (Gray and Flatt, 1998a), *Agaricus campestris* (Gray and Flatt, 1998b), and *Sambucus nigra* (Gray et al., 2000), on the uptake of glucose, oxidative glucose metabolism, and incorporation of glucose into glycogen. The paper on *Agaricus campestris* (Gray and Flatt, 1998b) gives good details of the methodology. Glucose uptake is followed using D-2-deoxy-[^{3}H] glucose and glucose oxidation by conversion of D-[U-^{14}C] glucose to labeled carbon dioxide (trapped in NaOH-saturated filter paper). Following incubation with D-[U-^{14}C] glucose, glycogen is precipitated with 95% ethanol and examined for ^{14}C content following hydrolysis and resolubilization.

Rat hemidiaphragm was used by Chattopadhyay et al. (1993) to study the effect of *Azadirachta indica* on muscle glycogen synthesis. *Momordica charantia* extracts have been studied in rat diaphragm muscle in which glucose uptake was found to be stimulated (Welihinda and Karunanayake, 1986).

A rat skeletal muscle cell line, L6, may be used for the study of antidiabetic agents. Cells are obtained as myoblasts that are induced, by adjusting the medium, to differentiate into an alignment stage and then into fused myotubes. Glucose transport (measured using ^{3}H-2-deoxyglucose) is most sensitive to insulin in the myotubes, corresponding to an increase in muscle/fat-specific GLUT4 transporters (Mitsumoto et al., 1991). GLUT1 transporters decreased during muscle cell differentiation. Glucose consumption and transport in L6 myotubes were sensitive to a thiazolidinedione antidiabetic drug, which showed additive effects to insulin (Arakawa et al., 1998). No reports were found of the use of this model for the study of antidiabetic natural products.

INTERACTIONS WITH THE INSULIN RECEPTOR

An approach that has been suggested to have a great deal of potential is to find agents capable of interacting directly with the insulin receptor, thereby acting as an insulin-mimetic in a variety of biochemical cascades. Based on this approach, Zhang et al. (1999) have developed a cell-based screening assay with Chinese hamster ovary cells that overexpress the human insulin receptor.

In their study, cells were incubated with the test compound, and the insulin receptor was purified and then assayed for tyrosine kinase activity. Tyrosine kinase is believed to be involved in the phosphorylation cascade that follows the binding of insulin to its receptor. Through this assay, they discovered an agent L-783,281 from a fungal species of *Pseudomassaria* that is capable of inducing tyrosyl protein phosporylation; the compound was shown to be selective to the insulin receptor and to exert a hypoglycemic effect *in vivo* in genetically diabetic mice (Zhang et al., 1999). In their

studies on cinnamon extract, Imparl–Radosevich et al. (1998) describe a method to measure autophosphorylation of purified insulin receptor kinase domain using [γ-^{32}P]ATP. Purified insulin receptor and many of its signal transduction components are available commercially.

GLUCAGON RECEPTOR ANTAGONISTS

Gluconeogenesis is reported to be increased in type 2 diabetes, is the primary contributor to fasting hyperglycemia, and can be stimulated by the hormone glucagon (Kurukulasuriya et al., 2003). The process can be inhibited using glucagon receptor antagonists or inhibitors of specific enzymes in the gluconeogenic pathway such as PEPCK (Kurukulasuriya et al., 2003). Progress in the development of glucagon antagonists was reviewed in 1999 (Connell, 1999). Although initial studies focused on peptide analogs as antagonists, nonpeptidic antagonists have been reported, suggesting that some plant secondary metabolites may possess this activity. Screening methods for glucagon antagonists include measuring the displacement of [^{125}I]-glucagon from binding sites in rat liver preparations or in Chinese hamster ovary cells and baby hamster kidney cells transfected with the human glucagon receptor (Azizeh et al., 1996; Connell, 1999).

A method measuring the inhibition of glucagon-stimulated adenylate cyclase activity in rat hepatocyte or liver membranes has also been described (Smith et al., 1993; Azizeh et al., 1996). The advantage of this last assay is that it detects compounds with glucagon antagonistic activity rather than mere binding to the receptor. Some natural products with glucagon antagonist activity mentioned in the Connell review include a "sugar-based material" isolated from an African medicinal plant by the British company Phytopharm, and skyrin, an orange pigment found in lichens and fungi described in a patent by Zymogenetics. Al-Habori et al. (2001) found that fenugreek extracts decreased the amount of glycogen phosphorylase-a activity only in hepatocytes stimulated with glucagon and not in unstimulated cells.

PRACTICAL CONSIDERATIONS

Potential Interferents in Plant Extracts

Three groups of plant constituents that may cause interference in diabetes-related *in vitro* bioassays are sugars, saponins, and polyphenols. Practical details for performing chemical tests to detect these compounds in plant extracts can be found in the laboratory handbook by Houghton and Raman (1998). Polar (i.e. water or alcohol) extracts of plant material can contain significant concentrations of sugars such as glucose, fructose, and galactose to name a few. Their presence can interfere with many of the bioassays described here, particularly those that measure glucose uptake. One effect could be to dilute the radiolabeled glucose used in the assay, which would result in artificially low counts and give the impression of decreased uptake. Another effect may be to increase the glucose concentration in the *in vitro* assay medium, stimulating certain glucose-sensitive processes such as insulin secretion from pancreatic β-cells. The starch-amylase inhibition assay is also prone to interference from plant-derived reducing sugars.

It is important to examine polar plant extracts for the presence of glucose and other monosaccharides. This can be done using simple laboratory spot-tests for reducing sugars — e.g., the standard Fehling's solution test or dinitrosalicylic acid reduction as described earlier under the starch-amylase inhibition assay. The actual sugars present can be identified and semiquantified using thin layer chromatography (Lewis and Smith, 1969). Gas or high-performance liquid chromatography can be used for more accurate quantitation; methods are readily available in the literature. Sugars in an extract can be removed by dialysis through a semipermeable membrane or by size exclusion chromatography through an appropriate gel column such as Sephadex G-10 (Houghton and Raman, 1998). However, one drawback is that other small molecules of interest may be lost in the process.

Saponins have the property of disrupting cell membranes. If they are present in significant quantities in plant extracts, they may have detrimental effects in cell-based *in vitro* assays. At the same time, they may overshadow a true mechanism-based effect of an extract in these cell systems. Cell membrane disruption by saponins can be investigated using the trypan blue exclusion method or by measuring LDH release as described in studies on pancreatic islets and beta cell lines (Persaud et al., 1999; Srijayanta et al., 1999).

It is recommended that dose–response studies be performed in parallel for the desired biological effect and cell damage in order to determine the extent to which they coincide. For example, in studies on *Anemarrhena asphodeloides* and its active components (Srijayanta et al., 1999), it was found that, at lower concentrations, insulin release from beta cells was stimulated in the absence of any damage to the membrane. The ability of some saponins to hemolyse blood cells can be used to test for their presence in a plant extract. Aqueous extracts containing saponins also form stable froths when shaken in a test tube. Saponins can often be extracted into butanol from aqueous solutions, leaving more water-soluble components in the aqueous layer. However, this risks losing other butanol-soluble components with the saponins.

Polyphenolic compounds, which are ubiquitous in nature, bind easily to proteins (thus their alternative name of "tannins") and often give rise to false positives or negatives in bioassays. The presence of polyphenols in a plant extract can be determined by testing the extract with iron (III) chloride solution. A dark blue/green color signifies the possible presence of these compounds. Polyphenols can be removed from an extract by a variety of methods that have been summarized and evaluated by Wall et al. (1996). These include size exclusion separation on Sephadex LH20 gels, binding to polyvinylpolypyrrolidone, and solvent–solvent extraction. Again, these methods may result in some loss of compounds of interest.

Solubilizing Plant Extracts for *In Vitro* Studies

Virtually all the *in vitro* bioassays described in this chapter utilize an aqueous environment. It is essential that plant extracts to be tested dissolve completely in the *in vitro* medium and this may present some difficulties when dealing with nonpolar extracts. Some options are to predissolve the extract at high concentration in a minimum quantity of water-soluble organic solvent such as ethanol, methanol, or dimethylsulfoxide (DMSO). The solution is then added to the bioassay medium in a volume so that the concentration of solvent is not detrimental to the assay. This "safe" concentration must be determined by prior experimentation. For example, a number of cell-based assays are able to tolerate up to 3% DMSO. Care should be taken that precipitation does not occur when the concentrated extract solution is added to the aqueous medium. An alternative is to use a surfactant solubilizing agent such as one from the Tween series.

An Alternative Glucose Substrate for *In Vitro* Uptake Studies

The radiolabeled substrate D-2-deoxy-[^{3}H]glucose is commonly used for studies on glucose uptake into muscle, fat, or liver. Ball et al. (2002) have proposed a nonradioactive fluorescent derivative of 2-deoxy-glucose, 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose, as an alternative. This compound demonstrates a favorable uptake profile into cardiomyocytes, including sensitivity to insulin.

CONCLUSIONS

In vitro tests offer a number of significant advantages for research on antidiabetic plants. A wide range of tests is available based on various mechanisms that would alleviate hyperglycemia in diabetes. The use of specific tests is recommended when screening natural products or other samples for a particular mode of action. However, if the mechanism by which a plant material is acting is

to be elucidated, a full range of tests should be used. Multiple mechanisms and active components are possible in antidiabetic plants. In conducting the tests, attention should be paid to potential interferents in the plant extracts.

REFERENCES

Abesundara KJM, Matsui T and Matusmoto K. Alpha-glucosidase inhibitory activity of some Sri Lanka plant extracts, one of which, *Cassia auriculata*, exerts a strong antihyperglycemic effect in rats comparable to the therapeutic drug acarbose. *J. Agric. Food Chem.*, 52(9), 2541–2545, 2004.

Agius L. Human liver *in vitro* techniques for metabolic studies, in *Ballière's Clinical Endocrinology and Metabolism*, Alberti K, Home P and Taylor R (Eds). London. Ballière Tindall, 1987, 999–1021.

Agius L, Peak M and Alberti K. Regulation of glycogen synthesis from glucose and gluconeogenic precursors by insulin in periportal and perivenous rat hepatocytes. *Biochem. J.*, 266, 91–102, 1990.

Ahmad F et al. Hypoglycemic activity of *Pterocarpus marsupium* wood. *J. Ethnopharmacol*. 35, 71–75, 1991a.

Ahmad F et al. Effect of (–)-epicatechin on cAMP content, insulin release and conversion of proinsulin to insulin in immature and mature rat islets *in vitro*. *Ind. J. Exp. Biol.*, 29, 516–520, 1991b.

Al-Habori M and Raman A. Antidiabetic and hypocholesterolemic effects of fenugreek. *Phytother. Res.*, 12, 233–242, 1998.

Al-Habori M et al. Effect of fenugreek extracts on intestinal sodium dependent glucose uptake and hepatic glycogen metabolism *in vitro*. *Int. J. Exp. Diabetes Res.*, 2, 91–99, 2001.

Ali H, Raman A and Houghton PJ. α-Amylase inhibition in Malayasian local plants. *J. Pharm. Pharmacol.*, 55(Suppl): S28, 2003.

Anderson RA, Brantner JH and Polansky MM. An improved assay for biologically active chromium. *J. Agric. Food Chem.*, 26, 1219–1221, 1978.

Arakawa K et al. Actions of a novel antidiabetic thiazolidinedione, T-174 in animal models of non-insulin–dependent diabetes mellitus (NIDDM) and in cultured muscle cells. *Br. J. Pharmacol.*, 12593, 429–436, 1998.

Artursson P. Epithelial transport of drugs in cell culture: a model for studying the passive diffusion of drugs over intestinal absorptive Caco-2 cells. *J. Pharm. Sci.*, 79, 476–482, 1990.

Audus K et al. The use of cultured epithelial and endothelial cells for drug transport and metabolism studies. *Pharm Res.,* 7, 435–451, 1990.

Azizeh BY et al. Topographical amino acid substitution in position 10 of glucagons leads to antagonists/partial agonists with greater binding differences. *J. Med. Chem.*, 39, 2449–2455, 1996.

Ball SW et al. A fluorescent compound for glucose uptake measurements in isolated rat myocytes. *Can. J. Phys. Pharmacol.*, 80, 205–209, 2002.

Bawden K, Quant J and Raman A. An investigation into the inhibitory effects of plant extracts on a starchñalphañamylase assay. *J. Pharm. Pharmacol.*, 54 (Suppl): S80, 2002.

Bawden K et al. Fractionation and characterization of compounds inhibiting α-amylase and their potential as antidiabetic remedies. *J. Pharm. Pharmacol.*, 55(Suppl): S31, 2003.

Bergmeyer H and Bernt E. D-glucose determination with glucose oxidase and peroxidase, in *Methods of Enzymatic Analysis,* 1st ed. Bergmeyer H. (Ed). Academic Press, New York, 1963, 123–130.

Bernfeld P. Amylase-α and -β, in *Methods in Enzymology,* Vol. I, Colowick SP and Kaplan NO (Eds), Academic Press, New York, 1955, 141–158.

Berry M and Friend D. High-yield preparation of isolated rat liver parenchymal cells. A biochemical and fine structural study. *J. Cell. Biol.*, 43, 506–520, 1969.

Bismut H and Plas C. Pathways of glycogen synthesis from glucose during the glycogenic response to insulin in cultured fetal hepatocytes. *Biochem. J.,* 263, 889–895, 1989.

Broadhurst CL, Polansky MM and Anderson RA. Insulin-like biological activity of culinary and medicinal plant aqueous extracts *in vitro*. *J. Agric. Food Chem.*, 48, 849–852, 2000.

Burant et al. Small intestine hexose transport in experimental diabetes. Increased transporter mRNA and protein expression in enterocytes. *J. Clin. Invest.,* 93, 578–585, 1994.

Chattopadhyay R, Chattopadhyay R and Maitra S. Possible mechanism of antihyperglycemic effect of *Azadirachta indica* leaf extract. Part III. *Fitoterapia*, LXIV, 533–538, 1993.

Connell RD. Glucagon antagonists for the treatment of type 2 diabetes. *Expert Opin. Therapeutic Patents*, 9(6), 701–709, 1999.

Day C. Thiazolidinediones: a new class of antidiabetic drugs. *Diabet. Med.,* 16, 179–192, 1999.

Edens NK et al. Yeast extract stimulates glucose metabolism and inhibits lipolysis in rat adipocytes *in vitro*. *J. Nutr.*, 132, 1141–1148, 2002.

Farzami B et al. Induction of insulin secretion by a component of *Urtica dioica* leave extract in perifused Islets of Langerhans and its *in vivo* effects in normal and streptozotocin diabetic animals. *J. Ethnopharmacol.*, 89(1), 47–53, 2003.

Fedorak RN et al. Intestinal adaptation to diabetes. Altered Na^+-dependent nutrient absorption in streptozotocin-treated chronically diabetic rats. *J. Clin. Invest*, 79, 1571–1578, 1987.

Fedorak RN et al. Altered glucose carrier expression: mechanism of intestinal adaptation during streptozotocin-induced diabetic rats. *Am. J. Physiol.*, 261. (*Gastrointest. Liver. Physiol.*, 24) G585–G591, 1991.

Fleig W et al. Modulation by a sulfonylurea of insulin-dependent glycogenesis, but not of insulin binding in cultured rat hepatocytes. *Diabetes*, 33, 285–290, 1984.

Fleig W et al. Regulation of insulin binding and glycogenesis by insulin and dexamethasone in cultured rat hepatocytes. *Biochim, Biophys. Acta*, 847, 352–361, 1985.

Fogh J, Fogh J and Orfeo T. H27 cultured human colon cancer cell lines producing tumors in nude mice. *J. Natl. Acad. Sci. USA*, 59, 221–226, 1977.

Gallagher AM et al. The effects of traditional antidiabetic plants on *in vitro* glucose diffusion. *Nutr. Res.*, 23, 413–424, 2003.

Good C, Kramer H and Somogyi M. The determination of glycogen. *J. Biol. Chem.*, 100, 491, 1933.

Gomez–Lechon M, Ponsoda X, and Castell J. A microassay for measuring glycogen in 96-well cultured cells. *Anal. Biochem.*, 236, 296–301, 1996.

Gray AM, Abdel–Wahab YHA and Flatt PR. The traditional plant treatment, *Sambucus nigra* (elder), exhibits insulin-like and insulin-releasing actions *in vitro*. *J. Nutr.*, 130, 15–20, 2000.

Gray AM and Flatt P. Pancreatic and extrapancreatic effects of the traditional antidiabetic plant, *Medicago sativa* (Lucerne). *Br. J. Nutr.,* 78, 325–334, 1997.

Gray AM and Flatt P. Actions of the traditional antidiabetic plant, *Agrimony eupatoriai* (agrimony). Effect on hyperglycemia, cellular glucose metabolism and insulin. *Br. J. Nutr.,* 80, 109–114, 1998a.

Gray AM and Flatt P. Insulin-releasing and insulin-like activity of *Agaricus campestris* (mushroom). *J. Endocrinol.*, 157, 259–266, 1998b.

Gray AM and Flatt P. Insulin-releasing and insulin-like activity of the traditional antidiabetic plant *Coriandrum sativum* (coriander). *Br. J. Nutr.*, 81, 203–209, 1999a.

Gray AM and Flatt P. Insulin-secreting activity of the traditional antidiabetic plant *Viscum album* (mistletoe). *J. Endocrinol.*, 160(3), 409–414, 1999b.

Guyton AC and Hall JE. Digestion and absorption in the gastrointestinal tract, in *Textbook of Medical Physiology,* 10th ed, Guyton AC and Hall JE (Eds). WB Saunders Company, U.K., 2000, 753–763.

Guyton AC and Hall JE. Insulin, glucagon and diabetes mellitus, in *Textbook of Medical Physiology,* 9th ed, Guyton AC and Hall JE (Eds), WB Saunders Company, U.K., 1997, 971–983.

Heacock PM et al. Effects of a medical food containing an herbal alpha-glucosidase inhibitor on post-prandial glycemia and insulinemia in healthy adults. *J. Am. Dietetic Assoc.*, 105(1), 65–71, 2005.

Hii C and Howell S. Effects of eipcatechin on rat islets of Langerhans. *Diabetes*, 33, 291–296, 1984.

Hii C and Howell S. Effects of flavonoids on insulin secretion and Ca^{2+} handling in rat islets of Langerhans. *J. Endocrinol.*, 107, 1–8, 1985.

Hikino H et al. Mechanism of hypoglycemic activity of ganoderan B: a glycan of *Ganoderma lucidum* fruit bodies. *Planta Med.*, 55, 423–428, 1989a.

Hikino H et al. Mechanisms of hypoglycemic activity of actonitan A, a glycan from *Aconitum carmichaeli* roots. *J. Ethnopharmacol.*, 25, 295–304, 1989b.

Hilgers A, Conradi R and Burton P. Caco-2 cell monolayers as a model for drug transport across the intestinal mucosa. *Pharm Res.,* 7, 902–910, 1990.

Houghton PJ and Raman A. *Laboratory Handbook for the Fractionation of Natural Extracts.* 1st ed. Chapman & Hall, London, 1998.

Imparl–Radosevich J et al. Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signaling. *Horm. Res.*, 50, 177–182, 1998.

Kamei R et al. Shikonin stimulates glucose uptake in 3T3-L1 adipocytes via an insulin-independent tyrosine kinase pathway. *Biochem. Biophys. Res. Comm.*, 292, 642–651, 2002.

Kanai F et al. Direct demonstration of insulin-induced GLUT4 translocation to the surface of intact cells by insertion of a *c-myc* epitope into an exofacial GLUT4 domain. *J. Biol. Chem.*, 268(19), 14523–14526, 1993.

Kessler M et al. A modified procedure for the rapid preparation of efficiently transporting vesicles from small intestinal brush border membranes. *Biochim, Biophys. Acta*, 506, 136–154. 1978.

Kim H et al. α-Glucosidase inhibitors from *Commelina communis*. *Planta Med.,* 65, 437–439, 1999.

Kimura Y, Okuda H and Arichi S. Effects of the extracts of *Ganoderma lucidum* on blood glucose level in rats. *Planta Med.*, 4, 290–294, 1988.

Kobayashi Y et al. Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism. *J. Agric. Food Chem.*, 48(11), 5618–5623, 2000.

Komaki E et al. The identification of anti-α-amylase components from olive leaf extracts. *Food Sci. Technol. Res.*, 9(1), 35–39, 2003.

Kurukulasuriya R et al. Potential drug targets and progress towards pharmacological inhibition of hepatic glucose production. *Curr. Med. Chem.*, 10, 123–153, 2003.

Lau C et al. Evidence for glucose transport inhibitors in *Momordica charantia* L. *Diabetologia*, 39(S1), A171, 1996.

Lebovitz H. Oral antidiabetic agents: the emergence of α-glucosidase inhibitors. *Drugs*, 44, 21–28, 1992.

Lewis B and Smith F. Sugars and derivatives, in *Thin Layer Chromatography: a Laboratory Handbook,* 2nd ed, Stahl E (Ed), George Allen & Unwin Ltd, London, 1969.

Li YM et al. Increasing the throughput and productivity of Caco-2 permeability assays using liquid chromatography-mass spectrometry: application to resveratrol absorption and metabolism. *Combinatorial Chem. High Throughput Scr.*, 6(8), 757–767, 2003.

Liu F et al. An extract of *Lagerstroemia speciosa* L. has insulin-like glucose uptake-stimulatory and adipocyte differentiation-inhibitory activities in 3T3-L1 cells. *J. Nutr.*, 131, 2242–2247, 2001.

Luo J et al. *Cryptolepis sanguinolenta*: an ethnobotanical approach to drug discovery and the isolation of a potentially useful new antihyperglycemic agent. *Diabet. Med.*, 15(5), 367–374, 1998.

Matsuda H et al. Antidiabetic principles of natural medicines. IV. Aldose reductase and alpha-glucosidase inhibitors from the roots of *Salacia oblonga* Wall. (Celastraceae): structure of a new friedelane-type triterpene, kotalagenin 16-acetate. *Chem. Pharm. Bull.*, 46, 1339–1340, 1998.

Matsui T et al. *In vitro* survey of alpha-glucosidase inhibitory food components. *Biosci. Biotech. Biochem.*, 60(12), 2019–2022, 1996.

Matsui T et al. Alpha-glucosidase inhibitory action of natural acylated anthocyanins. 1. Survey of natural pigments with potent inhibitory activity. *J. Agric. Food Chem.*, 49(4), 1948–1951, 2001a.

Matsui T et al. Alpha-glucosidase inhibitory action of natural acylated anthocyanins. 2. alpha-glucosidase inhibitory action of natural acylated anthocyanins. *J. Agric. Food Chem.*, 49(4), 1952–1956, 2001b.

Matsumoto K et al. Assay of α-glucosidase inhibitory activity using flow-biosensor. *Anal. Chim. Acta*, 479(2), 135–141, 2003.

Meir P and Yaniv Z. An *in vitro* study on the effect of *Momordica charantia* on glucose uptake and glucose metabolism in rats. *Planta Med.*, 3, 12–16, 1985.

Mitsumoto Y et al. Differential expression of the GLUT1 and GLUT glucose transporters during differentiation of L6 muscle cells. *Biochem. Biophys. Res. Commun.*, 175(2), 652–659, 1991.

Neef H et al. Inhibitory effects of *Galega officinalis* on glucose transport across a monolayer of human intestinal epithelial cells (Caco-2). *Pharm. Pharamcol. Lett.*, 6, 86–89, 1996.

Newgard C et al. Studies on the mechanism by which exogenous glucose is converted to liver glycogen in the rat. *J Biol Chem.*, 258, 8053–8059, 1983.

Ng TB et al. Insulin-like molecules in *Momordica charantia* seeds. *J. Ethnopharmacol.*, 15, 107–117, 1986.

Nishioka T, Kawabata J and Aoyama Y. Baicalein, an α-glucosidase inhibitor from *Scutellaria baicalensis*. *J. Nat. Prod.*, 61, 1413–1415, 1998.

Noor H, Hammonds P and Ashcroft S. The hypoglycemic and insulinotropic activity of *Tinospora crispa*. Studies with human and rat islets and HIT-T15 B cells. *Diabetologia*, 32, 354–359, 1989.

Ntambi JM and Kim YC. Adipocyte differentiation and gene expression. *J. Nutr.*, 130, 3122S–3126S, 2000.

Oki T, Matsui T and Matsumoto K. Evaluation of α-glucosidase inhibition by using an immobilized assay system. *Biol. Pharm. Bull.,* 23, 1084–1087, 2000.

Okubo M, Fujita N, and Nagasaka Y. Insulin regulates glycogen-synthase activity and its gene expression in rat hepatoma H4IIE cells. *Diabetes*, 42, A167, 1993.

Perl M and Hikino H. Effect of some hypoglycemic glycans on glucose uptake and glucose metabolism by inverted intestinal fragments. *Phytother. Res*., 3, 207–208, 1989.

Persaud SJ. Pancreatic β-cell lines: their roles in β-cell research and diabetes therapy, in *Advances in Molecular and Cell Biology,* Volume 29. JAI Press Inc., CT, 1999.

Persaud SJ et al. *Gymnema sylvestre* stimulates insulin release *in vitro* by increased membrane permeability. *J. Endocrinol*., 163, 207–212, 1999.

Phillips R et al. Human intestinal goblet cells in monolayer culture: characterization of a mucus-secreting subclone derived from the HT29 colon adenocarcinoma cell line. *Gastroenterology*, 94, 1390–1403, 1988.

Poitout V, Olson L and Robertson R. Insulin secreting cell lines: classification, characteristics and potential applications. *Diabetes Metab.*, 22, 7–14, 1996.

Plomp P et al. Stimulation of glycogen synthesis in hepatocytes by added amino acids is related to total intracellular content of amino acids. *J. Biochem.*, 191, 237–243, 1990.

Purello F et al. Metformin enhances certain insulin action in cultured rat hepatoma cells. *Diabetologia*, 31, 385–389, 1988.

Raman A and Lau C. Antidiabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae). *Phytomedicine*, 2(4), 349–362, 1996.

Rhabasa–Lhoret R and Chiasson JL. α-Glucosidase inhibitors, in *International Textbook of Diabetes Mellitus* (volume 1), 3rd ed, Defronzo RA, Ferrannini E, Keen H and Zimmet P (Eds). John Wiley & Sons Ltd, Chichester, U.K., 2004, 901–914.

Rinninger F et al. Extrapancreatic action of the sulfonylurea gliquidone: post-receptor effect on insulin-stimulated glycogen synthesis in rat hepatocytes in primary culture. *Diabetologia*, 26, 462–465, 1984.

Rotshteyn Y and Zito SW. Application of modified *in vitro* screening procedure for identifying herbals possessing sulfonyl-urea-like activity. *J. Ethnopharmacol*., 93, 337–344, 2004.

Ruitton–Ugilienco RL. [Comparison of two methods of insulin determination: enzymun-test insulin (Boering) and 125I insulin RIA-KIT (bioMerieux) used as a reference] [French]. *Ann Biologie Clinique*., 39(5), 295–296, 1981.

Salhanick A, Chang C and Amatruda J. Hormone and substrate regulation of glycogen accumulation in primary cultures of rat hepatocytes. *Biochem. J*., 261, 985–992, 1989.

Shibib BA, Khan LA and Rahman R. Hypoglycemic activity of *Coccinia indica* dn *Momordica charantia* in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. *Biochem. J*., 292, 267–270, 1993.

Shimizu K et al. Structure–activity relationships of triterpenoid derivatives extracted from *Gymnema inodorum* leaves on glucose absorption. *Jpn. J. Pharmacol*., 86(2), 223–229, 2001.

Sitaswad SL, Shewade Y and Bhonde R. Role of bittergourd fruit juice in STZ-induced diabetic state *in vivo* and *in vitro*. *J. Ethnopharmacol*., 73, 71–79, 2000.

Smith RA et al. Isolation of glucagon antagonists by random momlecular mutagenesis and screening. *Mol. Pharmacol*., 43(5), 741–748, 1993.

Solling H and Esmann V. A sensitive method of glycogen determination in the presence of interfering substances using the filter-paper technique. *Anal. Biochem*., 68, 668, 1975.

Srijayanta S et al. *In vitro* screening of medicinal plants for potential antidiabetic effects. *J. Pharm. Pharmacol*., 50(S), 219, 1998.

Srijayanta S et al. Mangiferin, an antidiabetic compound from *Anemarrhena asphodeloides*. *J. Pharm. Pharmacol*., 51(S), 98, 1999.

Suzuki Y and Hikino H. Mechanism of hypoglycemic activity of panaxan A and B, glycans of *Panax ginseng*: effects on plasma level, secretion, sensitivity and binding of insulin in mice. *Phytother. Res*., 3, 20–24, 1989a.

Suzuki Y and Hikino H. Mechanism of hypoglycemic activity of panaxan A and B, glycans of *Panax ginseng*: effects on key enzymes of glucose metabolism in the liver of mice. *Phytother. Res*., 3, 15–19, 1989b.

Thorens, B. Glucose transporters in the regulation of intestinal, renal and liver glucose fluxes (review). *Am. J. Physiol*., 270, (*Gastrointest., Liver. Physiol.* 33), G541–G553, 1996.

Tosh D, Beresford G and Agius L. Glycogen synthesis from glucose by direct and indirect pathways in hepatocyte cultures form different nutritional states. *Biochim. Biophys. Acta.*, 1224, 205–212, 1994.

Tremblay F, Dubois MJ and Marette A. Regulation of GLUT4 traffic and function by insulin and contraction in skeletal muscle. *Frontiers Biosci.,* 8, D1072–D1084, 2003.

Valentova K et al. The effect of *Smallanthus sonchifolius* leaf extracts on rat hepatic metabolism. *Cell Biol. Toxicol.*, 20(2), 109–120, 2004.

Valera A and Bosch F. Glucokinase expression in rat hepatoma cells induces glucose uptake and is rate limiting in glucose utilization. *Eur. J. Biochem.*, 222(2), 533–539, 1994.

Vedavanam K et al. Antioxidant action and potential antidiabetic properties of an isoflavonoid-containing soyabean phytochemical extract (SPE). *Phytother. Res.*, 13, 601–608, 1999.

Verspohl EJ. Recommended testing in diabetes research. *Planta Med.*, 68, 581–590, 2002.

Vu L et al. Short-term insulin-induced glycogen formation in primary hepatocytes as a screening bioassay for insulin action. *Anal. Biochem.*, 262, 17–22, 1998.

Wall ME et al. Effect of tannins on screening of plant extracts for their enzyme inhibitory activities and techniques for their removal. *Phytomedicine*, 3(4), 281–285, 1996.

Welihinda J and Karunanayake EH. Extrapancreatic effects of *Momordica charantia* in rats. *J. Ethnopharmacol.*, 17, 247–255, 1986.

Wikman A et al. A drug absorption model based on the mucus layer producing human intestinal goblet cell line HT29-H. *Pharm. Res.*, 9410, 843–850, 1993.

Wong CM, Ng TB and Yeung HW. Screening of *Trichosanthes kirilowii*, *Momordica charantia* and *Cucurbita maxima* (family Cucurbitaceae) for compounds with antilipolytic activity. *J. Ethnopharmacol.*, 13, 313–321, 1985.

Wood C and Lawrence MJ. Models for intestinal drug absorption. *J. Biopharm. Sci.*, 2, 147–172, 1991.

Yoshikawa M, Marakami T and Matsuda H. Medicinal foodstuffs. X. Structures of new triterpene glycosides, gymnemosides –c, –c, –e, and –f, from the leaves of *Gymnema sylvestre* R. Br: influence of gymnema glycosides on glucose uptake in rat small intestinal fragments. *Chem. Pharm. Bull.*, 45(12), 2034–2038, 1997.

Yoshikawa M et al. Kotalanol, a potent α-glucosidase inhibitor with thiosugar sulfonium sulfate structure, from antidiabetic Ayurvedic medicine, *Salacia reticulata*. *Chem. Pharm. Bull.*, 46, 1339–1340, 1998a.

Yoshikawa M et al. Antidiabetic principles of natural medicines II. Aldose reductase and α-glucosidase inhibitors from Brazilian natural medicines, the leaves of *Myrcia multiflora* DC (Myrtaceae). Structure of myrciacitrins I and II and myrciaphenones A and B. *Chem. Pharm. Bull.*, 46, 113–119, 1998b.

Yoshikawa M et al. *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lipolytic activity have mild antiobesity effects in rats. *J. Nutr.*, 132(7), 1819–1824, 2002.

Zhang B et al. Discovery of a small molecule insulin mimetic with antidiabetic activity in mice. *Science*, 284, 974–977, 1999.

5 Ayurvedic, Siddha, and Tribal Medicine

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CONTENTS

INTRODUCTION

India is a large country composed of people of different cultures, traditions, and heritages. This rich culture and tradition is reflected not only in daily life, but also in health practices. India has a long health tradition that dates back to 3000 B.C. or much earlier. The Indian medical tradition prevails at two levels: (1) the classical system, which includes Ayurveda, Siddha, and Unani traditions and is characterized by institutionally trained doctors and also well developed theories to support its practices; and (2) the folk system, termed *Lok Parampara*, which is an oral tradition passed on from father to son or mother to daughter. The folk tradition is rich, vibrant, and diverse and includes:

- Knowledge and belief regarding foods — *Pathyam* and *Apathyam* (i.e., foods to be preferred or avoided)
- Knowledge of diagnostic procedures and preventive measures
- Knowledge of *Rutucharya* or adaptation of food and regimen to suit the seasons
- Yoga and physical practices for disease prevention

The classical system of practice in recent times has gained a lot of interest, not only in the Indian subcontinent but also in the West. The characteristic feature of the classical system is that it considers the individual as a whole rather than considering the disease alone. The treatment of

the individual is done taking into consideration constitution, susceptibility to falling sick, mental make-up, food habits and lifestyle, surroundings, etc. Among all the classical systems, Ayurveda has been well refined to a very high degree. The basis of Ayurvedic treatment is its powerful concept of *prakriti*.

Ayurveda is a medical science that means the nature or natural or original form of the build and constitution of the human body. Disease occurs when the original form changes or alters at the psychological, physiological, or biochemical level. Ayurveda places importance on *prakriti*, the natural state of the individual; the disease, or *vikruthi*, is given second importance and is examined later. Ayurveda helps to keep the body and mind healthy and fit. In Ayurveda, three steps are used in treating any disease: (1) *Samsodhara* — cleansing process; (2) *Samsarvana* — palliative measure; and (3) *Vidanaprivarjara* — treating the cause. Ayurveda traces it etymology to *Ayush*, meaning life, and *veda* (vid), meaning knowledge. Ayurveda uses different indigenous plants, animal products, etc. to treat disease.

The Siddha system of medicine is based on remedies derived from the vegetable kingdom. The word *Siddha* comes from the word S*iddhi*, meaning an object to be attained or perfection of heavenly bliss. The fundamental principle on which Siddha is guided is that "nature is man" and "man is nature" and thus both are essentially one. Man is therefore the universe in a miniature form containing all the five elements — *Munn* (solid), *Neer* (fluid), *Thee* (radiance), *Vayu* (gas), and *Akasam* (ether) — and the various principles that constitute the mineral, vegetable, and animal kingdoms. The human anatomy and physiology, the causative factor of diseases, the materials for the treatment, the cure of the disease, and food for sustenance all fall within the five elements. In addition to this, the traditional forms of treatment all consider the physical elements of the external world: air, heat, and water. These three elements are known as "humors" and, as they enter the body, are called *tridoshaa*.

In the body, these elements are called air, bile, and phlegm and represent air, fire, and water of the external world. These humors maintain and sustain the body through their combined functioning. All the traditional forms — whether Ayurveda, Siddha, or Unani — advocate that, without these three humors, the individual cannot be normal and any imbalance that occurs in these three factors results in disease or death. If all three factors work properly and without any change, the body will be healthy and disease free. Imbalance due to astral or cosmic influence, poison or poisonous substances, or psychological or other factors causes these three factors and disease.

Medicines are prescribed to set right the imbalance in life factors by addition, reduction, or neutralization; all matter contains the five elements and thus the three factors. The Siddha system not only includes medicine and alchemy but also yoga and philosophy. By Indian tradition, yoga is the means by which one obtains omniscience and the power of achieving and controlling mighty things. Siddha acknowledges 64 kinds of yoga.

Phytomedicine had its genesis in India from time immemorial. There is evidence in the early Vedic period of plants being used for a wide range of medicinal purposes. This is evident in the living folk tradition in rural communities and also in the classical system of treatment in which plants have been used and are still in use. At the folk level in many ecosystems from the Himalayas, which has a wealth of green pharmacy to the coast, the local communities have observed and studied medicinal plants in their locality and identified their uses. In many cases, no written text proves or disproves the plants' utility because most of them are passed on from father or mother to son or daughter by word or practice.

Today, a number of plants are used in different Indian systems of medicine and several species overlap the different systems. In terms of life forms, medicinal plants are equally distributed across habits, namely, trees, shrubs, and herbs. Among these, one third are trees, an equal proportion is shrubs, and the rest are herbs, epiphytes, grasses, and climbers. Small numbers are lichens, ferns, and algae. These medicinal plants also have a wide distribution pattern. A vast majority are found in the tropical zone — the western and eastern ghats, the Vindhyas, etc. Less than 30% are confined to the temperate and colder zones.

The depth of study of plants is clearly reflected in their manifold application. It is not uncommon to see several different applications of the same plant in various formulations. A number of plants have been used in the treatment of diabetes.

Diabetes mellitus is a disease affecting more than 60 million individuals and may attain more than 300 million in the next decade. Diabetes was known to ancient Indian physicians as *Madumeha*; many herbs and herbal preparations have been used to treat the disease, as well as several metals and minerals. Ayurveda has given an elaborate description about this disease, its clinical features, patterns, and management using herbal or herbomineral drugs. Plants and plant drugs are frequently considered to be less toxic and freer from side effects than synthetic ones. It has been observed that certain resistant cases of diabetes that do not respond to modern medicines like tolbutamide, glibenclamide, etc. respond very well when treated with herbomineral and herbal preparations, alone or in combination with other oral hypoglycemic agents.

A number of plants and plant extracts have been used in the treatment of diabetes. Many of these plants are also used in the treatment of other diseases in India and many more are being identified. A few that have been extensively studied are reported in this chapter.

SYZIGIUM CUMINI LINN. (JAMUN)

Syzigium cumini L. (synonym: *Eugenia jambolana*) belongs to the family Myrtaceae and is widely cultivated in India for its delicious fruits. The Jamun tree is native to India and easily thrives in hardy tropical regions; it is found in all parts of Indian subcontinent as well as in Africa and Southeast Asia. The fruit has an unusual taste, flavor, and color. The fruit has a number of medicinal properties, especially for the treatment of diabetes. The fruit is generally purple and has a subacidic to sweet taste. The edible portion of the Jamun fruit forms 70% of the whole fruit.

Preliminary studies indicate that a decoction of the dry leaves of the Jamun exhibits hypoglycemic effects.[1] Mahapatra et al.[2] did some preliminary studies on the glycemic effect of Jamun seeds and found that they produce hypoglycemia. The fruit, bark, and seeds have been found to possess antidiabetic properties. Stanely Mainzen Prince et al.[3] have shown that the alcoholic as well as the aqueous extracts of the seeds of *Syzigium cumini* possess antidiabetic properties. The seed extracts also have a significant effect on key carbohydrate metabolic enzymes such as hexokinase and glucose-6-phosphatase in diabetic rats.[4] Studies have also shown that the seeds have hypolipidemic properties. The hypoglycemic and hypolipidemic properties are closely associated with their antioxidant properties.[3]

The natural history of diabetes is characterized by a series of complications that affect many organs of the body and also play a vital role in the final outcome of the disease. Reactive oxygen-derived radicals play an important role in the pathogenesis of diabetes mellitus. Other complications of diabetes, such as retinal damage and renal injury, occur through oxygen-related radical processes.[5] During diabetes, the free radical production is increased. Administration of Jamun seed extract decreases the formation of free radicals and protects the tissues from oxidative stress.[3]

Jamun seed extract has been found to increase the activity of antiperoxidative enzymes in diabetic rats. This shows that Jamun seed extracts possess an antioxidant property. Chemically, Jamun seeds contain quercetin, gallic acid, and ellagic acid, which are known antioxidants.[6] In diabetes, free radicals are formed and these react with the cell membrane components to produce a toxic reaction. They also bring about changes in the composition of the cell membrane components.

Diabetes mellitus also affects the molecular characteristics of collagen, which, because it is a protein with low turnover, is highly susceptible to advanced glycation *in vivo*. Furthermore, the molecular and structural modifications of collagen observed in diabetes are biochemically and physiologically linked to the development of complications. Advanced glycation end products (AGE) are directly implicated as one of the major factors responsible for the development and progression of multiorgan damage in diabetes. Jamun seed extract showed a significant effect on

cross linking, extent of glycation, collagen-linked fluorescence and the intensity of β-component in rat tail tendon of STZ-diabetic rats. Thus, Jamun seed extract reduces the formation of AGE products.[7]

One of the major events taking place during diabetes is the glycation of proteins and formation of Amadori products; finally, the Maillard reaction produces irreversible advanced glycation products. Administration of *Syzigium cumini* seed extract results in hypoglycemia and thus reduced formation of AGE products. Studies have shown that the aqueous and ethanolic extracts of *Syzigium cumini* prevent the formation of AGE products.[7]

Phytochemistry

Syzigium cumini seeds contain ellagic acid and the alkaloid jambosine. Alcoholic extracts of *Syzigium cumini* seeds contain gallic acid, ellagic acid, corilagin, and related ellagitannins, 3,6-hexahydroxydiphenoyl-glucose and its isomer, 4,6-hexahydroxydiphenoyl glucose, 1-galloyl glucose, 3-galloyl glucose, and quercetin. Acetone extract of the bark and seeds contains partially methylated derivatives of the ellagic acid-3,3′-di-o-methyl ellagic acid and 3,3′,4-tri-o-methyl ellagic acid. Alcoholic extraction of tannins results in their extensive degradation into simple phenolic compounds.[6]

TINOSPORA CORDIFOLIA MIERS

Tinospora cordifolia Miers (Menispermaceae) is a glabrous climbing succulent shrub commonly found in hedges. It is native to India and thrives easily in tropical regions. It also grows in Burma and Ceylon. *Tinospora cordifolia* (Guduchi) has long been known in Ayurvedic literature as a tonic, vitalizer, and a remedy for diabetes and metabolic disorders.[8] It is also one of the constituents of the Ayurvedic preparation *Amrithadi Churnam*, which has antidiabetic activity. In addition to *Tinospora*, the other constituents of this preparation are *Curcuma longa, Emblica officinalis, Salacia chinensis* Linn., and *Tribulus terrestris*.

In 1967, Gupta et al.[9] studied the antidiabetic effects of fresh green stems on fasting blood sugar, glucose tolerance, and adrenaline-induced hyperglycemia in rabbits and rats. The alcoholic (200 mg/kg) as well as the aqueous (200 mg/kg) extract of the plant caused a significant effect on glucose tolerance as judged from the marked inhibition of the rise in blood sugar level after the glucose meal (4 ml/100 g of 25% solution) in the treated rats compared to the controls. The sugar tolerance was, however, found to deteriorate after the third and fourth weeks of treatment, respectively, in animals treated with the alcoholic and aqueous extract. The authors concluded that the exhaustion of the β-cells of Langerhans undergoing continued stimulation during prolonged treatment with the drug may be the cause leading to a paradiabetic state similar to that reported after prolonged treatment with sulfonyl ureas.

Gupta et al.[10] also studied the effect of serial extracts of petroleum ether, ether, chloroform, alcohol, and water in a series of crossover tests. None of these extracts except the aqueous extract caused any significant reduction in blood sugar level. The last fraction extracted with water, however, caused an appreciable reduction (20.1%) in blood glucose compared to the other serial extracts, indicating that the hypoglycemic principle in the drug is water extractable.

They also observed that the bitter principle isolated from water extract did cause appreciable reduction in blood sugar compared to controls, but the percentage of reduction was not significant. The bitter principle also caused a marked and significant inhibition of the hyperglycemic response induced by 0.5 mg/kg intraperitoneal injection of epinephrine hydrochloride. The hyperglycemic response of epinephrine is known to be mediated partly by increased glycogenolysis and partly by the release of corticoids as a result of the stimulation of the adreno–hypophyseal axis; therefore, it is likely that *T. cordifolia* with its constituent bitter and nonbitter fractions might be preventing the rise in blood sugar level by inhibiting these mechanisms. This seems to be further substantiated

from another observation in which the drug inhibited the hepatic glucose release in dogs after epinephrine injections.[11] Furthermore, because the hypoglycemic effect of the bitter fraction isolated from the boiled aqueous decoction was insignificant, it is likely that the hypoglycemic principle in the plant may be thermolabile and of an enzymatic nature.

In 1965, Gupta et al.[12] reported that the fresh extracts also potentiate insulin effect on glucose uptake by rat diaphragm. A few chromatographic fractions of fresh extract per se influenced the glucose uptake by tissues in *in vitro* experiments.[10] It is therefore likely that the hypoglycemic activity of the drug may be related partly to the direct metabolic effect on tissues and partly to endogenous insulin secretion similar to that effect produced by sulfonyl urea derivatives. Studies were conducted on the aqueous, alcoholic, and chloroform extracts of the leaves of *T. cordifolia* in normal and alloxan-diabetic rabbits. The extracts exerted a significant hypoglycemic effect in normal as well as in alloxan-treated rabbits. The extracts of the leaves of *T. cordifolia* also had an insulin-like action.[13]

Grover et al.[14] studied the extracts of *T. cordifolia* in experimental diabetes. Aqueous extract of *T. cordifolia* (400 mg/kg/day) exhibited a hypoglycemic effect in moderate diabetes. Stanely Mainzen Prince and Menon[15] discovered that the aqueous and alcoholic extracts of *T. cordifolia* roots exhibit antihyperglycemic effect in diabetic rats. The possible mechanism by which *T. cordifolia* root extract brings about its hypoglycemic action may be potentiating the insulin effect of plasma by increasing the pancreatic secretion of insulin from the β-cells of islets of Langerhans or its release from bound form. The alcoholic extract returned glucose levels to near normal levels.

The effect of alcoholic and aqueous extracts of *T. cordifolia* roots on the activities of glucose-6-phosphatase and hexokinase in liver was also studied in diabetic rats. Administration of these extracts increases the activity of hepatic hexokinase and decreases the activity of glucose-6-phosphatase.[15] Stanely Mainzen Prince et al.[16] evaluated the effect of aqueous and alcoholic *T. cordifolia* root extract on serum and tissue lipids in diabetic rats. Administration of aqueous extract decreases the serum and tissue lipids in diabetic rats. The alcoholic *T. cordifolia* root extract maintained all the lipid levels at near normal level. The hypolipidemic effect of root extract can be explained as a direct result of the reduction in blood glucose concentration.

The effect of aqueous and alcoholic extracts of *T. cordifolia* root on lipid peroxidation in plasma and tissues was also evaluated in diabetic rats. These extracts decreased the levels of lipid peroxides in diabetic rats. The alcoholic extract brought back the level of the lipid peroxides to near normal level. The results of the study showed the antilipoperoxidative action of *T. cordifolia*.[15]

Studies on the aqueous and alcoholic extracts of *T. cordifolia* roots on ceruloplasmin, α-tocopherol, glutathione, and vitamin C in diabetic rats showed that administration of these extracts lowered the plasma ceruloplasmin and α-tocopherol and increased the plasma glutathione and vitamin C in diabetic rats. Alcoholic extracts restored the levels of all the nonenzymatic antioxidants to near normal levels in diabetic rats.[17] These extracts also increase the activity of superoxide dismutase and catalase in diabetic rats. The effects of alcoholic extract was more effective than aqueous extract and maintained the antioxidant enzymes at near normal levels.[17,18]

Stanely Mainzen Prince and Menon also evaluated the effect of aqueous and alcoholic *T. cordifolia* root extracts on the molecular characteristics of collagen in STZ-induced rat tail tendon. Diabetes mellitus causes changes in the metabolism of basement membrane and interstitial collagen. It also alters the acid solubility, extent of glycation, intensity of fluorescence, and α/β ratio of collagen. Oral administration of aqueous and alcoholic *T. cordifolia* increases the acid-soluble collagen and decreases the extent of glycation and intensity of collagen-linked fluorescence in STZ-induced diabetic rat tail tendon.

Additionally, Stanely Mainzen Prince and Menon evaluated the effect of aqueous and alcoholic *T. cordifolia* root extract on α/β ratio of collagen in STZ-induced diabetic rat tail tendons. Administration of aqueous *T. cordifolia* root extract decreases the intensity of β-component and alcoholic root extract returns the values to near normal.

Phytochemistry

Many compounds have been isolated from the stems of *T. cordifolia*. They include tinosporaside (18-norclerodane glucoside),[19] clerodane furano-diterpene, diterpenoid furano-lactone,[20] phytoecdysones (ecdysterone and makisterone),[21] and cordifoliosides A, B, C, D, and E (norditerpene furan glycosides),[22,23] in which cordifoliosides A and B are also called TC5 and TC6. Syringine (TC4) and syringine epiosyl glycoside,[24] two clerodane diterpenoids (tinosporane and tinocordioside),[25] and cordioside and its derivatives (a clerodane furano diterpene glucoside),[26] which are also known as TC-1 and TC-2, have been isolated from the stems of *T. cordifolia*. Cordiol (TC-7)[27] and cordioside (TC-3) are also isolated from the stems. Arabinogalactan from the dried stems and 20-β-hydroxy ecdysone, a steroid from the aerial parts of the plant, have been isolated.[28,29] Tinocordiofolioside (daucane-type sesquiterpene glucoside)[30] is also isolated from the stem. Two phenyl propane glycosides were isolated from the polar fractions of the aqueous extracts of *Tinospora cordifolia*. Jatrorrhizine (isoquinoline alkaloid) has been isolated from the alcoholic root extracts of the plant.[31] The bitter principles have been identified as columbin, chasmanthin, berberine, and paimarin.

TRIGONELLA FOENUM GRAECUM LINN. (FENUGREEK)

Fenugreek, an erect, strongly scented, robust annual herb, belongs to the family Papilionaceae–Leguminosae. It is extensively cultivated as a food crop in India, the Mediterranean region, North Africa, Yemen, and the U.S. Fenugreek seeds are used in India as a condiment and in Egypt as a supplement to wheat and maize flour for bread making; in Yemen, it is one of the main constituents of the normal daily diet of the general population. The leaves of fenugreek are widely consumed in India as a green leafy vegetable and are a rich source of calcium, iron, β-carotene, and other vitamins.[32]

In Indian Ayurvedic medicine, fenugreek is widely used as a remedy for diabetes mellitus. It is also a constituent of some of the herbal formulations used in Ayurveda to cure diabetes. Fenugreek seeds have been used for a long time for their antidiabetic action. Khosla et al.[33] have showed that the seed extract exhibits hypoglycemic effects. The extract also causes a significant hypoglycemic effect in cadmium and alloxan-induced hyperglycemic rats.[34] Supplementation of 20% fenugreek diet for 20 days prior to STZ injection resulted in a significant effect on hyperglycemia, free fatty acids, cholesterol, and triglycerides.[35]

Fenugreek seeds also showed a significant effect on blood glucose levels in dogs.[36] A decoction of fenugreek seeds (40 to 80% dilution) showed a hypoglycemic effect in mice. Ethanolic extracts of fenugreek seeds have been shown to have hypoglycemic action.[37] No change in plasma insulin was reported in rats or dogs after administration of fenugreek.[38,39] In chemically induced diabetes, some authors have established an increase in plasma insulin levels.[40,41] The observed increase in these levels may be due to a direct stimulatory effect on the β-cells. In this context, Sauvaire et al.[42] have reported an insulin secretion-stimulating compound (4-hydroxyisoleucine) in fenugreek.

In addition to fat, fenugreek seeds contain fiber, saponins, and proteins.[39,43] In normal and diabetic dogs, defatted portions of the seeds exhibited hypoglycemic and hypocholesterolemic effects. Defatted fenugreek improves oral glucose tolerance and modifies pancreatic hormone levels.[39] The two subfractions, a and b, of defatted fenugreek were investigated by Ribes et al.[36] They showed that the antidiabetic property was contained in the subfraction a, which consists of testa and endosperm.

Earlier studies indicated that the presence of trigonelline, a major alkaloid of fenugreek, is responsible for its hypoglycemic effect.[44,45] Later, the presence of an orally active principle isolated from fenugreek seeds was found to improve 0 glucose tolerance in alloxan-induced rabbits.[46] Treatment of this fraction daily for 30 days at a dose of 50 mg/kg decreased the levels of fasting

blood glucose in severely diabetic rabbits. They also reported an improvement in glycosylated hemoglobin and serum lipid profile and an increase in the activity of key glycolytic enzymes in muscle and inhibition on key gluconeogenic enzymes in the liver and kidney.

An insulin stimulating substance, 4-hydroxyisoleucine, was identified in the seeds of fenugreek.[47] Sauvaire et al.[42] have shown that this substance evoked a biphasic insulin response *in vitro* at a concentration of 200 μ*M*/l using isolated pancreas perfused with glucose. This 4-hydroxyisoleucine is an unusual amino acid isolated and identified by Fowden et al.[48] Alcock et al.[49] have established the conformation of 4-hydroxyisoleucine. Coumarin, one of the constituents of fenugreek, has also been reported to have a hypoglycemic effect in normal and alloxan-induced diabetic rats.[45] Another constituent of fenugreek, scopoletin, a coumarin, was found to have hypoglycemic effect in normal and alloxan-diabetic rats.[45] Ghosal et al.[50] reported the hypoglycemic effect of fenugreekine, a steroidal sapogenin peptide ester.

In 1984, Madar[38] suggested that fenugreek reduces plasma glucose levels by delaying gastric emptying and by direct interference with glucose absorption at the gastrointestinal level. Later it was reported that the dietary fiber in fenugreek was the major contributor for reducing plasma glucose.[51,52] Sharma[51] reported that when fenugreek was degummed, the seeds had little hypoglycemic effect. In 1990, Madar and Shomer[53] stated that galactomannan in the gel fraction of the seeds is responsible for the reduction in plasma glucose by increasing the viscosity of the gut contents.

Ali et al.[54] have reported that fenugreek powder, its methanol extract, and residue remaining after methanol extraction had significant antihyperglycemic effect when fed with glucose to animals. An additional possible mode of action of fenugreek is an effect on intestinal carbohydrate digestion. using an inverted sac technique, Madar and Shomer[53] observed that fenugreek decreases digestion of starch and also glucose absorption *in vivo* and *in vitro*. A significant decrease in the activity of intestinal sucrase was reported by Platel and Srinivasan[55] with the addition of 2% fenugreek seeds to the diet of rats. Clinical studies have showed that fenugreek seeds exhibit glucose-lowering effects in type I and type II diabetes. Fourier[56] reported that the administration of coarsely ground fenugreek seeds improved severe diabetes in human subjects.

Type I diabetics fed 100 g fenugreek/day in their diet showed a significant glucose-lowering effect.[57] There is also a report showing that type II diabetics fed 15 g of fenugreek daily showed a significant effect in hyperglycemia.[58] Sharma et al.[57] have reported that whole and extracted fenugreek seeds diminished blood glucose in diabetic subjects. When given in the diet for 15 days to NIDDM patients prior to an intravenous glucose load, fenugreek powder (25 g) significantly altered plasma glucose kinetics and increased the metabolic clearance rate.[59]

Phytochemistry

Fenugreek seeds are a rich source of protein, unavailable carbohydrates, mucilages, and saponins.[60–63] Fenugreek also contains high dietary fiber. Its viscosity is also high.[43,64] The seeds are also rich in saponins.[65] Three steroidal sapogenins, diosgenin, gitogenin, and tigogenin, have been reported by Anis and Aminuddin.[66] Ghosal et al.[50] have reported a sapogenin peptide ester called fenugreekine. Fenugreek is rich in arginine, alanine, and glycine; the lysine content is very low.[67,68] A major free amino acid, 4-hydroxyisoleucine, was reported in the seeds by Sauvaire et al.[69] Trigonelline is an important alkaloidal component of the seeds.[44] The seeds contain less starch but higher concentrations of minerals such as calcium, iron, phosphorus, Zn, and Mn.[70] The seeds also contain neutral lipids, glycolipids, and phospholipids.[71] Girardon et al.[72] have elucidated the aromatic constituents of the seeds. They include n-alkanes, sesquiterpenes, and oxygenated compounds such as hexanol and γ-nonalactone. Flavanoids, carotenoids, and coumarins are the other constituents present in the seeds.[73]

MOMORDICA CHARANTIA LINN.

Momordica charantia (MC) belongs to the family Curcurbitaceae and is cultivated throughout the tropics, particularly in India, China, East Africa, and Central and South America. It is occasionally grown as an ornamental creeper, but more commonly cultivated for the use of its unripe fruit as a vegetable. MC is a monocious climber cultivated throughout India as a vegetable. The fruit has a number of different local names: bitter gourd, bitter-melon, balsam pear, cundeamor (South America) and karela (India).

MC is also widely used in India and Srilanka as a tonic, emetic, and laxative.[74] Traditional Chinese uses for the fruit, seeds, vines, and leaves include treatment of gastroenteritis, diabetes, tumors, and some viral infections.[75] Karela juice prepared by crushing and straining the unripe fruit (ca. 50 ml) is taken once or twice a day as an antidiabetic remedy. The effects of MC juice or extracts have been studied in normal, alloxan-, and streptozotocin-diabetic rats, rabbits, and mice.

MC juice caused an improvement in glucose tolerance in alloxan-diabetic rabbits but not in normal rabbits. Akhtar et al.[76] observed that dried MC fruit exhibited a significant dose-dependent reduction in blood glucose. They also observed that a minimum dose was required for alloxan-treated rabbits. Kulkarni and Gaitonde[77] did not find a reduction in fasting blood glucose level on acute or chronic administration of dried karela juice to normal rabbits. Administration of a chloroform-soluble extract of the juice caused a marked hypoglycemic effect in alloxan-treated but not normal rabbits.[78] Oral administration of a benzene extract of MC improved glucose tolerance in alloxan-treated rabbits.[79]

A number of studies have been conducted with rats on the effects of MC extracts and juice. Acute administration of the juice has been reported to improve glucose tolerance in normal rats.[80] Gupta[81] also reported improved glucose tolerance in rats with anterior pituitary extract-induced hyperglycemia. Treatment with MC juice for a period of 1 month lowered the glucose tolerance in STZ-induced rats but the effect is not statistically significant.[82] A polar solvent of MC extract improved glucose tolerance of orally and intraperitoneally administered glucose.[83]

The insulin secretagogue activity of MC was studied by Ali et al.,[84] who observed improved glucose tolerance in NIDDM model STZ-treated rats and not in IDDM induced higher dose of STZ. Dale et al.[85] failed to show a significant increase in insulin level with MC treatment in normal rats. Acute administration of MC juice in fasted normal and STZ-treated animals showed a significant improvement in glucose tolerance.[80,82,83,85]

With very high doses of STZ, the effect of MC was abolished and it showed no effect.[86] Chronic administration of karela for 20 days to alloxan-diabetic rats resulted in a significant reduction in blood glucose in a dose-dependent manner.[87–89] Prior administration of MC juice to alloxan-diabetic animals did not show any protective effect.[90] Platel et al.[91] observed a significant lowering of serum cholesterol with MC administration in normal rats. Karela administration also delayed cataractogenesis in STZ-induced diabetic animals.[87-89]

In the normal glucose-primed rat model, MC fruit extract (500 mg/kg) depressed the plasma glucose levels. In STZ-diabetic rats, it improved the oral glucose tolerance test. The extract also caused a significant increase in the rate of glycogen synthesis in the liver of normally fed rats. The study showed that the mechanism of action of MC could be partly attributed to increase in glucose utilization in the liver rather than the insulin secretory effect.[92]

Raza et al.[93] investigated the effects of oral feeding of MC fruit juice on the hepatic cytochrome P_{450} and glutathione-S-transferase drug-metabolizing enzymes in STZ-diabetic rats. Diabetic rats exhibited a 50% increase in aniline hydroxylase, ethoxy resorufin-*o*-deethylase activities, which was reversed by MC juice feeding. Feeding of MC juice to the diabetic animals also showed a significant effect on aminopyrine N-demethylase activity and ethoxy resorufin-*o*-deethylase activity. The cytosolic glutathione concentration was also normalized by karela juice feeding.

Treatment with MC extract improved glucose tolerance in normal mice. The insulin levels in MC extract treated and untreated normal animals did not show any significant changes.[94]

M. charantia juice caused a reduction in STZ-induced apoptosis in RIN cells, indicating the mode of protection of *M. charantia* juice on RIN cells, islets, and pancreatic β-cells.[95]

Long-term feeding (10 weeks) of *M. charantia* fruit extracts on blood glucose and tissue lipid profiles (i.e., plasma, nonesterified cholesterol, triglycerides, and phospholipids showed a decrease in STZ-diabetic rats. HDL-cholesterol was increased by *M. charantia* treatment. The fruit extract also normalized kidney lipid peroxidation in STZ-diabetic rats. The results of this study suggest that the *M. charantia* fruit extract exhibits hypolipidemic as well as hypoglycemic effects.[96] P-insulin, a polypeptide isolated from MC when administered to fasted gerbils and langurs, caused a significant blood glucose-lowering effect.[97]

Charantin isolated from MC by Lotlikar and Rajarama Rao contained a mixture of sitosterol and stigmastadienol glucosides.[98] Oral or intravenous administration of charantin to fasted normal rabbits elicited a significant blood glucose-lowering effect. In alloxan-diabetic rabbits, the effects were more erratic. Pancreatectomy was found to reduce but not abolish the hypoglycemic effect of charantin indicating a dual mechanism of action.[99]

In STZ-induced diabetic rabbits, MC seeds showed a significant blood glucose-lowering effect.[100] The seed also normalized serum cholesterol, fatty acids, triglycerides, and glycogen in muscle and liver. Dubey et al. studied methanol, 50% aqueous ethanol, and normal saline extracts of MC seed on fasted albino rats and found a significant blood glucose-lowering effect. The methanol and saline extracts reduced adrenaline-induced hyperglycemia. In these two experiments, methanol extract showed a highly significant effect compared to the other extracts. In another experiment conducted on the seed extract, Ali et al.[84] failed to observe any decrease in blood glucose levels in fasting or postprandial states and STZ-treated IDDM rats by the seed extract.

Handa et al.[102] have isolated vicine from the seeds of MC. The yield was 0.6%. Vicine caused a hypoglycemic effect when administered intraperitoneally to normal fasted albino rats. Kedar and Chakrabarti[100] used a dose equivalent to about five times the amount of seed administered orally to obtain a response in normal fasting albino rats.

A tea prepared from the MC vines (Cerasee tea) lowered basal glucose concentrations in normal mice and also improved glucose tolerance, but the levels of plasma insulin did not change significantly.[103] Substitution of cerasee tea for drinking water improved glucose tolerance after 12 days of treatment. In normal rats, a methanolic extract and a saponin-free methanolic extract of the whole plant tested in normal rats did not show any effect on fasting blood glucose.[84]

Gupta and Seth[104] studied the effect of oral administration of MC juice (5 ml/kg) on glucose tolerance in albino rats. The treated rats showed a significant reduction in blood sugar compared to control rats. The juice did not influence the absorption from the intestine. In another experiment conducted on normal and alloxan-induced diabetic rats, it was shown that oral administration of MC fruit extract exhibits a reduction in blood sugar.[105] A mild hypoglycemic effect has been observed in normal and alloxanized rabbits after administration of the juice and the dried extract of *M. charantia*. In alloxan-diabetic rats, administration of MC juice at a dose of 10 ml/kg exerted a toxic effect.[106]

Lal and Choudhuri[107] conducted experiments on rabbits after the chronic administration of MC fruit (5 cc/kg) daily for 15 days. They found that the reduction of fasting blood sugar was 10.1% on the 7th day and 23.2% reduction by the 15th day. In another study, Vimala Devi et al.[108] reported the hypoglycemic action of the ether extract of MC leaves in rats. They also stated that the activity of MC leaves was comparable to that of tolbutamide.

Phytochemistry

Momordica charantia fruit contains steroids, charantin, momordicosides (G,F1,F2,I,K,L), acyl glucosyl sterols, linolenoylglucopyranosylclerosterol, amino acids, fatty acids, and phenolic compounds. The seeds of MC contain galactose-binding lectins, vicine, amino acids, fatty acids, terpenoids, and momodicosides (A, B, C, D, and E). The phytochemicals isolated from the whole plant, vines or leaves include saponin, sterols, steroidal glycosides, alkaloids, amino acids, and proteins.[109]

GYMNEMA SYLVESTRE R. BR.

Gymnema sylvestre is a climbing shrub belonging to the family Asclepiadaceae. It is widely used in Indian Ayurvedic medicine for a number of diseases, including diabetes mellitus. It is native to India, especially in Konkan, Maharastra, and western ghats. Reports have indicated that *G. sylvestre* leaf extracts decrease hyperglycemia in diabetic rabbits, rats, and humans.[110–112] Shanmugasundaram and Pannerselvam[113] stated that the glucose-lowering effects may be mediated by increase in insulin secretion.

The leaf extract also showed a significant blood glucose-lowering effect in normal and STZ-induced diabetic rats.[114] Chattopadhyay[115] also studied the effect of water-soluble fraction of alcoholic extract of *G. sylvestre* leaves on glycogen content by isolated rat hemidiaphragm in normal and glucose-fed hyperglycemic rats. In glucose-fed rats, the leaf extract lowered the glycogen content of the tissue significantly.

Persaud et al.[116] examined the effects of an alcoholic extract of *G. sylvestre* (GS_4) on insulin secretion from rat islets of Langerhans and several pancreatic β-cell lines. They have suggested that *G. sylvestre* stimulates insulin release *in vitro* by increased membrane permeability. *G. sylvestre* leaf extracts also regenerate the islets of Langerhans in STZ-diabetic rats.[117] Shanmugasundaram et al. also found that when two water-soluble extracts, GS_3 (60 days) and GS_4 (20 days), were given to diabetic rats, they returned the fasting blood glucose levels to normal levels. GS_3 and GS_4 also showed an increase in serum insulin levels closer to normal value. In diabetic pancreas, GS_3 and GS_4 were able to double the islet number and β-cell number.

Okabayashi et al.[118] studied the effect of GS_4 on glucose homeostasis in nondiabetic and streptozotocin-induced mildly diabetic rats. Administration of 1 g/kg body weight of GS_4 to 18-h fasted nondiabetic rats attenuated the serum glucose response to oral administration of 1 g/kg glucose. In streptozotocin diabetic rats, GS_4 was supplemented with diet. After 1 month, GS_4 showed a significant serum glucose-lowering effect and improved glucose tolerance. GS_3 has been reported to reduce hyperglycemia in diabetic rats, increase insulin release *in vivo* and *in vitro*, and increase β-cell number after STZ-induced diabetes.[117]

A few reports are available on the antidiabetic effect of *G. sylvestre* leaf extract in humans. Baskaran et al.[112] studied the antidiabetic effect of a leaf extract from *G. sylvestre* in NIDDM patients. In 22 type II diabetic patients, GS_4 (400 mg/day) administration for 18 to 20 months showed a significant decrease in blood glucose, glycosylated hemoglobin, and glycosylated proteins. They suggested that β-cells may be regenerated or repaired in type II diabetic patients by GS_4 supplementation. This observation was supported by the increase in the levels of serum insulin on patients after GS_4 supplementation.

Another study showed that administration of GS_4 at a dose of 400 mg/day to 27 patients with NIDDM reduces fasting blood glucose and serum lipids.[117] Conduritol A found in *G. sylvestra* has been reported to have small stimulatory effects on basal insulin secretion from pancreatic islets *in vitro*. The mechanism is not clear.[119]

Phytochemistry

Gymnema sylvestre leaves contain an antisaccharin principle called gymnemic acid. Aqueous ethanolic extractions of the leaves provide two potentially active fractions; one contains conduritol A, an acid-soluble polyol polyhydroxy cyclic compound, and the other contains a mixture of acid-insoluble triterpenoid saponins (gymnemic acids) designated GS_3 or GS_4.[117,120] Methanolic extracts of leaves of *G. sylvestre* contain gymnemic acids I to IV and gymnemasaponin (V).[121]

PTEROCARPUS MARSUPIUM ROXB.

Pterocarpus marsupium Roxb. (Leguminosae) is a large deciduous tree commonly found in hilly regions of India, especially in Deccan Peninsula. It is also distributed in Gujarat, Madhya Pradesh, Uttar Pradesh, Bihar, and Orissa. In different parts of India, *Pterocarpus marsupium* is one of the important drugs widely used in traditional Ayurvedic medicine for the treatment of diabetes mellitus.

Joglekar et al.[122] observed that the administration of *Pterocarpus marsupium* aqueous extract for 15 days to mice lowered glucose absorption from the gastrointestinal tract. This effect was due to the action of tannins in the extract. A similar effect was confirmed by another study, which showed that the infusion of aqueous extract of *P. marsupium* lowers blood glucose level after a glucose meal in rats pretreated with *P. marsupium*.[123] This effect was confirmed in normal and alloxan-induced diabetic rabbits in which the aqueous extract induced a significant hypoglycemic effect.[124,125] Intravenous administration of pterostilbene (10 mg/kg), a constituent of *P. marsupium* wood, showed antihyperglycemic effect in dogs.[126]

Pandey and Sharma[127] have shown that decoction of *P. marsupium* bark (1 g/100 g daily for 10 days) exhibits hypoglycemic action in alloxanized rats. Another report shows that the aqueous extract *P. marsupium* inhibits acute hyperglycemic response induced by the anterior pituitary extract in glucose-fed albino rats.[123]

Chakravarthy et al.[128] reported that the flavonoid fraction of *P. marsupium* regenerates β-cells in experimental diabetic rats. They also isolated a pure flavonoid, (–)-epicatechin, an insulin-stimulating substance from the bark of *P. marsupium*. This flavonoid was obtained from the ethyl acetate-soluble fraction of the ethanolic extract.[129,130] They also confirmed the antidiabetic property of (–)-epicatechin.[131] Epicatechin was found to regenerate the functional β-cells of islets of pancreas in alloxanized rats.[132]

Kolb et al.[133] studied the effect of (–)-epicatechin on alloxanized rats and streptozotocin-induced mice, but they failed to show a hypoglycemic action. Another study carried out by Sheehan et al.[134,135] showed that (–)-epicatechin did not protect the β-cells of pancreas against alloxan-diabetic rats. They also suggested that it did not stimulate β-cell after administration of alloxan. These findings are contrary to the reports of Chakravarthy and coworkers.[129,130] Studies on the effects of (–)-epicatechin and (+)-epicatechin in alloxan-induced rats also did not find a curative effect.[136]

Dharmadhikari and coworkers[137] suggested that the hypoglycemic action of *P. marsupium* may be partly due to the stimulation of insulin secretion from the β-cells of islets of Langerhans and partly due to reduced absorption from gastrointestinal tract. In 1995, Rizvi et al.[138] evaluated the effect of insulin on erythrocyte osmotic fragility and the insulin-like role of (–)-epicatechin on human erythrocytes. Insulin exerts a protective effect on erythrocyte osmotic fragility and (–)-epicatechin also shows a dose–response reaction.

In addition to epicatechin, studies have shown that the heartwood of *P. marsupium* also contains three other phenolic constituents: marsupin, pterosupin, and pterostilbene. These constituents were tested in STZ-induced diabetic rats. Marsupin and pterostilbene lowered the blood glucose level significantly in STZ-hyperglycemic rats and the effect was comparable to that of metformin.[139]

Few clinical reports show the effect of *Pterocarpus marsupium* in diabetic patients. Extracts of *P. marsupium* were found to exert a hypoglycemic effect in diabetic patients.[140] In another study, administration of a decoction of *P. marsupium* for 7 days improved glucose tolerance in diabetic patients. Reduced blood and urine sugar was noticed in *P. marsupium* heartwood capsules (250 mg) in diabetic patients.[141] Kedar and Chakravarti[142] have reported a hypoglycemic action in diabetic patients given the *P. marsupium* wood water (200 ml b.d) for a month. *P. marsupium* also lowered the blood glucose in newly diagnosed or untreated mild NIDDM patients after 12 weeks' treatment.

Phytochemistry

Several flavonoids and their derivatives have been isolated from various parts of the plant. *Pterocarpus marsupium* is a rich source of polyphenolic compounds. The key compounds include the diaryl propane derivative, propterol; the stilbene, pterostilbene; the hydrochalcone, pterosupin; the benzofuranone, marsupsin; the flavanoid, liquiritigenin; and the catechin, (–)-epicatechin. The first four are the main components of the heartwood and (–)-epicatechin is found in the bark. The phenolics marsupsin, pterosupin and pterostilbene have been identified as the blood sugar-lowering components of the heartwood[139] and (–)-epicatechin has been identified as the blood sugar-lowering compound in the bark.[134]

CONCLUSION

Phytomedicine is an interesting science of vast potential. A number of active principles that can be isolated from plants and herbs will revolutionize the mode of treatment of diabetes. Small quantities of these active principles may prove to be more active than the whole plant. Because diabetes is a multifunctional defect, care must be taken before the drugs are administered. The field is open for many to work, identify, and isolate the active principle. Phytomedicine is the medicine of tomorrow and, in the course of time, we shall see many interesting studies and results.

REFERENCES

1. Coimbra, T.C. et al., Plants employed in the treatment of diabetes mellitus: results of an ethnopharmacological survey in Porto Alegre, Brazil, *Fitoterapia*, 63, 320, 1992.
2. Mahapatra, P.K. et al., Preliminary studies on glycemic effects of *Syzigium cumini* seeds, *IRCS Med. Sci. — Biochem.*, 13, 631, 1985.
3. Stanely Mainzen Prince, P., Venugopal P. Menon., and Pari, L., Hypoglycemic activity of *Syzigium cumini* seeds: effect on lipid peroxidation in alloxan-diabetic rats, *J. Ethnopharmacol.*, 61, 1, 1998.
4. Stanely Mainzen Prince, P., Venugopal P. Menon., and Pari, L., Effect of *Syzigium cumini* extracts on hepatic hexokinase and glucose-6-phosphatase in experimental diabetes, *Phytother. Res.*, 11, 529, 1997.
5. Giugliano, D., Ceriello, A., and Paolisso, G., Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress, *Metabolism*, 44, 363, 1995.
6. Bhatia, I.S. and Bajaj, K.L., Chemical constituents of the seeds and bark of *Syzigium cumini*, *Planta Med.*, 28, 349, 1975.
7. Stanely Mainzen Prince, P. et al., Effect of *Syzigium cumini* seed extract on molecular characteristics of collagen in streptozotocin-diabetic rats. *J. Ethnopharmacol.*, (in press), 2005.
8. Nadkarni, A.K., *Indian Materia Medica*, 3rd ed. Bombay, 1982, 1221.
9. Gupta, S.S. et al., Antidiabetic effects of *Tinospora cordifolia*. Part 1. Effect on fasting blood sugar level, glucose tolerance and adrenaline induced hyperglycemia, *Indian J. Med. Res.*, 55, 733, 1967.
10. Gupta, S.S. et al., Antidiabetic effect of *Tinospora cordifolia*. *Indian J. Exp. Biol.*, 55, 733, 1967.
11. Gupta, S.S. et al., Further observation on the antidiabetic effects of *Tinospora cordifolia* and *Casearia esculenta*, *J. Physiol. Pharmacol.*, 1, 10, 1967.
12. Gupta, S.S. et al., A few observations on the antidiabetic effect of *Tinospora cordifolia* and *Casearia esculenta*, *Indian J. Physiol. Pharmacol.*, 9, 9, 1965.
13. Wadood, N., Wadood, A., and Shah, S.A., Effect of *Tinospora cordifolia* on blood glucose and total lipid levels of normal and diabetic rabbits, *Planta Med.*, 58, 131, 1992.
14. Grover, J.K., Vats, V., and Rathi, S., Antihyperglycemic effect of *Eugenia jambolana* and *Tinospora cordifolia* in experimental diabetes and their effects on key metabolic enzymes involved in carbohydrate metabolism, *J. Ethnopharmacol.*, 73, 461, 2000.
15. Stanely Mainzen Prince, P. and Venugopal P. Menon., Hypoglycemic and other related actions of *Tinospora cordifolia* roots in alloxan-induced diabetic rats, *J. Ethnopharmacol.*, 70, 9, 2000.

16. Stanely Mainzen Prince, P., Venugopal P. Menon., and Gunasekaran, G., Hypolipidaemic action of *Tinospora cordifolia* roots in alloxan-diabetic rats, *J. Ethnopharmacol*., 64, 53, 1999.
17. Stanely Mainzen Prince, P. and Venugopal P. Menon., Antioxidant activity of *Tinospora cordifolia* roots in experimental diabetes, *J. Ethnopharmacol*., 65, 277, 1999.
18. Stanely Mainzen Prince, P. and Venugopal P. Menon., Antioxidant action of *Tinospora cordifolia* root extract in alloxan diabetic rats, *Phytother. Res*., 15, 213, 2001.
19. Khan, M.A., Gray, A.I., and Waterman, P.G., Tinosporaside — an 18-norclerodane glucoside from *Tinospora cordifolia*, *Phytochemistry*, 28, 273, 1989.
20. Hanuman, J.B., Bhatt, R.K., and Sabata, B., A clerodane furanoditerpene from *Tinospora cordifolia*, *Phytochemistry*, 25, 1677, 1988.
21. Pradhan, P. et al., Two phytoecdysones (ecdysone and makisterone) from *Tinospora cordifolia*; structural assignments by 2D NMR spectroscopy, *Indian J. Chem.* — Section B, organic including medicinal, 36, 958, 1997.
22. Gangan, V.D. et al., Cordifolioside A, B, C; norditerpene furan glycosides from *Tinospora cordifolia*, *Phytochemistry*, 37, 781, 1994.
23. Gangan, V.D. et al., Norditerpene furan glycosides from *Tinospora cordifolia*, *Phytochemistry*, 39, 1139, 1995.
24. Sipahimalani, A. et al., Phenyl propanoid glycosides and tetrahydrofurofuran lignan glycosides from the adaptogenic plant drugs *Tinospora cordifolia* and *Drypetes roxyburghii*, *Planta Med*., 60, 596, 1994.
25. Maurya, R. et al., Clerodane diterpenoids from *Tinospora cordifolia*, *Phytochemistry*, 38, 659, 1995.
26. Varsha Wazir, et al., Cordioside, a clerodane furano diterpene glucoside from *Tinospora cordifolia*, *Phytochemistry*, 38, 447, 1995.
27. Kapil, A. and Sharma, S., Immunopotentiating compounds from *Tinospora cordifolia. J. Ethnopharmacol*., 58, 89, 1997.
28. Chintalwar, G. et al., An immunologically active arabinogalactan from *Tinospora cordifolia*, *Phytochemistry*, 52, 1089, 1999.
29. Pathak, A.K. et al., NMR studies of 20-beta hydroxy ecdysone, a steroid isolated from *Tinospora cordifolia*, *Indian J. Chem*., Section-B, Organic including Medicinal, 34, 674, 1995.
30. Maurya, R. et al., A sesquiterpene glucoside from *Tinospora cordifolia*, *Phytochemistry*, 44, 749, 1997.
31. Sarma, D.N., Khosa, K.L., and Sahai, M., Isolation of Jatrorrhizine from *Tinospora cordifolia*, *Planta Med*., 61, 98, 1995.
32. Al-Habori, M. and Raman, A., Antidiabetic and hypocholesterolemic effects of fenugreek, *Phytother. Res*., 12, 233, 1998.
33. Khosla, P., Gupta, D.D., and Nagpal, R.K., Effect of *Trigonella foenum graecum* (fenugreek) on blood glucose in normal and diabetic rats, *Indian J. Physiol. Pharmacol*., 39, 173, 1995.
34. Ghafghazi, T. et al., Antagonism of cadmium and alloxan-induced hyperglycemia in rats by *Trigonella foenum graecum*, *Shiraj Med. J*., 8, 14, 1977.
35. Amin, R., Abdul-Ghani, A.S., and Suleiman, M.S., Effect of fenugreek and lupin seeds on the development of experimental diabetes in rats, *Planta Med*., 54, 286, 1988.
36. Ribes, G. et al., Antidiabetic effects of subfractions from fenugreek seeds in diabetic dogs, *Proc. Soc. Exp. Biol. Med*., 182, 159, 1986.
37. Ajabnoor, M.A., and Tilmisany, A.K., Effect of *Trigonella foenum graecum* on blood glucose levels in normal and alloxan-diabetic mice, *J. Ethnopharmacol*., 22, 45, 1988.
38. Madar, Z., Fenugreek (*Trigonella foenum graecum*) as a means of reducing postprandial glucose level in diabetic rats, *Nutr. Rep. Int*., 29, 1267, 1984.
39. Ribes, G. et al., Effects of fenugreek seeds on endocrine pancreatic secretions in dogs, *Ann. Nutr. Metabolism*, 28, 37, 1984.
40. Petit, P. et al., Effect of a fenugreek seed extract on feeding behavior in the rat: metabolic-endocrine correlates, *Pharmacol. Biochem. Behav*., 45, 369, 1993.
41. Petit, P. et al., Insulin stimulating effect of an original amino acid, 4-hydroxyisoleucine, purified from fenugreek seeds, *Diabetologia*, 38, A101, 1995.
42. Sauvaire, Y. et al., Steroid saponins from fenugreek and some of their biological properties, *Nutr. Rep. Int*., 405, 37, 1996.

43. Valette, G. et al., Hypocholesterolaemic effect of fenugreek seeds in dogs, *Atherosclerosis*, 50, 105, 1984.
44. Mishkinsky, J., Joseph, B., and Sulman, F., Hypoglycemic effect of trigonelline, *Lancet*, 1, 1311, 1967.
45. Shani, J. et al., Hypoglycemic effect of *Trigonella foenum graecum* and *Lupinus teamis* (Leguminosae) seeds and their major alkaloids in alloxan diabetic and normal rats, *Archieves Internationals de Pharmacodynamic et de Therapie*, 30, 221, 1974.
46. Moorthy, R., Prabhu, K.M., and Murthy, P.S., Studies on the isolation and effect of an orally active hypoglycemic principle from the seeds of fenugreek (*Trigonella foenum graecum*), *Diabetes Bull.*, 9, 69, 1989.
47. Hillaire-Buys, D. et al., A recently identified substance extracted from fenugreek seeds stimulates insulin secretion in rat, *Diabetologia*, 36, A119, 1993.
48. Fowden, L., Pratt, H.M., and Smith, A., 4-Hydroxyisoleucine from seed of *Trigonella foenum graecum*, *Phytochemistry*, 12, 1701, 1973.
49. Alcock, N.W. et al., Stereochemistry of the 4-hydroxyisoleucine from *Trigonella foenum graecum*, *Phytochemistry*, 28, 1835, 1989.
50. Ghosal, S. et al., Extractives of *Trigonella* –1. Fenugreekine, a new steroidal sapogenin-peptide ester of *Trigonella foenum graecum*, *Phytochemistry*, 13, 2247, 1974.
51. Sharma, R.D., Effect of fenugreek seeds and leaves on blood glucose and serum insulin responses in human subjects, *Nutr. Res.*, 6, 1353, 1986a.
52. Madar, Z. et al., Glucose lowering effect of fenugreek in non-insulin dependent diabetics, *Eur. J. Clin. Nutr.*, 42, 51, 1988.
53. Madar, Z. and Shomer, I., Polysaccharide composition of a gel fraction derived from fenugreek and its effect on starch digestion and bile acid absorption in rats, *J. Agric. Food Chem.*, 38, 1535, 1990.
54. Ali, L. et al., Characterization of the hypoglycemic effects of *Trigonella foenum graecum* seed, *Planta Med.*, 61, 358, 1995.
55. Platel, K. and Srinivasan, K., Influence of dietary spices or their active principles on digestive enzymes of small intestinal mucosa in rats, *Int. J. Food Sci. Nutr.*, 47, 55, 1996.
56. Fourier, F., Plantes medicinales at venereuses de France, *Paris*, 111, 495, 1948.
57. Sharma, R.D., Raghuram, T.C., and Rao, N.S., Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes, *Eur. J. Clin. Nutr.*, 44, 301, 1990.
58. Sharma, R.D. and Raghuram, T.C., Hypoglycemic effect of fenugreek seeds in non-insulin-dependent diabetic subjects, *Nutr. Res.*, 10, 731, 1990.
59. Raghuram, T.C. et al., Effect of fenugreek seeds and intravenous glucose disposition in non-insulin dependent diabetic patients, *Phytother. Res.*, 8, 83, 1994.
60. Sauvaire, Y. and Baccou, J.S., Nutritional value of the proteins of leguminous seed, fenugreek (*Trigonella foenum graecum* L.), *Nutr. Rep. Int.*, 14, 527, 1976.
61. Baccou, J.C. et al., 'L' huile de fenugreec, composition, properties, possibilities d' utilisation dans, *Industrie Peintures Vernis*, 25, 353, 1978.
62. El-Mahdy, A.R., and El-sebaiy, L.A., Proteolytic activity, amino acid composition, protein quality of fermented fenugreek seeds (*Trigonella foenum graecum*), *Food Chem.*, 18, 19, 1985.
63. Udayasekhara Rao, P. and Sharma, R.D., An evaluation of protein quality of fenugreek seeds (*Trigonella foenum graecum*) and their supplementary effects, *Food Chem.*, 24, 1, 1987.
64. Chatterjee, B.P., Sekar, N., and Rao, A.S., Serologica and chemical investigations of the anomeric configuration of sugar units in the D-galacto-D-mannan of fenugreek (*Trigonella foenum graecum*) seeds, *Carbohyd. Res.*, 104, 348, 1982.
65. Sharma, R.D., An evaluation of hypocholesterolemic factor of fenugreek seeds (*T. foenum graecum*) in rats, *Nutr. Rep. Int.*, 33, 669, 1986b.
66. Anis, M. and Aminuddin, E., Estimation of diosgenin in seeds of induced autoploid *Trigonella foenum graecum*, *Fitoterapia*, 56, 51, 1985.
67. Gopalan, C., Rama Shastri, B.V., and Balasubramaniyan, S.C., Nutritive value of Indian Foods, National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, 1978.
68. Sharma, R.D., Hypocholesterolemic activity of fenugreek (*T. foenum graecum*): an experimental study in rats, *Nutr. Rep. Int.*, 30, 221, 1984.
69. Sauvaire, Y. et al., Changes in growth, proteins and free amino acids of developing seed and pod of fenugreek, *Phytochemistry*, 23, 479, 1984.

70. Sankara Rao, D.S., and Deosthale, Y.G., Mineral composition of four Indian food legumes, *J. Food Sci.*, 46, 1962, 1981.
71. Hemavathy, J. and Prabhakar, J.V., Lipid composition of fenugreek (*Trigonella foenum graecum* L.) seeds, *Food Chem.*, 31, 1, 1989.
72. Girardon, P. et al., Volatile constituents of fenugreek seeds, *Planta Med.*, 6, 533, 1985.
73. Varshney, I.P. and Sharma, S.C., Saponins XXXII — *Trigonella foenum graecum* seeds, *J. Ind. Chem. Soc.*, 43, 564, 1996.
74. Nadkarni, A.K., *Indian Materia Medica*, 3rd ed. Popular Prakashan, Bombay, 1982, 805.
75. Zhang., Preliminary report on the use of *Momordica charantia* extract by HIV patients. *J. Naturopathic Med.,* 3, 65, 1992.
76. Akthar, M.S., Athar, M.A., and Yagub, M., Effect of *Momordica charantia* on blood glucose level of normal and alloxan-diabetic rabbits, *Planta Med.*, 42, 205, 1981.
77. Kulkarni, R.D. and Gaitonde, B.B., Potentiation of tolbutamide action by *Jasad Bhasma* and *karela* (*Momordica charantia*), *Indian J. Med. Res.*, 50, 715, 1962.
78. Tiangda, C. et al., The hypoglycemic activity of *Momordica charantia* Linn. in normal and alloxan-induced diabetic rabbits, *J. Nat. Res. Counc.*, 19, 1, 1987.
79. Venkanna Babu, B. et al., Alloxan recovered rabbits as animal model for screening for hypoglycemic activity of compounds, *Indian J. Biochem. Biophys.*, 25, 714, 1988.
80. Chandrasekar, B., Mukherjee, B., and Mukherjee, S.K., Blood sugar lowering potentiality of selected cucurbitaceae plants of Indian origin, *Indian J. Med. Res.*, 90, 300, 1989.
81. Gupta, S.S., Experimental studies on pituitary diabetes. Part III. Effect of indigenous antidiabetic drugs against the acute hyperglycemic response of anterior pituitary extract in glucose fed albino rats, *Indian J. Med. Res.*, 51, 716, 1963.
82. Karunanayake, E.H., Jeevathayaparan, S., and Tennekoon, K.H., Effect of *Momordica charantia* fruit juice on streptozotocin induced diabetes in rats, *J. Ethnopharmacol.*, 30, 199, 1990.
83. Higashino, H. et al., Hypoglycemic effects of siamese *Momordica Charantia* and *Phyllanthus urinaria* extracts in streptozotocin-induced diabetic rats (the first report), *Nippon Yakurigaku Zasshi*, 100, 415, 1992.
84. Ali, L. et al., Insulin releasing properties of fractions from *Momordica charantia* fruit on isolated rat islets, *Diabetologia*, 36, 181, 1993.
85. Dale, L.B.A. et al., Improvement in glucose tolerance due to *Momordica charantia* (karela), *Br. Med. J.*, 282, 1823, 1981.
86. Ali, L. et al., Studies on the hypoglycemic effects of fruit pulp, seed and whole plant of *Momordica charantia* on normal and diabetic model rats, *Planta Med.*, 59, 408, 1993b.
87. Srivastava, Y. et al., Retardation of retinopathy by *Momordica charantia* L. (bitter gourd) fruit extract in alloxan-diabetic rats, *Indian J. Exp. Biol.*, 25, 571, 1987.
88. Srivastava, Y., Venkatakrishna-Bhatt, H., and Verma, Y., Effect of *Momordica charantia* Linn. pomous aqueous extract on cataractogenesis in murrin alloxan diabetics, *Pharmacol. Res. Commun.*, 20, 201, 1988.
89. Srivastava, Y. et al., Antidiabetic and adaptogenic properties of *Momordica charantia* extract: An experimental and clinical evaluation, *Phytother. Res.*, 7, 285, 1993.
90. Sharma, V.N., Sogani, R.K., and Arora, R.B., Some observations on hypoglycemic activity of *Momordica charantia*, *Indian J. Med. Res.*, 48, 471, 1960.
91. Patel, K., Shurpalekar, K.S., and Srinivasan, K., Influence of bitter gourd (*Momordica charantia*) on growth and blood constituents in albino rats, *Die Nahrung*, 37, 156, 1993.
92. Sarkar, S., Pranava, M., and Marita R., Demonstration of the hypoglycemic action of *Momordica charantia* in a validated animal model of diabetes, *Pharmacol. Res.,* 33, 1, 1996.
93. Raza, H. et al., Effect of bitter melon (*Momordica charantia*) fruit juice on the hepatic cytochrome P_{450} — dependent monooxygenases and glutathione S-transferases in streptozotocin-induced diabetic rats, *Biochem. Pharmacol.*, 52, 1639, 1996.
94. Day, C. et al., Hypoglycemic effect of *Momordica charantia* extracts, *Planta Med.*, 56, 426, 1990.
95. Sitasawad, S.L., Shewade, Y., and Bhonde, R., Role of bitter gourd fruit juice in STZ-induced diabetic state *in vivo* and *in vitro*, *J. Ethnopharmacol.*, 73, 71, 2000.

96. Ahmed, I. et al., Hypotriglyceridemic and hypocholesterolemic effects of anti-diabetic *Momordica charantia* (karela) fruit extract in streptozotocin-induced diabetic rats, *Diabetes Res. Clin. Pract.*, 51, 155, 2001.
97. Khanna, P. et al., Hypoglycemic activity of polypeptide-P from a plant source, *J. Nat. Prod.*, 44, 648, 1981.
98. Lotlikar, M.M. and Rajarama Rao, M.R., Note on a hypoglycemic principle isolated from the fruits of *Momordica charantia*, *J. Univ. Bombay*, 29, 223, 1960/1961.
99. Lotlikar, M.M. and Rajarama Rao, M.R., Pharmacology of a hypoglycemic principle isolated from the fruits of *Momordica charantia* Linn., *Indian J. Pharmacol.*, 28, 129, 1966.
100. Kedar, P. and Chakrabarti, C.H., Effect of bitter gourd (*Momordica charantia*) seed and glibenclamide in streptozotocin induced diabetes mellitus, *Indian J. Exp. Biol.*, 20, 232, 1982.
101. Dubey, D.K. et al., Hypoglycemic and antihyperglycemic effects of *Momordica charantia* seed extracts in albino rats, *Fitoterapia*, LVIII, 387, 1987.
102. Handa, G. et al., Hypoglycemic principle of *Momordica charantia* seeds, *Indian J. Nat. Prod.*, 6, 16, 1990.
103. Bailey, C.J. et al., Cerasee, a traditional treatment for diabetes. Studies in normal and streptozotocin-diabetic mice, *Diabetes Res.*, 2, 81, 1985.
104. Gupta, S.S. and Seth, C.B., Effect of *Momordica charantia* Linn. (karela) on glucose tolerance in albino rats, *J. Indian Med. Assoc.*, 39, 581, 1962.
105. Krishnamurthy, T.R. The effect of an extract of *Momordica charantia* on blood sugar in animals, *Antiseptic*, 59, 131, 1962.
106. Pabrai, P.R. and Sehra, K.B., Effect of *Momordica charantia* on blood sugar in rabbits, *Indian J. Pharmacol.*, 24, 209, 1962.
107. Lal, B.N. and Choudhuri, K.D., Observations on *Momordica charantia* Linn. (*Karvellaka*) and *Eugenia jambolana* Lam. (*Jamboo*) as oral antidiabetic remedies, *J. Res. Indian Med.*, 2, 161, 1968.
108. Vimala Devi, M., Venkateswarlu, M., and Krishna Rao, R.V., Hypoglycemic activity of the leaves of *Momordica charantia*, abstract of the paper presented at XXIX Indian Pharmaceutical Congress, Waltair, December 1977, 28–31, *Indian J. Pharmacol.*, 39, 167, 1977.
109. Raman, A. and Lau, C., Antidiabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae), *Phytomedicine*, 2, 349, 1996.
110. Shanmugasundaram, K.K. et al., Enzyme changes and glucose utilisation in diabetic rabbits: the effect of *Gymnema sylvestre*, R. Br., *J. Ethnopharmacol.*, 7, 205, 1983.
111. Srivastava, Y. et al., Hypoglycemic and life prolonging properties of *Gymnema sylvestre* leaf extract in diabetic rats, *Israel J. Med. Sci.*, 21, 540, 1985.
112. Baskaran, K. et al., Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin dependent diabetes mellitus patients, *J. Ethnopharmacol.*, 30, 295, 1990.
113. Shanmugasundaram, K.R. and Panneerselvam, C., The insulinotropic activity of *Gymnema sylvestre* R. Br. an Indian medical herb used in controlling diabetes mellitus, *Pharmacol. Res. Commun.*, 13, 475, 1981.
114. Chattopadhyay, R., A comparative evaluation of some blood sugar lowering agents of plant origin, *J. Ethnopharamcol.*, 67, 367, 1999.
115. Chattopadhyay, R., Possible mechanism of antihyperglycemic effect of *Gymnema sylvestre* leaf extract, part I, *Gen. Pharmacol.*, 31, 495, 1998.
116. Persaud, S.J. et al., *Gymnema sylvestre* stimulates insulin release *in vitro* by increased membrane permeability, *J. Endocrinol.*, 163, 207, 1999.
117. Shanmugasundaram, E.R. et al., Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus, *J. Ethnopharmacol.*, 30, 281, 1990.
118. Okayabayashi, Y. et al., Effect of *Gymnema sylvestre* R. Br. on glucose homeostasis in rats, *Diabetes Res. Clin. Pract.*, 9, 143, 1990.
119. Billington, D.C. et al., Total synthesis of novel conduoritol-related compounds capable of modulating insulin release, *Bioorganic Med. Chem. Lett.*, 4, 2307, 1994.
120. Miyatake, K. et al., Isolation of conduritol A from *Gymnema sylvestre* and its effect against intestinal glucose absorption in rats, *Biosci., Biotech. Biochem.*, 57, 2184, 1993.
121. Sugihara, Y. et al., Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice, *J. Asian Nat. Prod. Res.*, 2, 321, 2000.

122. Joglekar, G.V., Chaudhary, N.Y., and Aiman, R., Effect of indigenous plant extracts on glucose-absorption in mice, *Indian J. Physiol. Pharmacol.*, 3, 76, 1959.
123. Gupta, S.S., Effect of *Gymnema sylvestre* and *Pterocarpus marsupium* on glucose tolerance in albino rats, *Indian J. Med. Sci.*, 17, 501, 1963.
124. Shah, D.S., A preliminary study of the hypoglycemic action of heartwood of *Pterocarpus marsupium* Roxb., *Indian J. Med. Res.*, 55, 166, 1967.
125. Trivedi, C.P., Observations on the effect of some indigenous drug on blood sugar level of normal and diabetic rabbits, *Indian J. Physiol. Pharmacol.*, 7, 11, 1963.
126. Haranath, P.S.R.K. et al., Studies on the hypoglycemic and pharmacological actions of some stilbenes, *Indian J. Med. Sci.*, 12, 85, 1958.
127. Pandey, M.C. and Sharma, P.V., Hypoglycemic effect of bark of *Pterocarpus marsupium* Roxb. (*Bijaka*): a clinical study, *Med. Surg.*, 11, 21, 1975.
128. Chakravarthy, B.K. et al., Pancreatic beta-cell regeneration. A novel antidiabetic mechanism of *Pterocarpus marsupium* Roxb., *Indian J. Pharmacol.*, 12, 123, 1980.
129. Chakravarthy, B.K. et al., 1-Epicatechin, a novel antidiabetic drug, *Indian Drugs*, 18, 184, 1981.
130. Chakravarthy, B.K. et al., The prophylactic action of (–)-epicatechin against alloxan-induced diabetes in rats, *Life Sci.*, 29, 2043, 1981.
131. Chakravarthy, B.K. et al., Pancreatic beta-cell regeneration in rats by (–)-epicatechin, *Lancet,* II, 8249, 759, 1981.
132. Chakravarthy, B.K., Gupta, S., and Gode, K.D., Functional beta-cell regeneration in the islets of pancreas in alloxan-induced diabetic rats by (–)-epicatechin, *Life Sci.*, 31, 2693, 1982.
133. Kolb, H. et al., Lack of antidiabetic effect of (–)-epicatechin, *Lancet,* I, 8284, 1303, 1982.
134. Sheehan, E.W. et al., A constituent of *Pterocarpus marsupium*, (–)-epicatechin has a potential antidiabetic effect, *J. Nat. Prod.*, 46, 232, 1983.
135. Sheehan, E.W. et al., The lack of effectiveness of (–)-epicatechin against alloxan induced diabetes in Wistar rats, *Life Sci.*, 33, 593, 1983.
136. Ryle, P.R. et al., Alloxan-induced diabetes in the rat-protective action of (–)-epicatechin, *Life Sci.*, 34, 591, 1984.
137. Dharmadhikari, S.D., Patki, V.P., and Dashputra, P.G., Study of mechanism of hypoglycemia due to *Pterocarpus marsupium*', Abstract of paper presented at XVI Annual Conference, Indian Pharmacological Society, Ajmeer, *Indian J. Pharmacol.*, 16, 61, 1984.
138. Rizvi, S.I., Abu Zaid, M., and Suhail, M., Insulin-mimetic effect of (–) epicatechin on osmotic fragility of human erythrocytes, *Indian J. Exp. Biol.,* 33, 791, 1995.
139. Manickam, M. et al., Antihyperglycemic activity of phenolics from *Pterocarpus marsupium*, *J. Nat. Prod.*, 60, 609, 1997.
140. Sepaha, G.C. and Bose, S.N., Clinical observations on the antidiabetic properties of *Pterocarpus marsupium* and *Eugenia jambolana, J. Indian Med. Assoc.*, 27, 388, 1965.
141. Rajasekharan, S. and Tuli, S.N., *Vijaysar, Pterocarpus marsupium*, in the treatment of *madhumeha* (diabetes mellitus) — a clinical trial, *J. Res. Ind. Med. Yoga Homeo.*, 11, 9, 1976.
142. Kedar, P. and Chakrabarti, C.H., Blood sugar, blood urea and serum lipids as influenced by *Gurmar* preparation, *Pterocarpus marsupium* and *Tamarindus indica* in diabetes mellitus, *Maharashtra Med. J.*, 28, 165, 1981.

6 Traditional Chinese and Kampo Medicines

Masayuki Yoshikawa and Hisashi Matsuda

CONTENTS

INTRODUCTION

Traditional Chinese medicine and Kampo medicine (traditional Japanese medicine) are used to treat sick people; they use formulations that combine several kinds of crude drugs prescribed based on certain rules corresponding to the patient's condition rather than to the name of a disease. Many

clinical studies of formulations for diabetes mellitus in China and Japan have been reported. In traditional Chinese and Japanese medicines, except for urorrhagia and nephropathy, diseases that present with symptoms such as overintake of water due to polyuria and thirst ("Shokati" in Japanese) are considered to be diabetes mellitus in modern medicine. Though Kampo medicines have been suggested not to be so effective for the treatment of hyperglycemia clinically, they are effective for the improvement of the accompanying symptoms of diabetes mellitus such as polydispia, polyuria, and neuropathy.

Abnormalities in the blood or vasculature are important factors in the development of diabetic complications. In traditional Chinese and Japanese medicines, the syndrome caused by blood stagnation or microcirculation difficulties is termed "Oketsu" (in Japanese), and anti-Oketsu drugs such as Keishi-bukuryo-gan (Gui-zhi-fu-ling-wan) and Hachimi-jio-gan (Bai-wei-di-huang-wan) are clinically applied for retinopathy, nephrosis, cerebral infarct, ischemic heart disease, and arteriosclerosis. The pharmacological study of anti-Oketsu medicines (Kampo medicines for overcoming blood stagnation) on microcirculation difficulties is not satisfactory. However, administration of anti-Oketsu medicines at the initial stage of diabetes was suggested to prevent the development of diabetic complications by improving the coagulation and fibrolysis systems.[1] On the other hand, there are few clinical reports about each crude drug except for Ginseng Radix. In experimental models, many studies of *in vitro* examinations or of the effects on diabetes by nonoral administration have been undertaken. Therefore, it is unclear whether the reported crude drugs are effective or not by oral administration.

This chapter first describes several representative formulations that have been applied for treatment of diabetes mellitus and then the hypoglycemic effect, inhibition of aldose reductase, and anti-Oketsu effect of the crude drugs composed of the formulations in experimental models.

KAMPO MEDICINES WITH ANTIDIABETIC EFFECTS

Latin binomial and plant family names of crude drugs that appear in this section are listed in Table 6.1.

Bakumondo-to (Mai-men-dong-tang)

(Ginseng Radix, Glycyrrhizae Radix, Ophiopogonis Tuber, Oryzae Fructus, Pinelliae Tuber, and Zizyphi Fructus)

This agent is prescribed in patients in whom physical fitness is slightly reduced. In treating diabetes, the agent is indicated for pharyngeal dryness, but not for polydipsia and polyuria.[2]

Bofu-tsusho-san (Fang-feng-tong-sheng-san)

(Angelicae Radix, Atractylodis Rhizoma, Cnidii Rhizoma, Ephedreae Herba, Scutellariae Radix, Forsythiae Fructus, Gardeniae Fructus, Gycyrrhizae Radix, Gypsum Fibrosum, Talcum (talc), Saposhinikoviae Radix, Menthae Herba, Natrium Sulfuricum (sodium sulfate), Paeoniae Radix, Platycodi Radix, Rhei Rhizoma, Schizonepetae Spica, Zingiberis, and Rhizoma)

This prescription is prescribed to treat obesity, constipation, rush of blood to the head, hyperidrosis, and stiff shoulders. In the abdomen, abdominal strength involving the navel is enhanced.[2]

KK-A^y mice are characterized not only by hyperglycemia, but also by polydipsia and polyuria, similar to human diabetes mellitus. Bofu-tsusho-san (BOF) as the food admixture (1.5% of food weight) for 4 weeks decreased increases in body weight without affecting food intake, water intake, blood glucose level, and urine volume. In addition, the crude drug with acceleration of insulin secretion was suggested to exist in BOF because an increase in serum insulin levels was observed in rats administered BOF. BOF was suggested to be effective against polydipsia, as well as polyuria and hyperglycemia, in diabetes mellitus.[3]

TABLE 6.1
Latin Binomial and Plant Family Names of Crude Drugs Prescribed in Kampo Medicines

Pharmaceutical Name	Latin Binomial	Plant Family
Achyranthis Radix	*Achyranthes fauriei* Leveillé et Vaniot, *A. bidentata* Blume	Amaranthaceae
Aconiti Tuber	*Aconitum carmichaeli* Debx.	Ranunclaceae
Alismatis Rhizoma	*Alisma orientale* Juzepczuk	Alismataceae
Anemarrhenae Rhizoma	*Anemarrhena asphodeloides* Bunge	Liliaceae
Angelicae Radix	*Angelica acutiloba* Kitagawa, *A. actiloba* Kitagawa var. *sugiyamae* Hikino	Umbelliferae
Astragali Radix	*Astragalus membranaceus* Bunge, *A. mongholicus* Bunge	Leguminosae
Atractylodis Lanceae Rhizoma	*Atractylodes lanceae* De Candolle, *A. chinensis* Koidzumi	Compositae
Atractylodis Rhizoma	*Atractylodes japonica* Koidzumi ex Kitamura, *A. ovata* De Candolle	Compositae
Auranti Fructus Immaturus	*Citrus aurantium* Linné var. *daidai* Makino, *C. aurantium* Linné, *C. natsudaidai* Hayata	Rutaceae
Bupleuri Radix	*Bupleurum falcatum* Linné, *B. chinense* DC., *B. scorzonefolium* Wild.	Umbelliferae
Cimicifugae Rhizoma	*Cimicifuga simplex* Wormskjord, *C. dahurica* (Turcz.) Maximmowicz, *C. foetida* Linné, *C. heracleifolia* Komarov	Ranunculaceae
Cinnamomi Cortex	*Cinnamomum* cassia Blume	Lauraceae
Cnidii Rhizoma	*Cnidium officinale* Makino	Umbelliferae
Corni Fructus	*Cornus officinalis* Siebold et Zuccarini	Cornaceae
Dioscoreae Rhizoma	*Dioscorea japonica* Thunberg, *D. batatas* Decaisne	Dioscoreaceae
Ephedreae Herba	*Ephedra sinica* Stapf, *E. intermedia* Schrenk et C.A. Meyer, *E. equisetina* Bunge	Ephedraceae
Forsythiae Fructus	*Forsythia suspensa* Vahl, *F. viridissima* Lindley	Oleaceae
Gardeniae Fructus	*Gardenia jasminoides* Ellis	Rubiaceae
Ginseng Radix	*Panax ginseng* C.A. Meyer	Araliaceae
Gycyrrhizae Radix	*Glycyrrhiza uralensis* Fisher, *G. glabara* L.	Leguminosae
Gypsum Fibrosum	gypsum	
Poria	*Poria cocos* Wolf	Polyporaceae
Saposhnikoviae Radix	Saposhnikovia divaricata Schischkin	Umbelliferae
Menthae Herba	*Mentha arvensis* Linné var. *piperascens* Malinvaud	Labiatae
Moutan Cortex	*Paeonia suffruticosa* Andrews (= *P. moutan* Sims)	Paeoniaceae
Natrium Sulfuricum		
Ophiopogonis Tuber	*Ophiopogon japonicus* Ker-Gawler	Liliaceae
Oryzae Semen	*Oryza sativa* Linné	Gramineae
Ostreae Testa	*Ostrea gigas* Thunberg	Ostreidae
Paeoniae Radix	*Paeonia lactiflora* Pallas	Paeoniaceae
Persicae Semen	*Prunus perscia* Batsch., *P. persica* Batsch. var. *davidiana* Maximowicz	Rosaceae
Pinelliae Tuber	*Pinellia ternata* Breitenbach	Araceae
Plantagini Semen	*Plantago asiatica* Linné	Plantaginaceae
Platycodi Radix	*Platycodon garndiflorum* A. De Candolle	Campanulaceae
Rehmanniae Radix	*Rehmannia glutinosa* Liboschitz var. *purpurea* Makino, *R. glutinosa* Liboschitz	Scrophulariaceae

(continued)

TABLE 6.1 (CONTINUED)
Latin Binomial and Plant Family Names of Crude Drugs Prescribed in Kampo Medicines

Pharmaceutical Name	Latin Binomial	Plant Family
Rhei Rhizoma	*Rheum palmatum* Linné, *R. tanguticum* Maximowicz, *R. officinale* Baillon, *R. coreanum* Nakai	Polygonaceae
Schizonepetae Spica	*Schizonepeta tenuifolia* Briquet	Labiatae
Scutellariae Radix	*Scutellaria baicalensis* Georgi	Labiatae
Trichosanthis Radix	*Trichosanthes kirilowii* Maximowicz, *T. kirilowii* Maximowicz var. *japonicum* Kitamura, *T. bracteata* Voigt	Cucurbitaceae
Zingiberis Rhizoma	*Zingiber officinale* Roscoe	Zingiberaceae
Zingiberis Siccatum Rhizoma	*Zingiber officinale* Roscoe	Zingiberaceae
Zizyphi Fructus	*Zizyphus jujuba* Miller var. *inermis* Rehder	Rhamnaceae

Hypertriglyceridemia and body fat accumulation were observed in female SD rats when rats were freely allowed to drink 25% (w/w) fructose solution for 6 weeks. As the food admixture (1.5 and 4.5% of food weight), BOF suppressed body weight gain and prevented the elevation of serum triglyceride (TG) levels and body fat accumulation in fructose-loaded rats without affecting food and fructose intake. Furthermore, BOF prevented the increase in TG content in the liver and the reduction of mitochondrial cytochrome c oxidase activity in the brown adipose tissue induced by fructose. These results suggested that BOF has a preventive effect against body fat accumulation caused by excess intake of sugar or other fructose-containing foods.

The inhibition of triglyceride synthesis in the liver and the enhancement of lipolysis in adipocytes and of thermogenesis in brown adipose tissue have been presumed as the mechanism of action of BOF. BOF reduced body weight and rat retroperitoneal white adipose tissue weight decreased without affecting food intake in MSG obese mice. BOF was suggested to act *via* activation of thermogenesis in brown adipose and inhibition of phosphodiesterase activity in mice.[4,5] Among the crude drugs combined in BOF, Angelicae Radix and Cnidii Rhizoma were reported to exhibit inhibitory effects on platelet aggregation and blood coagulation.[6,7]

Byakko-ka-ninjin-to (Bai-hu-jia-ren-sheng-tang)

(Anemarrhenae Rhizoma, Ginseng Radix, Glycyrrhizae Radix, Gypsum Fibrosum, and Oryzae Semen)

Byakko-ka-ninjin-to (BNT) is used to treat thirst sensation, local burning sensation, rush of blood to the head, exanthema, dermal pruritus, increased urine volume, and sweating. This agent is prescribed in obese patients with initial phase type 2 diabetes.[2]

Okumura et al. reported that BNT at 100 mg/kg inhibited the increase in serum glucose and TG levels after 4 to 8 weeks of treatment in KK-A^y mice — an animal model of non-insulin-dependent diabetes mellitus (NIDDM) — but did not inhibit the increase in serum insulin levels.[8] However, Morimoto et al. reported that treatment with BNT as a food admixture (1.5 and 4.5% of food weight) for 4 weeks did not affect blood glucose levels and body weight in KK-A^y mice, but decreased water intake and urine volume.[3] Miura et al. also reported that BNT at 90 mg/kg/day decreased the blood glucose levels of KK-A^y mice with exercise for 1 and 2 weeks after the administration, but did not decrease the blood glucose levels of the mice without exercise.[9] These studies suggested that BNT was effective against the polydipsia and polyuria that accompany diabetes mellitus.[3]

Anemarrhenae Rhizoma and Ginseng Radix prescribed in this formulation were reported to show hypoglycemic effects, and Glycyrrhizae Radix was reported to inhibit the accumulation of sorbitol due to its inhibition of aldose reductase activity (see Anemarrhenae Rhizoma, Ginseng Radix, and Glycyrrhizae Radix in this chapter).

Dai-sakiko-to (Dai-chai-hu-tang)

(Auranti Fructus Immaturus, Bupleuri Radix, Paeoniae Radix, Pinelliae Tuber, Rhei Rhizoma, Scutellariae Radix, Zingiberis Rhizoma, and Zizyphi Fructus)

Dai-sakiko-to (DST) is used to treat fullness, tenderness, or discomfort of the hypochondrium ("Kyokyo-kuman" in Japanese) and upper abdominal pain. In addition, DST is prescribed in patients with stiff shoulders, anorexia, dyspnea, obesity, or constipation and is commonly indicated for obese patients with type 2 diabetes.[2]

Goto et al. reported that DST improved impairment of glucose tolerance and reduced serum TG levels in cyproheptadine-induced diabetic rats by oral administration of five- to tenfold doses for humans (5.4 g/60 kg/day) for 4 weeks.[10] In spontaneous diabetic rats (WBN/Kob) treated with vitamin D_2 and hyperlipidemic diet, DST at tenfold doses for humans improved impairment of glucose tolerance and normalized mineral metabolic disorder.[11] In addition, it was reported that DST inhibited the increase in the blood glucose level, but not insulin level, and improved the high TG after its administration for 4 weeks at 100 mg/kg/day in KK-A^y mice.[8] Among the crude drugs combined in DST, Rhei Rhizoma showed inhibition of advanced glycation end-products (AGE) formation, experimental renal failure induced by adenine feeding, and platelet aggregation,[12–14] and Paeoniae Radix showed hypoglycemic effects (see Paeoniae Radix in this chapter).

Gosha-jinki-gan (Niu-che-shen-qi-wan)

(Achyranthis Radix, Aconiti Tuber, Alismatis Rhizoma, Cinnamomi Cortex, Corni Fructus, Dioscorea Rhizoma, Poria, Moutan Cortex, Plantagini Semen, and Rehmanniae Radix)

Gosha-jinki-gan (GJG) is prepared by adding two crude drugs, Achyranthis Radix and Plantagini Semen, to Hatimi-jio-gan (Bai-wei-di-huang-wan). Indications are similar to those for Hatimi-jio-gan (see Hatimi-jio-gan in this chapter). However, GJG is prescribed when symptoms such as decreased urine volume, edema, lower limb pain, numbness, and lumbar pain are severe. In addition, GJG was reported to be effective in diabetic neuropathy clinically.[2]

Suzuki et al. reported that the enhanced platelet aggregation was inhibited by a single treatment with GJG at doses of 0.3 and 1.5 g/kg (p.o.) in streptozotocin (STZ)-induced diabetic rats.[15] GJG (0.1 to 1.0 g/kg, p.o.) showed a more potent antinociceptive effect in diabetic mice than in nondiabetic mice, and it was concluded that GJG was useful for treating painful diabetic neuropathy.[16]

Hatimi-jio-gan (Bai-wei-di-huang-wan)

(Aconiti Tuber, Alismatis Rhizoma, Cinnamomi Cortex, Corni Fructus, Dioscorea Rhizome, Poria, Moutan Cortex, and Rehmanniae Radix)

Hatimi-jio-gan (HJG) is generally used to treat reduced physical strength, unfavorable diuresis, erectile dysfunction, weakness or pain of the inferior half body, and numbness. General symptoms include hot sensation of the hands and feet, especially hot sensation of the foot back, a thirsty sensation, and lumbar pain. This preparation is indicated for relative softness of the lower abdomen. In the lower abdomen, the straight muscle of the abdomen is sometimes tense without reduction of abdominal strength. Concerning urine volume, HJG is appropriate for conflicting symptoms, oliguria, and polyuria.[2] HJG-associated prescriptions include Gosha-jinki-gan and Rokumi-gan (Liu-wei-wan).

HJG was reported to exhibit hypoglycemic effects and to improve glucose tolerance in experimental animal models such as cyproheptazine and alloxan-induced mice and genetically diabetic KK-CA^y mice and WBN/Kob rats,[10,11,17] and carbohydrate and lipid metabolism in aged rats.[18]

Among the crude drugs combined in HJG, Corni Fructus, Dioscorea Rhizome, Poria, and Rehmanniae Radix were reported to show hypoglycemic effects (see Corni Fructus, Dioscorea Rhizome, Poria, and Rehmanniae Radix in this chapter). Moutan Cortex and its principal constituent, paeonol, improved blood circulation disorder[7,19–22] and Rehmanniae Radix enhanced the improvement. Alismatis Rhizoma and its terpene constituents were reported to show vasorelaxant and anticoagulant effects, and are effective for chronic renal failure.[7,23]

Hochu-ekki-to (Bu-zhong-yi-qi-tang)

(Angelicae Radix, Astragali Radix, Atractylodis Lanceae Rhizoma, Bupleuri Radix, Cimicifugae Rhizoma, Ginseng Radix, and Zingiberis Rhizoma)

This prescription is used when a chronic disease makes reduction of physical fitness, general malaise, night sweat, palpitation, and thirst sensation more marked.[2]

Keishi-bukuryo-gan (Gui-zhi-fu-ling-wan)

(Cinnamomi Cortex, Poria, Moutan Cortex, Paeoniae Radix, and Persicae Semen)

Keishi-bukuryo-gan (KBG) is applied to treat menalgia, irregularity of menstruation, menopause symptoms, rush of blood to the head, bruise, and inflammation as an anti-Oketsu drug. When arteriosclerosis or a cold constitution and pain of the hands and feet is observed in patients with chronic diabetes, KBG and Sokei-kakketsu-to (Shu-jing-huo-xie-tang) are prescribed.[2]

Rokumi-gan (Liu-wei-wan)

(Alismatis Rhizoma, Corni Fructus, Dioscoreae Rhizoma, Poria, Moutan Cortex, and Rehmanniae Radix)

This prescription is prepared by removing Aconiti Tuber and Cinnamomi Cortex from Hatimi-jio-gan. It is generally used when symptoms such as a cold constitution, pain and numbness of the inferior half body, and general malaise are milder than those for which Hatimi-jio-gan is indicated.[2]

Saiko-keishi-kankyo-to (Chai-hu-gui-zhi-gan-jian-tang)

(Bupleuri Radix, Cinnamomi Cortex, Glycyrrhizae Radix, Ostreae Testa, Scutellariae Radix, Trichosanthis Radix, and Zingiberis Siccatum Rhizoma)

Among various agents containing Bupleuri Radix, this agent is prescribed in patients with the most marked reduction of physical fitness. The agent is prescribed when symptoms such as mild fullness, tenderness or discomfort of the hypochondrium, leptosomatic type, reduced physical fitness, fatigue, slight fever, anorexia, thirst sensation, sweating in the head, saccharephidrosis, palpitation, and dyspnea are observed.[2]

HERBS WITH HYPOGLYCEMIC EFFECTS

Anemarrhenae Rhizoma (Anemarrhena Rhizome)

(Rhizome of *Anemarrhena asphodeloides* Bunge [Liliaceae])

The water extract reduced the blood glucose levels 7 h after oral administration (90 mg/kg) in KK-A^y mice, but the extract did not affect the blood glucose levels in normal rats; this was different from an oral hypoglycemic drug, tolbutamide. The extract decreased blood glucose levels in an insulin tolerance test, suggesting that it decreased insulin resistance. In addition, xanthone

constituents mangiferin and mangiferin-7-*O*-β-D-glucopyranoside were isolated from this herb as active constituents (see the chapter on xanthones, flavonoids, and polyphenols).[24,25]

In previous study of antidiabetic constituents in an Ayurvedic natural medicine, *Salacia reticulata*, mangiferin was found to inhibit intestinal α-glucosidase and rat lens aldose reductase.[26] In addition, steroidal saponins, pseudoprototimosaponin A-III, prototimosaponin A-III, and timoaponin A-III were found to show hypoglycemic effects in alloxan- or STZ-induced diabetic mice after intraperitoneal administration (see Chapter 15). Anemarsaponin B, anemarrhenasaponins I and Ia, and timosaponins B-I, B-II, and B-III showed antiplatelet aggregation *in vitro*.[27,28]

Araliae Cortex (Aralia Bark)

(Root cortex of *Aralia elata* Seem. [Araliaceae])

The bark and root cortex of *Aralia elata* (Araliaceae) have been used in traditional Japanese and Chinese medicines as a tonic and as antidiabetic and antiarthritic agents. The methanolic extracts of the bark, root cortex, and young shoots of this plant and triterpene saponin constituents, elatosides, and related saponins have an inhibitory effect on the increase in serum glucose levels in sucrose- or glucose-loaded rats (see the chapter on saponins).

Corni Fructus (Cornus Fruit)

(Sarcocarp of *Cornus officinalis* Siebold et Zuccarini (Cornaceae) from which the seed has been removed)

The water extract of Corni Fructus was found to show insulin-like activity in fat cells isolated from rat epididymal adipose tissue.[29] Among the components of Hatimi-jio-gan, the ether extract of Corni Fructus showed an antidiabetic effect and its triterpene constituents, oleanolic acid and urosolic acid, decreased the amount of water consumption and urine volume in STZ-induced diabetic rats.[30]

Dioscoreae Rhizoma (Dioscorea Rhizome)

(Rhizome of *Dioscorea japonica* Thunberg or *D. batatas* Decaisne (Dioscoreaceae) from which the periderm has been removed)

Dioscoreae Rhizoma is prescribed in many Kampo medicines, such as Gosha-jinki-gan, Hatimi-jio-gan, and Rokumi-gan, for treatment of diabetes. Hikino et al. reported that glycan constituents, dioscorans A–F (100 mg/kg, i.p.) showed marked hypoglycemic effect in mice.[31] *D. dumetorum* was also reported, by intraperitoneal administration of the methanolic extract, to exhibit a hypoglycemic effect in alloxan-induced diabetic rabbits; an alkaloid constituent, dioscoretin, was isolated as an active constituent.[32,33]

Ginseng Radix (Ginseng)

(Root of *Panax ginseng* C.A. Meyer (Araliaceae) from which rootlets have been removed or the root has been quickly passed through hot water)

Ginseng is prescribed in many formulations as a tonic and is an important herb in traditional Chinese and Japanese medicines. Red ginseng (Ginseng Radix Rubra), which is processed from the roots of *P. ginseng*, has been used for treatment of arteriosclerosis, hyperlipemia, diabetes, cerebral apoplexy, collagen disease, climacteric disorder, autonomic imbalance, and impairment of microcirculations in these diseases. Many multifunctional pharmacological studies of ginseng, including the antidiabetic effects, were reported[34] and ginseng was suggested to be a useful therapeutic adjunct in the management of NIDDM from the results in a double-blind placebo-controlled study.[35]

After 4 weeks' oral administration of white ginseng and red ginseng, the fasting blood glucose levels were lower than those of the control group in KK-A^y mice. White ginseng can improve hyperglycemia in KK-A^y mice (possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase) and red ginseng through the up-regulation of adipocytic PPAR-γ protein expression as well as inhibiting intestinal glucose absorption.[36]

Apart from its hypoglycemic effects, ginseng was reported to show anti-Oketsu effects. The effects of 70% methanolic extract of Korean red ginseng on experimental models of disseminated intravascular coagulation (DIC) induced by endotoxin or thrombin in rats were reported. In the coagulative system, the extract prevented the exchange of values of clinical examination (blood platelet, fibrinogen, and prothrombin time) at a dose of 500 mg/kg in rats on DIC induced by endotoxin or thrombin in rats. The mechanism of action was suggested to be inhibition of platelet aggregation and the conversion of fibrinogen to fibrin induced by thrombin, and enhancement of fibrinolytic activity.[37–41] Intraperitoneal administration of a saponin constituent ginsenoside-Rb_2 and glycan constituents panaxans A–E, I–L, and Q–U was also reported to show hypoglycemic effects in STZ-induced diabetic rats or in normal and alloxan-induced hyperglycemic mice.[42–45]

Vuksan et al. reported that American ginseng (the roots of *Panax quinquefolium* L.) reduced postprandial hyperglycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus.[46–48]

Mori Folium (Mulberry Leaf)

(Leaf of *Morus alba* L., *M. bombycis* Koidz)

Mori Folium has been used in traditional Chinese medicines as an antihyperglycemic agent. The nitrogen-containing sugar, 1-deoxynojirimycin, exhibited strong inhibition against α-glucosidase, inhibiting absorption of carbohydrate by inhibition of conversion of carbohydrates to monosaccharide.[49] The water extract of Mori Folium at a dose of 150 mg/kg for 14 days significantly reduced the blood glucose level in GK rats, one of the experimental NIDDM models. Mori Folium has unique properties, such as raising insulin sensitivity and improving insulin resistance.[50] The aqueous methanolic extract of Mori Cortex (mulberry root-bark) and its glycoprotein constituent, moran A, showed marked hypoglycemic effects in normal and alloxan-induced hyperglycemic mice by intraperitoneal administration. Mori Cortex also inhibits α-glucosidase; 1-deoxynojirimycin is an active component.[51–53]

Ophiopogonis Tuber (Ophiopogon Tuber)

(Enlarged part of the root of *Ophiopogon japonicus* Ker-Gawler [Liliaceae])

The *n*-butanol extract of Ophiopogonis Tuber was reported to show hypoglycemic effects in normal and STZ-induced diabetic mice,[54] but active constituents remain unclarified.

Paeoniae Radix (Peony Root)

(Root of *Paeonia lactiflora* Pallas [Paeoniacea])

The principal constituents of Paeoniae Radix, paeoniflorin and 8-debenzylpaeoniflorin, showed hypoglycemic effects without affecting serum insulin levels in STZ-induced diabetic rats.[55] With regard to the anti-Oketsu effects, the extract exhibited endothelium-dependent vasodilator effects on rat aorta; its active component was gallotannin.[56]

Platycodi Radix (Platycodon Root)

(Root of *Platycodon garndiflorum* A. De Candolle [Campanulaceae])

Dietary feeding of Platycodi Radix for 4 weeks resulted in a significant decrease in plasma TG levels in lean and obese Zucker rats. Furthermore, Platycodi Radix decreased the postprandial glucose levels at 30 min after glucose-loading in obese Zucker rats. Dietary intake of Platycodi

Radix may be useful in the prevention and improvement of metabolic disorders characterized by hyperinsulinemia states such as NIDDM.[57]

Polygonati Rhizoma (Polygonatum Rhizome)

(Rhizome of *Polygonatum falcutum* A. Gray. and *P. sibiricum* Redoute [Liliaceae])

Polygonati Rhizoma has been used traditionally for the treatment of diabetes (polyurea and polydipsia). Kato et al. reported the hypoglycemic effects of the methanolic extract of Polygonati Rhizoma originated from *P. falcutum* by intraperitoneal administration. The extract (800 mg/kg, i.p.) reduced the blood glucose of normal mice and also significantly lowered the blood glucose of STZ-induced diabetic mice; however, it did not affect the serum insulin levels. In epinephrine-induced hyperglycemic mice, the extract increased glycogen levels in the liver and reduced hyperglycemia.[58]

Increased hepatic glucose output is known as one of the major pathogenic factors of NIDDM, together with insulin resistance in peripheral tissues and impairment of glucose-induced insulin secretion from pancreatic β-cells. Kato et al. reported that the extract significantly reduced the hepatic content of facilitative glucose transporter isoform 2 (GLUT2) mRNA and its protein content in the total membrane fraction from rat liver by intraperitoneal administration in rats.[59,60] In addition, diosgenin glycosides (PO-1 and PO-2) were identified as the hypoglycemic constituents of Polygonati Rhizoma (see Chapter 15). In addition, the rhizomes of *P. officinale, P. sibricum,* and *P. odoratum* were found to exhibit hypoglycemic effects.[61–63]

Poria (Hoelen)

(Sclerotium of *Poria cocos* Wolf (Polyporaceae) from which the external layer has usually been mostly removed)

Poria is prescribed in Kampo medicines as a diuretic, sedative, and tonic. A triterpene constituent of Poria, dehydrotrametenolic acid, reduced hyperglycemia in obese hyperglycemic *db*/*db* mice, and Poria was suggested to act as an insulin sensitizer from the results of the glucose tolerance test. In addition, from the results of *in vitro* experiments, the activation of PPAR-γ by Poria was suggested to be one of the mechanisms of action.[64]

Rehmanniae Radix (Rehmannia Root)

(Root of *Rehmannia glutinosa* Liboschitz var. *purpurea* Makino and *R. glutinosa* Liboschitz (Scrophulariaceae), with or without the application of steaming)

Rehmanniae Radix is classified into fresh rehmannia root ("Shojioo" in Japanese), dried rehmannia root ("Kanjioo"), and prepared rehmannia root ("Jyukujioo") by different processing methods. The three agents are used for different purposes.

A Kampo medicine, Seishin-kanro-to (Shen-jin-gan-lu-tang), showed hypoglycemic effects in KK-A^y mice and Rehmanniae Radix and Anemarrhenae Rhizoma were identified as active crude drugs of this formulation.[65] The methanolic extract and its fraction, which contained a principal iridoid constituent, catalpol, showed hypoglycemic effects in alloxan-induced diabetic mice.[66] The fraction, which is mainly composed of pectin-like polysaccharide, exhibited hypoglycemic activity in normal and STZ-induced mice by intraperitoneal administration and increased the activity of hepatic glucokinase and glucose-6-phosphatase dehydrogenase.[67] The 70% methanolic extract of "Jukujioo" inhibited blood coagulation and promoted the activation of the fibrinolytic system *in vitro* and *in vivo*.[68]

Swertiae Herba (Swertia Herb)

(Whole herb of *Swertia japonica* Makino (Gentianaceae) collected during the blooming season)

Swertiae Herba has been widely used as a folk medicine for stomach complaints because of the characteristic bitter taste. The whole plants of *S. japonica* and *S. chirayita* were reported to exhibit hypoglycemic effects by oral administration, and xanthone constituents, bellidifolin and swerchirin, were isolated as active constituents.[69–73]

Others

Among the crude drugs composing the other Kampo medicines, the glycans such as aconitans A–C,[74] atractans A–C,[75] ephedrans A–E,[76] oryzabrans A–D,[77] plantago-mucilage A,[78] and trichosans A–E[79] from Aconiti Tuber (aconite root), Atractylodis Rhizoma (atractylodes rhizome), Ephedrae Herba (ephedra herb), Oryzae Semen (brown rice), Plantaginis Semen (plantago seed), and Trichosanthis Radix (trichosanthes root) were reported to exhibit hypoglycemic activity by intraperitoneal administration.

HERBS WITH INHIBITORY ACTIVITY AGAINST ALDOSE REDUCTASE

As a key enzyme in the polyol pathway, aldose reductase (AR) catalyzes the reduction of glucose to sorbitol. In diabetes mellitus, the increased availability of glucose in insulin-insensitive tissues such as the lens, nerves, and retina leads to the increased formation of sorbitol through the polyol pathway. Sorbitol does not readily diffuse across cell membranes and the intracellular accumulation of sorbitol has been implicated in the chronic complications of diabetes such as cataract, neuropathy, and retinopathy. Therefore, the AR inhibitor can prevent the conversion of glucose to sorbitol and may have the capacity to prevent and/or treat several diabetic complications.

Glycyrrhizae Radix (Glycyrrhiza)

(Root and stolon, with [unpeeled] or without [peeled] the periderm, of *Glycyrrhiza uralensis* Fischer or *G. glabra* L. [Leguminosae])

Aida et al. reported the effects of four Kampo medicines (Gosha-jinki-gan, Hatimi-jio-gan, Keishi-ka-jutsu-bu-to [Gui-zhi-jia-shu-fu-tang], and Sokei-kakketsu-to (Shu-jing-huo-xie-tang]), which were used for the alleviation of the subjective symptoms of diabetic neuropathy, on rat lens AR *in vitro*; they exhibited potent inhibitory activities at a concentration of 100 μg/ml.[80] Glycyrhizae Radix and Cinnamomi Cortex compose Sokei-kakketsu-to, which showed the most potent activity among the formulations, and were found to exhibit potent inhibitory activity.[81] Twelve active constituents were isolated from Glycyrhizae Radix; in particular, a chalcone constituent, isoliquiritigenin, showed strong inhibition with an IC_{50} of 3.2×10^{-7} *M*. In addition, isoliquiritigenin inhibited sorbitol accumulation in human red blood cells *in vitro* with an IC_{50} of 2.0×10^{-6} *M* and it (100 mg/kg, p.o., twice per day) reduced the accumulation of sorbitol in the red blood cells, the sciatic nerve, and the lens as effectively as the synthetic AR inhibitor epalrestat.[82]

On the other hand, hyperaggregability of platelets in diabetic patients was also reported as a cause of chronic diabetic complications. The antiplatelet activity of the constituents from Glycyrhizae Radix was examined. A 3-arylcoumarin constituent GU-7 inhibited platelet aggregation by increasing the intraplatelet cAMP concentration.[83]

In our studies on antidiabetic principles of natural medicines, various flavonoids with aldose reductase inhibitory activity were isolated from *Centella asiatica*, *Chrysanthemum indicum*, *C. morifolium*, *Prunus mume*, and *Myrcia multiflora*. In particular, desmanthin-1 from *Myrcia multiflora*, which has been used as a remedy for diabetes and is called "plant insulin" in Brazil, was found to show potent inhibitory activity equivalent to that of a commercial synthetic aldose reductase inhibitor, epalrestat. In addition, inhibitory effects of flavonoids on formation of AGE *in vitro* and

some structural requirements of flavonoids for the inhibitory activity against aldose reductase and AGE formation were clarified from the evaluation of various natural and synthetic flavonoids.[84,85]

REFERENCES

1. A. Yuhara, Guide line of Chinese herb therapy of diabetes mellitus, *J. Traditional Sino-Jpn. Med.* 7, 1986, 9–13 (in Japanese).
2. T. Kikutani, Treatment of diabetes mellitus by ethical Kampo drugs, applied to health insurance system, *J. Traditional Sino-Jpn. Med.* 7, 1986, 29–33 (in Japanese).
3. Y. Morimoto, M. Sakata, A. Ohno, T. Maegawa and S. Tajima, Effects of Byakko-ka-ninjin-to, Bofu-tsusho-san and Gorei-san on blood glucose level, water intake and urine volume in KKA^{y} mice, *Yakugaku Zasshi* 122, 2002, 163–168 (in Japanese).
4. Y. Morimoto, M. Sakata, A. Ohno, T. Maegawa, S. Tajima, Effects of Bofu-tsusho-san, a traditional Chinese medicine, on body fat accumulation in fructose-loaded rats, *Folia Pharmacol. Japon.* (*Nippon Yakurigaku Zasshi*) 117, 2001, 77–86 (in Japanese).
5. T. Yoshida, N. Sakane, Y. Wakabayashi, T. Umekawa, M. Kondo Thermogenic, anti-obesity effects of Bofu-tsusho-san in MSG-obese mice, *Int. J. Obesity Related Metab. Disord.* 19, 1995, 717–722.
6. K. Toriizuka, P. Nishiyama, I. Adachi, N. Kawashiri, M. Ueno, K. Terasawa and I. Horikoshi, Isolation of a platelet aggregation inhibitor from Angelicae Radix, *Chem. Pharm. Bull.* 34, 1986, 5011–5015.
7. K. Terasawa, M. Kimura, N. Sakuragawa, Y. Uchiyama, K. Toriizuka, M. Ueno and I. Horikoshi, Effects of anti-"Oketsu" drugs on blood coagulation and fibrinolysis, *Yakugaku Zasshi* 103, 1983, 313–318 (in Japanese).
8. M. Okumura, K. Suzuki, K. Yamaura, M. Uchiyama, S. Nakayama and K. Oguchi, Antidiabetic effects of Kampo medicines in a non-insulin-dependent diabetes mellitus model using KK-Ay mice, *J. Trad. Med.* 18, 2001, 81–88.
9. T. Miura, M. Ishihara, H. Ichiki, M. Kubo, Y. Komatsu, E. Ishihara, H. Sasaki, K. Tanigawa, Effect of Byakko-ka-ninjin-to with exercise in early stage symptoms of non-insulin dependent diabetic mice, *J. Trad. Med.* 16, 1999, 79–82.
10. M. Goto, H. Inoue, Y. Seyama, S. Yamashita, O. Inoue, E. Yumioka, Comparative effects of traditional Chinese medicines (Dai-saiko-to, Hatimi-zio-gan and Byakko-ka-ninzin-to) on experimental diabetes and hyperlipidemia, *Folia Pharmacol. Japon.* (*Nippon Yakurigaku Zasshi*) 93, 1989, 179–186 (in Japanese).
11. M. Goto, M. Hayashi, T. Todoroki, Y. Seyama and S. Yamashita Effects of traditional Chinese medicines (Dai-saiko-to, Sho-saiko-to and Hachimi-zio-gan) on spontaneously diabetic rat (WBN/Kob) with experimentally induced lipid and mineral disorders, *Folia Pharmacol. Japon.* (*Nippon Yakurigaku Zasshi*) 100, 1992, 353–358 (in Japanese).
12. T. Yokozawa, T. Nakagawa and K. Terasawa, Effects of Oriental medicines on the production of advanced glycation endproducts, *J. Trad. Med.* 18, 2001, 107–112.
13. X. Wang, M. Hattori, K. Toriizuka, K. Terasawa, Z. Lou and T. Namba, Pharmacognostical studies on Chinese crude drug Da-huang (Rhubarb) (V) Effect of aqueous extract of *Rheum* species on human platelet aggregation, *Shoyakugaku Zasshi* 45, 1991, 57–61 (in Japanese).
14. T. Yokozawa, N. Suzuki, I Okuda, H. Oura and I. Nishioka, Changes in the urinary constituents in rats with chronic renal failure during oral administration of rhubarb extract, *Chem. Pharm. Bull.* 33, 1985, 4508–4514, and references cited therein.
15. Y. Suzuki, K. Goto, A. Ishige, Y. Komatu and J. Kamei, Effect of Gosha-jinki-gan, a Kampo medicine, on enhanced platelet aggregation in streptozotocin-induced diabetic rats, *Jpn. J. Pharmacol.* 78, 1998, 87–91.
16. Y. Suzuki, K. Goto, A. Ishige, Y. Komatsu and J. Kamei, Antinociceptive effect of Gosha-jinki-gan, a Kampo medicines, in streptozotocin-induced diabetic mice, *Jpn. J. Pharmacol. 79*, 1999, 169–175.
17. J. Suzuki and M. Kimura, Hypoglycemic effects of the blended Chinese traditional medicines in genetically diabetic mice, *Folia Pharmacol. Japon.* (*Nippon Yakurigaku Zasshi*) 83, 1984, 1–10 (in Japanese).

18. R. Haranaka, N. Mochizuki, S. Watabe, S. Owada, H. Kosoto, H. Takemura, Y. Kuwabara, N. Hirose, R. Hasegawa and M. Kobayashi, Studies of Ba-wei-wan: Part I. Lipid and carbohydrate metabolism in aged rats and mice, *Proc. Symp. WAKAN-YAKU* 15, 1982, 15–20 (in Japanese).
19. H. Ishida, M. Takamatsu, K. Tsuji and T. Kosuge, Studies on active substances in herbs used for Oketsu ("stagnant blood") in Chinese medicine. V. On the anticoagulative principle in Moutan Cortex, *Chem. Pharm. Bull.* 35, 1987, 846–848.
20. A. Hirai, T. Terano, T. Hamazaki, K. Tahara, H. Saito, Y. Tamura and A. Kumagai, Studies on the anti-aggregatory effects of Moutan Cortex and paeonol, *Proc. Symp. WAKAN-YAKU* 16, 1983, 114–118 (in Japanese).
21. M. Kubo, H. Matsuda, S. Izumi, T. Tani, S. Arichi, M. Yoshikawa and I. Kitagawa, Studies on Moutan Cortex (VI). Inhibitory effects on the intravascular coagulation (Part I), *Shoyakugaku Zasshi* 36, 1982, 70–77 (in Japanese).
22. M. Kubo, H. Matsuda and R. Matsuda, Studies on Moutan Cortex VIII. Inhibitory effects on the intravascular coagulation (Part 2), *Shoyakugaku Zasshi* 38, 1984, 307–312 (in Japanese).
23. M. Yoshikawa and H. Matsuda, Terpenoid constituents of Alimatis Rhizoma — structure, biological activity, and chemical change of terpenoids during processing, *J. Trad. Med.* 19, 2002, 199–128 (in Japanese).
24. T. Miura, H. Ichiki, N. Iwamoto, M. Kato, M. Kubo, H. Sasaki, M. Okada, T. Ishida, Y. Seino and K. Tanigawa, Antidiabetic activity of the rhizoma of *Anemarrhena asphodeloides* and active components, mangiferin and its glucoside, *Biol. Pharm. Bull.* 24, 2001, 1009–1011.
25. T. Miura, N. Iwamoto, M. Kato, H. Ichiki, M. Kubo, Y. Komatsu, T. Ishida, M. Okada and K. Tanigawa, The suppressive effect of mangiferin with exercise on blood lipids in type 2 diabetes, *Biol. Pharm. Bull.* 24, 2001, 1091–1092.
26. M. Yoshikawa, N. Nishida, H. Shimoda, M. Takada, Y. Kawahara and H. Matsuda, Polyphenol constituents from *Salacia* species: quantitative analysis of mangiferin with α-glucosidase and aldose reductase inhibitory activities, *Yakugaku Zasshi* 121, 2001, 371–378 (in Japanese).
27. J.X. Dong and G.Y. Han, A new active steroidal saponin from *Anemarrhena asphodeloides*, *Planta Med.* 57, 1991, 460–462.
28. J. Zhang, Z. Meng, M. Zhang, D. Ma, S. Xu and H. Kodama, Effect of six steroidal saponins isolated from Anemarrhenae Rhizoma on platelet aggregation and hemolysis in human blood, *Clin. Chim. Acta.* 289, 1999, 79–88.
29. H. Ohminami, Y. Kimura, S. Maki, Y. Yamanouchi, R. Doi, H. Okuda and S. Arichi, Studies on insulin-like substances in Hachimi-gan, *Proc. Symp. WAKAN-YAKU* 15, 1982, 9–14 (in Japanese).
30. J. Yamahara, H. Mibu, T. Sawada, H. Fujimura, S. Takino, M. Yoshikawa and I. Kitagawa, Biologically active principles of crude drugs. Antidiabetic principles of Corni Fructus in experimental diabetes induced by streptozotocin, *Yakugaku Zasshi* 101, 1981, 86–90 (in Japanese).
31. H. Hikino, C. Konno, M. Takahashi, M. Murakami, Y. Kato, M. Karikura and T. Hayashi, Isolation and hypoglycemic activity of dioscorans A, B, C, D, E, and F, glycans of *Dioscorea japonica* rhizophors, *Planta Med.* 52, 1986, 168–171.
32. M.M. Iwu, C.O. Okunji, P. Akah, M.S. Tempesta, D. Corley, Dioscoretine: the hypoglycemic principle of *Dioscorea dumetorum*, *Planta Med.* 55, 1990, 119–120.
33. M.M. Iwu, C.O. Okunji, G.O. Ohiaeri, P. Akah, D. Corley and M.S. Tempesta, Hypoglycemic activity of dioscoretine from tubers of *Dioscorea dumetorum* in normal and alloxan diabetic rabbits, *Planta Med.* 56, 1990, 264–267.
34. Y.C. Ong and E.L. Yong, Panax (ginseng) — panacea or placebo? Molecular and cellular basis of its pharmacological activity, *Ann. Acad. Med. Singapore* 29, 2000, 42–46.
35. E.A. Sotaniemi, E. Haapakoski and A. Rautio, Ginseng therapy in non-insulin-dependent diabetic patients, *Diabetes Care* 18, 1995, 1373-1375.
36. S.H. Chung, C.G. Choi and S.H. Park, Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKA^{y} mice, *Arch. Pharm. Res.* 24, 2001, 214–218.
37. H. Matsuda and M. Kubo, Pharmacological study on *Panax ginseng* C.A. MEYER. I. Effects of red ginseng on the experimental disseminated intravascular coagulation (1), *Yakugaku Zasshi* 103, 1983, 1269–1277 (in Japanese).

38. H. Matsuda, K. Namba, S. Fukuda, T. Tani and M. Kubo, Pharmacological study on *Panax ginseng* C.A. MEYER. III. Effects of red ginseng on experimental disseminated intravascular coagulation. (2). Effects of ginsenosides on blood coagulative and fibrinolytic systems, *Chem. Pharm. Bull.* 34, 1986, 1153–1157.
39. H. Matsuda, K. Namba, S. Fukuda, T. Tani and M. Kubo, Pharmacological study on *Panax ginseng* C.A. MEYER. IV. Effects of red ginseng on experimental disseminated intravascular coagulation. (3). Effect of ginsenoside Ro on the blood coagulative and fibrinolytic system, *Chem. Pharm. Bull.* 34, 1986, 2100–2104.
40. H. Matsuda, M. Kubo, T. Tani, S. Arichi and I. Kitagawa, Pharmacological study on *Panax ginseng* C.A. MEYER. V. Effects of red ginseng on the experimental disseminated intravascular coagulation (4). On ginsenoside-Rg3, Rh1 and Rh2, *Shoyakugaku Zasshi* 39, 1985, 123–125.
41. K. Yamamoto, A. Hirai, Y. Tamura and S. Yoshida, *In vitro* and *in vivo* effect of ginseng saponins, major components of Korean red ginseng on human platelet aggregation and arachidonic acid metabolism, *J. Trad. Med.* 5, 1988, 184–190.
42. T. Yokozawa, T. Kobayashi, H. Oura and Y. Kawashima, Studies on the mechanism of the hypoglycemic activity of ginsenoside-Rb2 in streptozotocin-diabetic rats, *Chem. Pharm. Bull.* 33, 1985, 869–872.
43. C. Konno, K. Sugiyama, M. Kano, M. Takahashi and H. Hikino, Isolation and hypoglycaemic activity of panaxans A, B, C, D, and E, glycans of *Panax ginseng* roots, *Planta Med.* 50, 1984, 434–436.
44. Y. Oshima, C. Konno and H. Hikino, Isolation and hypoglycemic activity of panaxans I, J, K, and L, glycans of *Panax ginseng* roots, *J. Ethnopharmacol.* 14, 1985, 255–259.
45. C. Konno, M. Murakami, Y. Oshima and H. Hikino, Isolation and hypoglycemic activity of panaxans Q, R, S, T, and U, glycans of *Panax ginseng* roots, *J. Ethnopharmacol.* 14, 1985, 69–74.
46. V. Vuksan, J.L. Sievenpiper, V.Y. Koo, T. Francis, U. Beljan-Zdravkovic, Z. Xu and E. Vidgen, American ginseng (*Panax quinquefolius* L.) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus, *Arch. Intern. Med.* 160, 2000, 1009–1013.
47. V. Vuksan, M.P. Stavro, J.L. Sievenpiper, U. Beljan-Zdravkovic, L.A. Leiter, R.G. Josse and Z. Xu, Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes, *Diabetes Care* 23, 2000, 1221–1226.
48. V. Vuksan, J.L. Sievenpiper, J. Wong, Z. Xu, U. Beljan-Zdravkovic, J.T. Arnason, V. Assinewe, M.P. Stavro, A.L. Jenkins, L.A. Leiter and T. Francis, American ginseng (*Panax quinquefolius* L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals, *Am. J. Clin. Nutr.* 73, 2001, 753–758.
49. H. Nojima, I. Kimura, F.J. Chen, Y. Sugihara and M. Haruno, Antihyperglycemic effects of N-containing sugars from *Xanthocercis zambesiaca*, *Morus bombycis*, *Aglaonema treubii*, and *Castanospermum australe* in streptozotocin-diabetic mice, *J. Nat. Prod.* 61, 1998, 397–400.
50. Y. Iizuka, E. Sakurai and Y. Tanaka, Antidiabetic effect of Folium Mori in GK rats, *Yakugaku Zasshi* 121, 2001, 365–369 (in Japanese).
51. H. Hikino, T. Mizuno, Y. Oshima and C. Konno, Isolation and hypoglycemic activity of moran A, a glycoprotein of *Morus alba* root barks, *Planta Med.* 51, 1985, 159–160.
52. F. Chen, N. Nakashima, I. Kimura and M. Kimura, Hypoglycemic activity and mechanisms of extract from mulberry leaves (Folium Mori) and Cortex Mori Radicis in streptozotocin-induced diabetic mice, *Yakaugaku Zasshi* 115, 1995, 476–482 (in Japanese).
53. N. Asano, T. Yamashita, K. Yasuda, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, R.J. Nash, H.S. Lee and K.S. Ryu, Polyhydroxylated alkaloids isolated from mulberry trees (*Morus alba* L.) and silkworms (*Bombyx mori* L.), *J. Agric. Food Chem.* 49, 2001, 4208–4213.
54. M. Kako, T. Miura, M. Usami, A. Kato and S. Kadowaki, Hypoglycemic effect of the rhizomes of Ophiopogonis Tuber in normal and diabetic mice, *Biol. Pharm. Bull.* 18, 1995, 785–787.
55. F.L. Hsu, C.W. Lai and J.T. Cheng, Antihyperglycemic effects of paeoniflorin and 8-debenzoylpaeoniflorin, glucosides from the root of *Paeonia lactiflora*, *Planta Med.* 63, 1997, 323–325.
56. H. Goto, Y. Shimada, Y. Akechi, K. Kohta, M. Hattori and K. Terasawa, Endothelium-dependent vasodilator effect of extract prepared from the roots of *Paeonia lactiflora* on isolated rat aorta, *Planta Med.* 62, 1996, 436–439.
57. K. Kim, E. Seo, Y. Lee, T. Lee, Y. Cho, O. Ezaki and C. Kim, Effect of dietary *Platycodon grandiflorum* on the improvement of insulin resistance in obese Zucker rats, *J. Nutr. Biochem.* 11, 2000, 420–424.

58. A. Kato and T. Miura, Hypoglycemic activity of Polygonati Rhizoma in normal and diabetic mice, *Biol. Pharm. Bull.* 16, 1993, 1118–1120.
59. A. Kato, T. Miura, H. Yano, K. Masuda, H. Ishida and Y. Seino, Suppressive effects of Polygonati Rhizoma on hepatic glucose output, GLUT2 mRNA expression and its protein content in rat liver, *Endocr. J.* 41, 1994, 139–144.
60. T. Miura, A. Kato, M. Usami, S. Kadowaki and Y. Seino, Effect of Polygonati Rhizoma on blood glucose and facilitative glucose transporter isoform 2 (GLUT2) mRNA expression in Wistar fatty rats, *Biol. Pharm. Bull.* 18, 1995, 624–625.
61. A. Kato and T. Miura, Hypoglycemic action of the rhizomes of *Polygonatum officinale* in normal and diabetic mice, *Planta Med.* 60, 1994, 201–203.
62. T. Miura and A. Kato, The difference in hypoglycemic action between Polygonati Rhizoma and Polygonati Officinalis Rhizoma, *Biol. Pharm. Bull.* 18, 1995, 1605–1606.
63. H. Chen, R. Feng, Y. Guo, L. Sun and J. Jiang, Hypoglycemic effects of aqueous extract of Rhizoma Polygonati Odorati in mice and rats, *J. Ethnopharmacol.* 74, 2001, 225–229.
64. M. Sato, T. Tai, Y. Nunoura, Y. Yajima, S. Kawashima and K. Tanaka, Dehydrotrametenolic acid induces preadipocyte differentiation and sensitizes animal models of non-insulin-dependent diabetes mellitus to insulin, *Biol. Pharm. Bull.* 25, 2002, 81–86.
65. T. Miura, M. Kako, E. Ishihara, M. Usami, H. Yano, K. Tanigawa, K. Sudo and Y. Seino, Antidiabetic effect of Seishin-kanro-to in KK-A^y mice, *Planta Med.* 63, 1997, 320–322.
66. I. Kitagawa, T. Nishimura, A. Furubayashi and I. Yosioka, On the constituents of rhizome of *Rehmannia glutinosa* LIBOSCH. forma *hueichingensis* HSIAO, *Yakugaku Zasshi* 91, 1971, 593–596 (in Japanese).
67. T. Kiho, T. Watanabe, K. Nagai and S. Ukai, Hypoglycemic activity of polysaccharide fraction from rhizome of *Rehmannia glutinosa* LIBOSH. f. *hueichingensis* HSIAO and the effect on carbohydrate metabolism in normal mouse liver, *Yakugaku Zasshi* 112, 1992, 393–400 (in Japanese).
68. H. Matsuda, S. Fukuda, J. Nakanishi, S. Fukuda and M. Kubo, Inhibitory effect of oriental medicine "Rehmanniae Radix" on disseminated intravascular coagulation (DIC), *Shoyakugaku Zasshi* 40, 1986, 182–187 (in Japanese).
69. P. Basnet, S. Kadota, M. Shimizu, Y. Takata, M. Kobayashi and T. Namba, Bellidifolin stimulates glucose uptake in rat 1 fibroblasts and ameliorates hyperglycemia in streptozotocin (STZ)-induced diabetic rats, *Planta Med.* 61, 1995, 402–405.
70. P. Basnet, S. Kadota, M. Shimizu and T. Namba, Bellidifolin: a potent hypoglycemic agent in streptozotocin (STZ)-induced diabetic rats from *Swertia japonica*, *Planta Med.* 60, 1994, 507–511.
71. A.M. Saxena, M.B. Bajpai, P.S. Murthy and S.K. Mukherjee, Mechanism of blood sugar lowering by a swerchirin-containing hexane fraction (SWI) of *Swertia chirayita*, *Indian J. Exp. Biol.* 31, 1993, 178–181.
72. A.M. Saxena, M.B. Bajpai and S.K. Mukherjee, Swerchirin induced blood sugar lowering of streptozotocin treated hyperglycemic rats, *Indian J. Exp. Biol.* 29, 1991, 674–675.
73. M.B. Bajpai, R.K. Asthana, N.K. Sharma, S.K. Chatterjee and S.K. Mukherjee, Hypoglycemic effect of swerchirin from the hexane fraction of *Swertia chirayita, Planta Med.* 57, 1991, 102–104.
74. C. Konno, M. Murayama, K. Sugiyama, M. Arai, M. Murakami, M. Takahashi and H. Hikino, Isolation and hypoglycemic activity of aconitans A, B, C, and D, glycans of *Aconitum carmichaeli* roots, *Planta Med.* 51, 1985, 160–161.
75. C. Konno, Y. Suzuki, K. Oishi, E. Munakata and H. Hikino, Isolation and hypoglycemic activity of atractans A, B, and C, glycans of *Atractylodes japonica* rhizomes, *Planta Med.* 51, 1985, 102–103.
76. C. Konno, T. Mizuno and H. Hikino, Isolation and hypoglycemic activity of ephedrans A, B, C, D, and E, glycans of *Ephedra distachya* herbs, *Planta Med.* 51, 1985, 162–163.
77. H. Hikino, M. Takahashi, Y. Oshima and C. Konno, Isolation and hypoglycemic activity of oryzabrans A, B, C and D, glycans of *Oryza sativa* bran, *Planta Med.* 54, 1988, 1–3.
78. M. Tomoda, N. Shimizu, Y. Oshima, M. Takahashi, M. Murakami and H. Hikino, Hypoglycemic activity of 20 plant mucilages and three modified products *Planta Med.* 53, 1987, 8–12.
79. H. Hikino, M. Yoshizawa, Y. Suzuki, Y. Oshima and C. Konno, Isolation and hypoglycemic activity of trichosans A, B, C, D, and E: glycans of *Trichosanthes kirilowii* roots, *Planta Med.* 55, 1989, 349–350.

80. K. Aida, H. Shindo, M. Tawata and T. Onaya, Inhibition of aldose reductase activities by Kampo medicines, *Planta Med*. 53, 1987, 131–135.
81. K. Aida, M. Tawata, H. Shindo, T. Onaya, H. Sasaki, H. Nishimura, M. Chin and H. Mitsuhashi, The existence of aldose reductase inhibitors in some Kampo medicines (Oriental herb prescriptions), *Planta Med*. 55, 1989, 22–26.
82. K. Aida, M. Tawata, H. Shindo, T. Onaya, H. Sasaki, T. Yamaguchi, M. Chin and H. Mitsuhashi, Isoliquiritigenin: a new aldose reductase inhibitor from Glycyrrhizae Radix, *Planta Med*. 56, 1990, 254–258.
83. M. Tawata, Y. Yoda, K. Aida, H. Shindo, H. Sasaki, M. Chin and T. Onaya, Anti-platelet action of GU-7, a 3-arylcoumarin derivative, purified from Glycyrrhizae Radix, *Planta Med*. 56, 1990, 259–263.
84. H. Matsuda, T. Morikawa, I. Toguchida and M. Yoshikawa, Structural requirements of flavonoids and related compounds for aldose reductase inhibitory activity, *Chem. Pharm. Bull*. 50, 2002, 788–795.
85. H. Matsuda, T. Wang, H. Managi and M. Yoshikawa, Structural requirements of flavonoids for inhibition of protein glycation and radical scavenging activities, *Bioorg. Med. Chem*. 11, 2003, 5217–5323.

7 Treating Non-Insulin-Dependent Diabetes Mellitus from a Western Herbalist's Perspective

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CONTENTS

INTRODUCTION

Diabetes mellitus has become a worldwide epidemic. A century ago it was uncommon, but today it affects more than 135 million people, over 17 million in the U.S. alone. The consequences of this epidemic are staggering; consider the facts about diabetes shown in Table 7.1.[1–4]

Fewer than 10% of diabetics have type I (T1DM), or insulin-dependent diabetes, which is usually diagnosed in childhood. Type I diabetes is a serious condition and must be managed by insulin injections. It has traditionally been regarded as a condition that can be managed with insulin but never reversed or improved. Research with certain botanical therapies discussed here has shown this to be not entirely true. Improvement in the condition is possible with the use of natural medicine including herbs. However treatments for type I diabetes will be alluded to briefly but will not be the focus of this discussion. This chapter will discuss natural remedies for the remaining 90% of people with diabetes — those who have type II (T2DM), or non-insulin-dependent diabetes.

Non-insulin-dependent diabetes usually affects adults, but in recent years it has become a condition that affects children, although to a much lesser extent. Type II can run in families. Heredity has been blamed for the large increase in the number of cases in recent years, but other factors, such as a lack of regular exercise, an alarming increase in obesity, and diets high in processed, nutrient-depleted, sugar-laden foods, should be examined more closely. It is interesting to observe that, although the disease is uncommon in cultures consuming a more primitive diet, diabetes has always been present in Western culture, as described in Western medical writings. The Eclectic Physicians defined it as a "constitutional disease" in their medicinal manual, *The Eclectic Practice of Medicine*.[5] This manual describes that diabetes is more common in wealthy people and notes the geographical predominance of the disease in Southern Italy, India, Sweden, and Germany. Within this manual, the herbs recommended are fragrant sumac (*Rhus aromatica* Ait.; Anacardiaceae), fringetree (*Chionanthus virginicus* L.; Oleaceae) and bugleweed (*Lycopus virginica* L.; Laminaceae).

As cultures increase the proportion of processed food in their native diets, the rate of diabetes incidence increases. Within the Native American and Latino populations, the increase in diabetes has been alarming. The Arizona Pima Indians appear to have a genetic predisposition for T2DM.

TABLE 7.1
Diabetes Facts

Worldwide, 2.8 million people die every year of diabetes. It is the sixth leading cause of death in the U.S. It is also a contributing factor to a large number of deaths.
Diabetes is the principal cause of blindness in the U.S.; 75 people lose their sight each day.
Diabetes is the largest cause of kidney failure in the U.S. Every day, 80 people will suffer kidney failure. Diabetes is responsible for 43% of all new cases.
Diabetes is the leading cause of nontraumatic, lower limb amputations. Every year, 56,000 limbs are lost due to complications of diabetes. This number is growing.
Diabetes leads to a greatly increased risk of heart disease. It creates a two to four times higher risk of stroke.
Diabetes causes a greatly increased risk of nerve function impairment. Within the diabetic population, 60 to 70% have at least some nerve damage.
Almost half the people with type II diabetes are unaware of their condition. They are undiagnosed and untreated.
In the U.S., type II diabetes is most prevalent in ethnic minority groups, but not exclusive to them.
The number of cases of diabetes worldwide is currently almost 200 million. At the present rate of increase, the affected population will double every 15 years.
The number of deaths from diabetes, worldwide, is expected to double within 10 years.
The costs of this disease are enormous. One of every seven health care dollars spent in the U.S. is spent on diabetes and adjunct treatments, currently over $132 billion. Lost productivity in the U.S. is $7.3 billion per year.

However, this is a recent characteristic that arose after this population adopted Western food shopping and dietary habits such as increased consumption of calories, refined carbohydrates, and total fat. According to Szathmary, T2DM was virtually unknown in North American indigenous populations before 1940.[6]

The apparent heredity factor may well have more to do with inherited habits. Children learn from parents and adopt their habits of a sedentary lifestyle and consuming a poor diet. Although genetics may make people susceptible to the consequences of poor lifestyle choices, it is not a mandatory sentence for life as a diabetic. Genetics may be an important factor, but it is far less important than has been previously thought.

The physical problems brought on by type II diabetes are further compounded for people who lack treatment. As stated earlier, approximately half of all cases are undiagnosed. This is currently estimated to be approximately 9 million Americans. The classic symptoms of extraordinary thirst, frequent urination, and a large appetite are not noticed, or they are dismissed by the unaware diabetic as nothing unusual. Therefore, health care is not sought. Unfortunately, this lack of care leads over time to several other deadly conditions. For example, many sudden heart attacks could have been prevented if the victim had been receiving care for an unknown diabetes II condition.

In 1988, Gerald Reaven, a Stanford endocrinologist, coined the term "syndrome X" for a condition that can be a precursor to diabetes T2DM. Syndrome X is brought on by excessive consumption of refined rather than complex carbohydrates. The syndrome includes at least two of the following symptoms: insulin resistance, abdominal obesity, high blood pressure, elevated cholesterol, and elevated triglycerides. Syndrome X can be treated naturally in much the same way as T2DM (discussed later).[7,8]

In type I or type II, the same herbs may be used for similar reasons. Diabetes type II responds particularly well to botanical and nutritional therapies and some lifestyle changes, so full health and full function may be restored. The body's ability to accept the insulin that is produced can be optimized. With a change in diet, regular exercise, and a loss of weight, the body will require less insulin. With herbs, the body is more able to create insulin and effectively utilize what is made.

TRADITIONAL WESTERN ANTIDIABETIC HERBS

This section will discuss herbs that were historically used in Europe. Some may not be native plants from Europe but their traditional use is documented.

Bitters

Plants traditionally classified as bitters have been used by herbalists in the West for the management of diabetes. These include:

Gentian root (*Gentiana lutea* L.; Gentianaceae)
Centaury herb (*Erythraea centaurium* Pers; Gentianaceae)
Wormwood herb (*Artemisia absinthium* L.; Compositae)
Dandelion root and leaf (*Taraxacum officinale* Weber; Compositae)
Unicorn root (*Aletris farinose* L; Haemodoraceae)
Bogbean leaf (*Menyanthes trifoliata* Tournef.; Gentianaceae)
Quassia bark (*Picraena excelsa* Lindl; Simarubaceae)
Chiretta herb (*Swertia chirata* Buch.-ham.; Gentianaceae)
Black root (*Leptandra virginica* Nutt; Scrophulariaceae)
Fringetree root bark (*Chionanthus virginicus* L.; Oleaceae)

Pharmacologically active plant phytochemicals include flavonoids, saponins, lignans, and tannins.[9] Due to the bitter taste of many of these compounds, horticulturists have selectively bred them

down to low levels or concentrated them in peels, which are often never consumed. The result is that produce in the diet is larger, sweeter, and milder.[10,11] It is postulated that bitters trigger digestive secretions including from the pancreas. Stimulation of the islets of Langerhans within the pancreas creates a mild change in the level of circulating insulin and glucagon. Studies of the extremely bitter chemical denatonium have shown that it activates receptors in the tongue, which consequently triggers the endocrine response in the pancreas.[12] Bitters as medicine are prevalent in many cultures. Of the bitters traditionally used in Western medicine, only a few are in common usage today. Barberry and milk thistle have evolved as modern herbs and have recently been studied for their hypoglycemic properties.

Barberry Root Bark (*Berberis vulgaris* L.; Berberidaceae)

Barberry is native to Europe, where it is commonly used as an ornamental shrub. Closely related to Oregon grape, which is a native of North America, it also contains the compound berberine. *King's American Dispensary* states that it was commonly used during the late 19th century, primarily as a tonic herb.[13]

Berberine, the principal component in barberry root bark, has been shown to be effective in the treatment of diabetes. An uncontrolled study of 60 patients with T2DM with differing severity of the disease was performed. They were given oral doses of 0.3 to 0.5 g of berberine three times per day for up to 3 months and a therapeutic diet for 1 month. The study showed positive results. Fasting blood glucose levels were controlled in 60% of patients and major symptoms of diabetes disappeared. The patients' strength improved, blood pressure normalized, and blood lipids decreased.[14] Further tests performed on animals showed improved pancreatic tissue compared to controls. It is thought that the hypoglycemic action of berberine, like gymnemic acid and other botanical compounds, may be due to the regeneration and recovery of pancreatic beta-cells.[15,16]

Milk Thistle (*Silybum marianum* Gaertn; Asteraceae/Compositae)

Milk thistle is traditionally thought of as a remedy for liver disorders. It has been found that alcoholic cirrhosis causes insulin resistance (a type of T2DM). This condition is partly due to the lipoperoxidation of hepatic cell membranes. Therefore antioxidizing agents may be useful in treating or preventing damage due to free radicals. Several studies (animal and human) have shown milk thistle to be potentially beneficial in treatment of diabetes. In an Italian study, patients with cirrhosis-related diabetes mellitus received 600 mg of silymarin or a placebo for 12 months. The insulin requirement was reduced by 25% due to the significant decrease in fasting glucose levels. The authors observed that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.[17]

Bilberry Leaf and Fruit (*Vaccinium myrtillus* L.; Vacciniaceae)

Bilberry is also known as European blueberry and is native to Europe. Traditionally, bilberry leaves were used to treat diabetes. Modern research has supported the folklore of the use of bilberry in the treatment of diabetes. Studies have shown that animals were better able to tolerate sugar when given bilberry leaf.

The mechanism in diabetes may be related to the high chromium content in bilberry leaf (9 ppm), but further research is needed to determine this. To date, no human clinical trials have been conducted. In streptozotocin-induced diabetic rats, 4 days of bilberry leaf administration caused plasma glucose levels to decrease consistently by 26%.[18]

Although the leaves may be useful in the control of diabetes, it has been discovered that the fruit and its extracts are of greater benefit, primarily for the reduction of complications that result from diabetes. The most threatening complications are the vascular and metabolic complications

(diabetic neuropathy, angiopathy, cataract, glaucoma, optic neuropathy, retinopathy, and diabetic nephropathy). Adjunct therapies for these complications will be covered later in this chapter.

Extracted from the fruit with a slightly acidic alcohol solution, the bilberry anthocyanoside, myrtillin, is apparently the most active constituent. It was found to be useful as a mild, nontoxic, insulin-like agent, with long lasting effects. Upon injection, myrtillin is somewhat weaker than insulin, but less toxic even at high doses. It is interesting that a single dose can reportedly produce beneficial results lasting for several weeks.[19]

Aloe Vera (*Aloe vera* L.; Liliaceae)

This well known plant has been studied for its hypoglycemic properties. An early study using mice had shown aloe vera juice to be effective. Subsequent to this animal study, two placebo-controlled single-blind clinical studies performed in Thailand have shown promise for use of aloe in controlling high blood sugar and triglyceride levels.[20,21]

The first study used 72 men and women. The two groups were matched for sex, body weight, age, former hypoglycemic drug use (none), fasting blood sugar levels, and exhibiting a typical diabetic curve of glucose intolerance. The treatment group received 1 tablespoonful of aloe vera juice (80%), twice per day, for 42 days. The control group received a placebo mixture given in the same way as the aloe vera. Blood samples were drawn weekly for blood sugar and biweekly for cholesterol and triglycerides. The blood sugar levels of the treatment group were significantly lower after 1 week and continued to fall steadily for the duration of the study. Additionally, the triglyceride levels of the treatment group were lowered after 2 weeks and continued to fall during the study. Cholesterol levels were unaffected in both groups.

An additional Thai study was performed later using 72 men and women divided into two equal sized groups and paired similarly to the first study. These subjects were chosen from diabetics who had been treated with the conventional drug glibenclamide and who had failed to respond positively with lowered blood glucose levels. The treatment group, once again, received 1 tablespoon of aloe vera juice, twice per day, but also continued to take two tablets of glibenclamide (5 mg) for 42 days. The control group was given a placebo that resembled the aloe vera juice and also continued to take glibenclamide.

Once again, blood samples were taken weekly to examine blood glucose levels and biweekly to analyze triglycerides and total cholesterol. The treatment group showed a significant decrease in blood glucose within 2 weeks. Triglycerides were lowered in 4 weeks and both levels continued to decline for the duration of the study. The control group remained with stable levels of fasting blood glucose and triglycerides, but did not display any improvement. Cholesterol levels were unchanged for both groups.

Aloe vera shows considerable promise as an aid in treating diabetes. The studies show that it has the ability to lower blood glucose levels; however, these levels did not fall to normal desired levels. It has been suggested that the dose of aloe vera juice was not high enough and further studies need to be done using varied higher doses. Higher doses should be well tolerated because these studies, as well as ancient folklore, have confirmed that aloe vera appears to show no harm to the kidneys or liver. Pending further studies, this herb may be safely used in combination with other botanical treatments.

Juniper (*Juniperus communis* L.; Coniferae)

Familiar to most people as an original ingredient of gin, juniper berries of several species are common throughout Western herbal *materia medica*. The part used is the berry, or pungent fruit. Since the medieval era, juniper species have been valued for their diuretic and digestive properties. Two animal studies have showed that juniper had a blood glucose-lowering effect.[22,23]

Juniper berries may act as a cholesterol-lowering and diuretic remedy, in some ways similar to artichoke leaf or goat's rue. It was previously believed that the diuretic effect of juniper was through nephron irritation by the volatile oil constituents. The use of juniper has resulted in a history of renal infection or damage. However, the volatile oil is not a renal irritant in rats. It is hypothesized that the adulteration of berries with needles, branches, and unripe berries may result in abnormally high levels of alpha- and beta-pinene, which may be the agents acting as urinary irritants.[24] Further studies in human subjects are warranted.

Goat's Rue *(Galega officinalis* L.; Leguminosae/Fabaceae)

So named from the Greek word for milk, galega is considered a noxious weed across North America. The common name in English presumes that dairy goats rue having this plant introduced to fodder because it increases milk production.

The conventional oral glucose-lowering drug metformin was originally developed from this medicinal plant to treat diabetes. Goat's rue is rich in galegine, the hypoglycemic component that reduces plasma glucose via inhibition of hepatic glucose production and increase of muscle glucose uptake. It also reduces plasma triglyceride and LDL-cholesterol levels. Unfortunately, it is too toxic for unmonitored clinical use and its side effects include weakness, fatigue, shortness of breath, nausea, dizziness, lactic acidosis, and kidney toxicity.

One Scottish study of normal-weight mice and obese mice showed that goat's rue caused loss of weight unrelated to a reduced food intake. The mice were given an ethanolic extract of a mixture of four herbs (containing 10% by weight of goat's rue). Over 7 days, food intake dropped and, over 28 days, weight dropped even while food intake restabilized or rose; in both treatment groups, total body fat was lower. In obese and normal-weight mice, the blood glucose was reduced significantly compared to controls, but only in the obese mice was insulin also reduced.[25]

Western herbalists frequently use this herb in combination with others to manage long-term health of people with type II diabetes mellitus or as an adjuvant in type I. It may also lessen the needed dose of oral hypoglycemic drugs. This herb must not replace insulin therapy, however, and should be used only under professional supervision. Because this herb is so effective, careful monitoring is needed to safeguard the diabetic patient on insulin.

TREATMENT OF DIABETES BY THE MODERN WESTERN HERBALIST

The herbs available to the Western herbalist for the alternative treatment of diabetes have evolved with today's current global market. The herbalist will commonly use herbs that are native to foreign continents and may employ the diverse knowledge that originates from a world of different cultures. This section of the chapter will detail the herbs that are recent additions to the Western herbalist's cornucopia.

Gymnema *(Gymnema sylvestre* R. Br.; Asclepiadaceae*)*

Gymnema is a very unusual herb. When applied to the tongue, it will temporarily suppress the ability to taste sugar. It has been used in Ayurvedic medicine for centuries and its Sanskrit name, "gurmar," means "sugar destroyer." In India, it has been used to treat diabetes II for the last two millennia. Western herbalists are now finding it useful and effective in controlling hyperglycemia and restoring pancreatic function.[26,27]

The gymnema leaf contains 4 to 10% of a group of more than 20 saponin glycosides of the oleanane type. These include gymnemic acids I through XVIII and gymnemasaponins I through V.[28,29] Studies show that the herb is able to mediate hyperglycemia by three possible mechanisms:

- Inhibition of intestinal absorption of glucose. Studies of humans and rats have shown gymnema extract and gymnemic acids to be useful in inhibiting intestinal glucose absorption.[30–37]
- Possible regeneration of the pancreas. A study showed two gymnema extracts returned fasting blood glucose levels to normal after 20 to 60 days of oral administration with diabetic rats. Fasting insulin levels returned toward normal and the number of beta-cells in the pancreas increased.[32–35]
- Stimulation of the release of endogenous insulin[38] or via interactions with insulinotropic enteric hormones. In animals that have their pancreas removed, gymnema possesses no apparent effects, suggesting that it enhances the production of endogenous insulin rather than supplying an insulin substitute.

Studies in humans with both types of diabetes seem to support the possibility of pancreas regeneration or of gymnema's ability to stimulate the release of endogenous insulin. Two published studies used 400 mg/day of a water-soluble gymnema extract to study its effects on T1DM and T2DM. In the type I diabetic study, the group given the gymnema reduced their insulin dose by 50%. In the type II study, after 18 to 20 months of treatment, fasting glucose levels were reported to be 29% lower in the group given gymnema compared to those on oral diabetic drugs. Additionally, glycosylated hemoglobin and glycosylated plasma protein were reduced. Of the treated group, 95% were able to reduce their intake of drugs and 5% were able to discontinue drug use completely. They maintained a normal blood glucose level by continuing with the gymnema extract alone. Although these results are promising, the studies were not blind or randomized, which is a weakness.[34,35]

The usual response to gymnema is slow, requiring 6 months to 1 year of continuous use for the desired effect.

Fenugreek Seeds (*Trigonella foenum-graecum* L.; Leguminosae/Fabaceae)

Fenugreek seeds have shown significantly positive effects in controlling diabetes in clinical studies and in animal experiments. The effect of fenugreek seeds on blood glucose and the serum lipid profile was evaluated in T1DM diabetic patients in a small study of short duration. Defatted fenugreek seed powder (100 g), divided into two equal doses, was served twice daily. The fenugreek diet significantly reduced fasting blood sugar and improved results of the glucose tolerance test.[39]

In a controlled clinical study, the effect of fenugreek on glucose and insulin levels following the meal tolerance test (MTT) was studied in T2DM diabetics. In this study, 15 g of powdered fenugreek seed, soaked in water, was given and appeared to reduce glucose levels significantly.[40] A small, randomized, controlled, double-blind trial was performed at India's Diabetes and Research Centre in 2001 using patients with mild T2DM. The 25 patients were administered 1 g per day of a hydroalcoholic extract of fenugreek seeds. The group receiving the fenugreek extract had significantly lower blood sugar. The authors concluded that adjunct use of fenugreek seeds improves glycemic control and decreases insulin resistance. They also observed a favorable effect on triglyceride levels.[41]

Suma (*Pfaffia paniculata* (Mart.) Kuntze; Amaranthaceae)

Used by South American indigenous people for centuries, suma is another promising herb in the treatment of diabetes. It is known in South America as "para todo" ("for everything"). An herbal pharmacologist would call it an adaptogen. It has been mistakenly called Brazilian ginseng for advertising reasons, although it is not of the genus *Panax* and cannot be defined as a ginseng.

Suma was brought to the attention of the general population shortly after its uses were discovered by a Brazilian herbalist in 1975. Since that time, many studies have been conducted in Brazil,

Great Britain, Japan, and the U.S. Suma has traditionally been used as a folk medicine in its native country, particularly with respect to the treatment of diabetes. However, no published studies to date support this belief. Many anecdotal reports tell of diabetics who have been successfully weaned off insulin.[42]

American Ginseng (*Panax quinquefolium* L.; Araliaceae)

Ginseng is another herb that has been used since ancient times to control diabetes. All ginseng species have some hypoglycemic effects in studies, but American ginseng has been the most successful. Several studies were conducted at the University of Toronto to test the herb's effects on blood glucose levels and to investigate its dependency on time of administration and dose.[43–46] During the most recent study, a dose of 1, 2, or 3 g of American ginseng was given to 12 healthy people. The doses were given at 40, 20, 10, or 0 min before a 25-g oral glucose challenge. Capillary blood was collected before administration and at 0, 15, 30, 45, 60, and 90 min after the start of the glucose challenge.

The researchers found that these reductions were time dependent but not dose dependent: an effect was seen only when the ginseng was administered 40 min before the challenge. Doses within the range of 1 to 3 g were equally effective. Three additional human studies were conducted with similar results. The Toronto researchers hypothesize that ginseng stimulates insulin secretion and improves nitric oxide-mediated uptake of glucose into cells. These results indicate that yet another useful herb has been found in the quest to control diabetes. These studies show much promise, but are somewhat limited; therefore, more research should be done on American ginseng. Meanwhile, this herb is considered nontoxic in the therapeutic dosage range. It is useful for a long list of complaints, so Western herbalists may sometimes use it with other remedies for control of hyperglycemia.

Prickly Pear (*Opuntia* spp.; Cactaceae)

Opuntia streptacantha Lemaire (nopal), or the prickly pear cactus, can be found in arid regions throughout the Western hemisphere, including the southwestern U.S., and is commonly used for glucose control by those of Mexican descent. It has a high-soluble fiber and pectin content, which may affect intestinal glucose uptake, partially accounting for its hypoglycemic actions.[47] Animal models have reported decreases in postprandial glucose and glycated hemoglobin levels with synergistic effects with insulin. Additionally, after cessation of insulin administration, the purified extract from the prickly pear cactus (*Opuntia fuliginosa*) controlled blood glucose alone.[48]

In Mexico, cactus capsules are touted as being efficient in lowering blood glucose levels in non-insulin-dependent or type II diabetics. Their effects have been questioned by Mexican researchers because processing and dehydration of the plant probably reduce its medicinal (hypoglycemic) activity. In a study undertaken in Mexico, the daily intake of 30 *Opuntia* capsules by patients with diabetes mellitus had a discrete beneficial effect on glucose and cholesterol. However, this dose was considered impractical and therefore was not recommended in the management of diabetes mellitus.[49] Dehydrated extracts of nopal (*Opuntia ficus-indica* Mill) did not show acute hypoglycemic effect, although they could attenuate postprandial hyperglycemia.[50]

Two controlled, short-term metabolic trials published in the English language by the same investigator suggest a possible hypoglycemic effect of nopal. The subjects ingested 500 g of broiled nopal stems (*Opuntia streptacantha*). The small trials reported improvements in patients with T2DM having decreased fasting glucose and decreased insulin levels, suggesting enhanced insulin sensitivity. Although no side effects were reported in these trials, longer term clinical trials are needed.[51,52]

Devil's Club (*Oplopanax horridum* (Sm.) Torr. & A. Gray ex. Miq.; Araliaceae)

Synonyms for this herb are *Panax horridum* (Sm.), *Fatsia horrida* ((Sm.) S. Watson.), *Echinopanax horridus* ((Sm.) Decne. & Planch.). So called for the thorny nature of the stem and leaf, devil's club is probably the most important plant to the indigenous people who live near it. Ethnobotanical records show that it is highly regarded by many First Nation tribes for its medicinal and spiritual properties. At least 13 First Nation tribes studied by Nancy Turner used devil's club traditionally for diabetes mellitus as an infusion or decoction of inner bark and sometimes roots, alone and in mixtures.[53]

A few poor and conflicting studies suggest its use as a hypoglycemic, but clinical human studies are warranted to prove its efficacy in the treatment of T2DM. Whether it is a pancreatic tonic or works by increasing the efficiency of insulin production is unclear.[54] Research on devil's club following early reports of its use for diabetes showed that a white precipitate isolated from extracts of "root bark" had a blood sugar-lowering effect in rabbits.[55] Later, two human studies also found hypoglycemic activity of root and stem bark.[56] Four other studies, however, did not find this effect from extracts of root bark and decoction of stems.[57–60]

Devil's club is presently being harvested and marketed as "pacific ginseng." However, there is little credible research to prove its immune-enhancing and adaptogenic properties in spite of its relationship to ginseng. The devil's club sold in commerce is wild crafted and many people, including the indigenous people, have raised concerns that this practice is not sustainable. Clearly, the current commercialization and use of this plant is problematic and a lot of research must be done before it can be a viable option in the treatment of diabetes.

Queen's Crepe Myrtle (*Lagerstroemia speciosa* L.; Lythraceae)

Used for centuries in Asia, this herb, also known as banaba, is now used in the West and is very promising as an aid for blood sugar control. The blood sugar regulating properties of queen's crepe myrtle have been demonstrated *in vitro* and *in vivo* in animal and human studies. In diabetic mice, rats, and rabbits, queen's crepe myrtle feeding reduces elevated blood sugar and insulin levels to normal. In humans with T2DM, queen's crepe myrtle extract given for 2 weeks has been shown to be effective in reducing blood sugar levels (30% reduction) and maintaining tighter control of blood sugar fluctuations.[61]

HERBS FOR USE IN ADJUNCT THERAPIES

Because herbalists work in patient-centered therapy, there is a long list of potential Western herbal adjuvants. According the scientific data,[62] the most commonly used plants are: ginkgo biloba (*Ginkgo biloba* L. Ginkgoaceae), garlic (*Allium sativum* L.; Liliaceae), milk thistle *(Silybum marianum* Gaertn; Compositae*),* ginseng (*Panax* spp; Araliaceae), papaya *(Carica papaya*; Acanthaceae), and bilberry fruit *(Vaccinium myrtillus* L.; Vacciniaceae). Some of them are proposed for:

- Treatment of symptoms related to venous and lymphatic vessel insufficiency
- Prophylaxis and treatment of liver damage caused by metabolic toxins
- Chronic degenerative liver conditions
- Therapy of digestive disorders
- Increasing in an unspecific way the resistance of the organism to various environmental influences
- Stabilizing membranes through antioxidant and radical scavenging actions

Evening primrose oil (*Oenothera biennis* L.; Onagraceae), alpha-lipoic acid, and cayenne (*Capsicum* spp.; Solanaceae) have received the greatest attention for their use in diabetic neuropathy, but further studies are needed to confirm their efficacy.[63] This section will only focus on ginkgo, bilberry fruit, and cayenne because they have been the most prominent in studies with respect to diabetic complications.

Bilberry Fruit (*Vaccinium myrtillus* L.; Vacciniaceae)

Bilberry fruit may be used in diabetic adjunct therapy in the treatment of diabetic retinopathy and cardiovascular disease. It assists vision and was used by RAF pilots during World War II to improve their night vision. It is vasoprotective, antioxidant, and anti-inflammatory. Modern research has proven that the anthocyanoside bioflavonoids in bilberry are supportive of retinal tissue.[64–66] The anthocyanosides have an affinity for the blood vessels of the eye and the retina, especially the macula. They improve circulation to the retina. Bilberry extracts have been prescribed for diabetic retinopathy in France since 1945.

Ginkgo Biloba (*Ginkgo biloba* L.; Ginkgoaceae)

Ginkgo used in this context has significant therapeutic overlaps with bilberry, previously discussed. Because of its ability to increase peripheral blood flow, ginkgo leaf extract has been found effective in aiding peripheral vascular insufficiency (claudication), which is quite common in diabetics. Numerous trials have focused on ginkgo's effect on claudication. These include three meta-analyses and 12 clinical trials to date. Most statistically significant studies have administered 120 mg ginkgo extract standardized to 24% ginkgo flavoglycosides and 6% terpene lactones per day (in two to three divided doses), although one dosing trial found better results with 240 mg/day. Treatment was evaluated for up to 6 months. Outcome parameters included measurements of mean pain-free walking distance and mean maximum walking distance.[67]

Another important role that ginkgo plays is to protect the retina. Diabetics are prone to an eye condition known as diabetic retinopathy. Two *in vitro* studies and one double-blind clinical study have observed visual function of diabetic subjects. The group given ginkgo showed significant improvement, suggesting that ginkgo has a specific role because of its antioxidant activity against harmful free oxygenated radicals.[68,69]

Cayenne (*Capsicum* spp.; Solanaceae)

Capsaicin, the active constituent of hot chili pepper, is thought to stimulate unmyelinated C fiber neurons selectively and cause the release of substance P. Continued application of capsaicin reversibly depletes stores of substance P and possibly other neurotransmitters from sensory nerve endings. This diminishes the transmission of painful stimuli from the peripheral nerve fibers to the central nervous system.

In clinical studies of patients with diabetic neuropathy, adjunctive therapy with topical capsaicin achieved better relief than placebo in most studies. Despite some initial mild stinging and burning, its advantage is that topical capsaicin is not associated with any severe systemic adverse effects. According to a recent meta-analysis, four trials have addressed the efficacy of topical capsaicin for neuropathic pain. Capsaicin cream gave more pain relief to patients with diabetic neuropathy than did placebo.[70] Another trial studied the effects of Capsaicin cream when applied to the feet of 13 patients with symptomatic diabetic neuropathy over a period of 8 weeks. The researchers investigated the impact on small nerve fiber function and neurovascular control. A significant improvement in total symptoms was observed.[71]

The largest study was a multicenter double-blind, vehicle-controlled study with parallel randomized treatment assignments. The investigators at 12 sites enrolled 277 men and women with painful peripheral polyneuropathy and/or radiculopathy in an 8-week period. A visual analogue

scale of pain intensity and baseline measurements of the pain's interference with the ability to walk, work, participate in recreational activities, use shoes and socks, sleep, and eat were recorded. The results indicate that topical 0.075% capsaicin is effective for reducing pain in patients with painful neuropathy.[72] A subsequent double-blind, multicenter parallel study compared the safety and efficacy of topical capsaicin and oral amitriptyline in patients with painful diabetic neuropathy involving the feet. In the study, 235 patients were randomized to treatment with capsaicin cream or amitriptyline capsules. Both groups had a 40% reduction in pain. However, the capsaicin group did not experience side effects.[73]

NUTRITIONAL THERAPIES AND EXERCISE

Nutrition plays a vital part in the cause and the control of diabetes type II. Nutritional therapies should begin with an assessment of a patient's lifestyle. It is important to identify any problems present in the patient's diet and environment that may be contributing to his or her pancreatic dysfunction. To achieve the best results, the patient's weight must be normalized. A diet, exercise, and a supplement program should be created and strictly followed to address these problems. Any toxic exposures in the home or workplace must be cleaned up.

Diet

Dietary modification is absolutely fundamental to a successful natural treatment of diabetes. Diabetes is usually the result of a lifetime of consuming the standard American diet: nutrient-depleted, fiber-depleted, and filled with highly refined carbohydrates, most notably sugar and high-fructose corn syrup. The evidence is clear that the Western diet and lifestyle is the primary factor in diabetes II.[74,75]

The American Diabetes Association has a recommended diet; however, the evidence is mounting that this is not the ideal diet for managing blood sugar levels. It has been suggested that metabolic typing is useful in determining the proper diet for prevention of diabetes. One metabolic type, type one (no relation to diabetes type I), is given a diet with emphasis on complex carbohydrates, with low fat and protein; the type two diet is given more protein and fat, with less emphasis on complex carbohydrates. The criteria for selection of the appropriate diet are based upon the metabolic dynamics of an individual's carbohydrate metabolism. This is determined by a procedure that Dr. Harold Kristal has pioneered to test carbohydrate tolerance. In a study published in *The Townsend Letter for Doctors* (March 2003), 1444 individuals were given a miniglucose challenge test and it was found that 72% of patients with a diagnosis of diabetes or prediabetics (commonly called syndrome X) were of the metabolic type that has difficulty processing carbohydrates.[76] Metabolic typing has not yet been widely accepted and more research should be done in this area. However, the emphasis remains with a diet rich in complex carbohydrates and less protein and fat.

A diet created by Dr. James Anderson, known as the HCF diet (high-carbohydrate, high plant fiber) has been successful. In a published study of 20 diabetic subjects, the experimental group significantly reduced its insulin need by following the diet. This diet has been shown to produce reduced postprandial hyperglycemia, delayed hypoglycemia, increased tissue sensitivity to insulin, reduced cholesterol, and increased HDL cholesterol levels.[77] Anderson recommends a diet high in cereal grains, legumes, and root vegetables in which fat and simple sugars are restricted. The caloric intake consists of 70 to 75% complex carbohydrates, 15 to 20% protein, and 10 to 25% fat. The total fiber content is almost 100 g per day.

Clinical trials of a more primitive diet that is predominantly vegetarian with an emphasis on complex carbohydrates and low fat intake have shown superior therapeutic effects. A change in diet is certainly a superior treatment option for diabetes T2DM, rather than pharmaceutical drugs or insulin. It has even been shown to be a first line of defense, with herbal therapies as a secondary step in treatment.[78–81]

Fiber is critical in the diabetic maintenance diet. Research has shown diabetes prevalence is closely related to a low intake of dietary fiber. The fibers that have the most beneficial effects on blood sugar control are water soluble. These include hemicelluloses, mucilages, gums, and pectins. They slow down the digestion and absorption of carbohydrates, thus preventing rapid rises in blood sugar, increasing the sensitivity of tissues to insulin, and improving uptake of glucose by the liver and other tissues. Of particular use are legumes, oat bran, nuts, seeds, psyllium seed husks, pears, apples, and most vegetables.

Although there are no specific fiber dietary guidelines for diabetics, studies have compared a diet containing 24 g fiber per day (high usual intake as recommended by the American Dietetics Association) to a diet containing 50 g fiber per day. They found that the higher intake of dietary fiber showed greater improvement in glycemic control, hyperinsulinemia, and plasma lipid concentrations in patients with T2DM.[82] The ideal diet for controlling diabetes should be a natural foods diet, preferably organic foods. The foods of choice are complex carbohydrates and high-fiber foods, with a low level of fats. Legumes, onions, and garlic are encouraged. Processed foods and concentrated carbohydrates are to be eliminated.

The current attention on the glycemic index of foods (discussed elsewhere in this book) is best taken in context of the rate at which sugars are released, not just the amount of sugars in vegetables, fruits, and whole foods. The glycemic load, defined as the product of the glycemic index value of a food and its carbohydrate content, has been reported to be positively associated with the risk of developing type II diabetes in men and women[83,84] and coronary heart disease in women.[85] However, studies in T2DM patients have not consistently reported a relation between glycemic index and insulin and lipid levels, although studies in other populations have reported an association between lower glycemic index diets or lower glycemic loads with lipids — in particular HDL cholesterol — and insulin levels. Examples of foods with a low glycemic index include:

Apples	Jerusalem artichokes
Bananas	Lettuce
Barley	Medicinal mushrooms
Beans	Oats
Blackberries	Olives
Broccoli	Onions
Cabbage	Papayas
Cashews	Peas
Cauliflower	Raspberries
Celery	Spinach
Citrus fruit	Sunflower seeds
Cranberries	Turnips
Garlic	

A number of useful nutritional supplements are also recommended in diabetes (Table 7.2).

Exercise

Exercise improves many symptoms of diabetes. Diabetics who participate in a regular routine of physical activity experience many benefits: enhanced insulin sensitivity with a consequent diminished need for exogenous insulin, improved glucose tolerance, and reduced total serum cholesterol and triglycerides with increased HDL levels, resulting in an improvement in body fat and weight.[120–123] An exercise program is essential. However, this program must reflect the patient's abilities. As time goes on and physical fitness is increased, the program can increase to reflect increased abilities. Ideally, the activities should elevate the heart rate at least 50% for half an hour,

TABLE 7.2
Nutritional Supplements Recommended in Treatment of Diabetes

Supplement	Ref.
Chromium	86–88
Ascorbic acid (vitamin C)	89, 90
Niacinamide (vitamin B3)	91–96
Biotin	97–99
Pyridoxine (vitamin B6)	100, 101
Natural d α-tocopherol (vitamin E)	102–104
Selenium	105
Magnesium	106
Manganese	107, 108
Zinc	109, 110
Mixed flavonoids	111,112
Fiber (dietary and supplemental)	113, 114
Vanadium	115–119

three times per week. Walking is an ideal activity; however, the patient's varied interests can be accommodated and the intended goal still reached.

CONCLUSION

Dietary supplements, lifestyle changes, and alternative therapies are increasingly used by patients with diabetes. This is in keeping with the belief that alternative treatments have been most widely used in chronic diseases, which may be only partially alleviated by allopathic medicine. Herbal medications are the most commonly used alternative therapy for glucose control and as an adjunct therapy for the many underlying complications of diabetes. Although a lot of early research has been done, their safety and efficacy need to be evaluated further by well-designed, controlled clinical studies. Despite the fact that herbs used for diabetes are less likely to have the drawbacks of conventional drugs, potential adverse herb–drug interactions should be kept in mind for patients also receiving conventional medications.

The good news is that most herbs have been shown to work in various preclinical and clinical studies. A great deal of patience will undoubtedly be required from patient and practitioner, but successful natural management of diabetes will make it worthwhile for everyone. As with all holistic therapies, results may be gradual and are not the "magic bullet" offered through allopathic medicine. Because T2DM generally occurs in older adults, many of the patients will need to change habits that may be deeply ingrained and difficult to change.

It is to be hoped that, with continued research, the use of herbal therapies for diabetes will become more widespread (because it will be better understood) in the West, just as herbs for diabetes are used in many developing countries.

REFERENCES

1. Data from the Centers for Disease Control and Prevention (CDC), and the National Health Interview Survey (NIHS). www.biotechwatch.com/knowledge.
2. Gaeddert A. How do you treat diabetes and syndrome X? Part I, *Townsend Lett*. 233, 138.

3. Pizzorno JE, Murray M. *A Textbook of Natural Medicine*, Bastyr University Publications, VI, Kenmore, WA: DiabMe 1–2, ND.
4. Rubin RJ et al. Health care expenditures for people with diabetes mellitus, *J Clin Endocrin Metab.*, 78:809 A809, 1994.
5 Rolla L, Thomas MD. *The Eclectic Practice of Medicine*, Medical Publishing Company, Cincinnati, Ohio, 1907.
6. Szathmary EJE. Non-insulin-dependent diabetes mellitus among aboriginal North Americans, *Ann Rev Anth.* 23:457–482, 1994.
7. Reaven G. Syndrome X, *Clin Diabetes* 3–4:32–52, 1994
8. Reaven G. Syndrome X: 6 years later, *J Int Med Suppl.* 736:13–22, 1994.
9. Duke JA, Beckstrom–Sternberg S, Broadhurst CL. U.S. Dept. of Agriculture Phytochemical and Ethnobotanical Data Base; 1997 (http://www.ars-grin.gov/duke/).
10. Cook NC, Samman S. Flavonoids — chemistry, metabolism, cardioprotective effects, and dietary sources. *J Nutr Biochem.* 7:66–76, 1996.
11. Broadhurst CL, Schmidt WS, Anderson RA et al. Lipids, chromium, and phytochemicals: a synergistic approach to non-insulin-dependent diabetes mellitus. Essential fatty acids and eicosanoids: invited papers from the Fourth International Conference July 1997, *Prostaglandins Leukot Essent Fatty Acids* 57:202, 1997.
12. Straub SG, Mulvaney–Musa J, Yajima H, Weiland GA, Sharp GW. Stimulation of insulin secretion by denatonium, one of the most bitter tasting substances known, *Diabetes* Feb; 52(2):356–364, 2003.
13. Felter HW, Lloyd JU. *King's American Dispensory*, 1898.
14. Ni YX. Therapeutic effect of berberine on 60 patients with type II diabetes mellitus and experimental research, *Zhong Xi Yi Jie He Za Zhi.* Dec; 8(12):711–713, 707, 1988.
15. Leng S, Lu F, Xu L. Therapeutic effects of berberine in impaired glucose tolerance rats and its influence on insulin secretion, *Acta Pharmacol Sin.* 25(4):496–502, 2004.
16. Mills S, Bone K. *Principles and Practice of Phytotherapy*, Churchill Livingston, London, 2000, p 294.
17. Velussi M, Cernigoi AM, De Monte A et al. Long-term (12 months) treatment with an antioxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients, *Hepatology* Apr; 26(4):871–879, 1997.
18. Cignarella A, Nastasi M, Cavalli E, Puglisi L. Novel lipid-lowering properties of *Vaccinium myrtillus* L. leaves a traditional antidiabetic treatment, in several models of rat dyslipidemia: a comparison with ciprofibrate, *Thromb Res.* Dec 1; 84(5):311–322, 1996.
19. Pizzorno JE, Murray M. *A Textbook of Natural Medicine*, Bastyr University Publications, ND, Kenmore, WA.
20. Yongchaiyudha S, Rungpitarangsi V, Bunyapraphatsara N, Chokechaijaroenporn O. Antidiabetic activity of *Aloe vera* L. juice I. Clinical trial in new cases of diabetes mellitus, *Phytomedicine* 3(3):241–243, 1996.
21. Yongchiyudha S, Rungpitarangsi V, Bunyapraphatsara N, Chokechaijaroenporn O. Antidiabetic activity of *Aloe vera* L. juice II. Clinical trial in new cases of diabetes mellitus, *Phytomedicine* 3(3):245–248,1996.
22. Sanchez de Medina F, Gamez MJ, Jimenez I et al. Hypoglycemic activity of juniper "berries," *Planta Med.* 60:197–200, 1994.
23. Swanston–Flatt, SK, Day C, Bailey CJ et al. Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice, *Diabetologica* 33(8):462–464, 1990.
24. Heil BM, Schilcher H. Poster presentation, 24th International Symposium on Essential Oils, Berlin, 1993.
25. Palit P, Furman BL, Gray AI. Novel weight-reducing activity of *Galega officinalis* in mice, *J Pharm Pharmacol.* Nov; 51(11):1313–1319, 1999.
26. Bone K. Gymnema: a key herb in the management of diabetes, *Townsend Lett.* 233:28, 2002.
27. Shanmugasundaram KR, Panneerselvam C, Samudram P et al. The insulinotropic activity of *Gymnema sylvestre*, R. Br. An Indian medical herb used in controlling diabetes mellitus, *Pharmacol Res Commun.* 13:475, 1981.
28. Waller GR et al. (Eds). Saponins used in food and agriculture, in *Advances in Experimental Medicine and Biology*, Vol. 405, Plenum Press, New York, 1996.

29. Yoshikawa K. A new type of antisweet principles occurring in *Aymnema sylvestre, Tetrahedron Lett*. 32(6):789–792, 1991.
30. Shimizu K et al. Inhibitory effects of glucose utilization by gymnema acids in the guinea-pig ileal longitudinal muscle, *J Smooth Muscle Res*. 32(5):219, 1996.
31. Wang LF, Luo H, Miyoshi M et al. Inhibitory effect of gymnemic acid on intestinal absorption of oleic acid in rats, *Can J Physiol Pharmacol*. 76:1017, 1998.
32. Shanmugasundaram KR, Panneerselvam C, Samudram P et al. Enzyme changes and glucose utilization in diabetic rabbits: the effect of *Gymnema sylvestre*, R. Br.*, J Ethnopharmacol*. 7:205, 1983.
33. Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K et al. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts, *J Ethnopharmacol*. (3):265–279, 1990.
34. Shanmugasundaram ER, Rajeswari G, Baskaran K et al. Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus, *J Ethnopharmacol*. 30(3):281–294, 1990.
35. Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K et al. Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin-dependent diabetes mellitus patients, *J Ethnopharmacol*. Volume 30, 295–305, 1990.
36. Kyremateng PH, cited in Prendergast HDV (Ed). Plants for food and medicine, Royal Botanic Gardens, Kew, 1998.
37. Yoshikawa M, Murakami T, Matsuda H. Medicinal foodstuffs. X. Structures of new triterpene glycosides, gymnemosides-c, -d, -e, and -f, from the leaves of *Gymnema sylvestre* R. Br.: influence of gymnema glycosides on glucose uptake in rat small intestinal fragments, *Chem Pharm Bull*. Dec; 45(12):2034–2038, 1997.
38. Persaud SJ, Al Majed H, Raman A et al. *Gymnema sylvestre* stimulates insulin release *in vitro* by increased membrane permeability, *J Endocrinol*. 163(2):207–212, 1999.
39. Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type 1 diabetes, *Eur Clin Nutr*. 44:301–306, 1990.
40. Mada Z, Abel R, Samish S, Arad J. Glucose lowering effect of fenugreek in non-insulin-dependent diabetics, *Eur J Clin Nutr*. 42:51–54, 1988.
41. Gupta A et al. Effect of fenugreek seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus, *J Assoc Physicians India*. 49:1057–1061, 2001.
42. Crawford, AM. Text from a 1988 interview.
43. Vuksan V et al. American ginseng attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals, *Am J Clin Nutr*. 73:4, 753–758, April 2001.
44. Vuksan V, Stavro MP, Sievenpiper JL, Koo VY, Wong E, Beljan–Zdravkovic U, Francis T, Jenkins AL, Leiter LA, Josse RG, Xu Z. American ginseng improves glycemia in individuals with normal glucose tolerance: effect of dose and time escalation, *J Am Coll Nutr*. Nov–Dec; 19(6):738–744, 2000.
45. Vuksan V, Stavro MP, Sievenpiper JL, Beljan–Zdravkovic U, Leiter LA, Josse RG, Xu Z. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes, *Diabetes Care* Sep; 23(9):1221–1226, 2000.
46. Vuksan V, Sievenpiper JL, Koo VY, Francis T, Beljan–Zdravkovic U, Xu Z, Vidgen E. American ginseng (*Panax quinquefolius* L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus, *Arch Intern Med*. Apr 10; 160(7):1009–1013, 2000.
47. Shapiro K, Gong WC. Natural products used for diabetes, *J Am Pharm Assoc*. 42:217–226, 2002.
48. Trejo–Gonzalez A, Gabriel–Ortiz G, Puebla–Perez AM et al. A purified extract from prickly pear cactus (*Opuntia fuliginosa*) controls experimentally induced diabetes in rats, *J Ethnopharmacol*. Dec; 55(1):27–33, 1996.
49. Frati–Munari AC, Vera–Lastra O, Ariza–Andraca CR. Evaluation of nopal capsules in diabetes mellitus, *Gac Med Mex*. Jul–Aug; 128(4):431–436, 1992.
50. Frati–Munari AC, de Leon C, Ariza–Andraca R et al. Effect of a dehydrated extract of nopal (*Opuntia ficus indica* Mill.) on blood glucose *Arch Invest Med*. (Mex) Jul–Sep; 20(3):211–216, 1989.
51. Frati AC, Gordillo BE, Altamirano P et al. Acute hypoglycemic effects of *Opuntia streptacantha Lemiare* in NIDDM (letter), *Diabetes Care* 13:455–456, 1990.
52. Frati–Munari AC, Gordillo BE, Altamirano P, Ariza CR. Hypoglycemic effect of *Opuntia streptacantha Lemaire* in NIDDM, *Diabetes Care* 11:63–66, 1988.

53. Turner NJ. Traditional use of devil's club (*Oplopanax horridus*: Araliaceae) by native peoples in western North America, *J. Ethnobiol*. 2:1–11, 1982.
54. Green J. *The Male Herbal: Health Care for Men and Boys*. 7th ed. Berkeley (CA): Crossing Press; 1991.
55. Large RG, Brocklesby HN. A hypogylcemic substance from the roots of devil's club (*Fatsia horrida*), *CMAJ* 39:32–35, 1938.
56. Justice JW. Use of devil's club in southeast Alaska, *Alaska Med*. 8(2):36–39, 1966.
57. Piccoli LJ et al. A pharmacologic study of devil's club root, *J. Am Pharm. Assoc*. 29:11–12, 1940.
58. Thommasen HV et al. Effects of devil's club tea on blood glucose in diabetes mellitus, *Can Fam Physician* 36:62–65, 1990.
59. MacDermot JH. Food and medicinal plants used by the Indians of British Columbia, *CMAJ* 61:177–183, 1949.
60. Stuhr ET et al. An investigation of the root bark of *Fatsia horrida*, *Pharm Arch*. 15:9–15, 1944.
61. Judy WV, Hari SP, Stogsdill WW et al. Antidiabetic activity of a standardized extract (glucosol) from *Lagerstroemia speciosa* leaves in type II diabetics. A dose-dependence study, *J Ethnopharmacol*. Jul; 87(1):115–117, 2003.
62. Savickiene N, Dagilyte A, Lukosius A, Zitkevicius V. Importance of biologically active components and plants in the prevention of complications of diabetes mellitus, *Medicina (Kaunas)* 38(10):970–975, 2002.
63. Halat KM, Dennehy CE. Botanicals and dietary supplements in diabetic peripheral neuropathy, *J Am Board Fam Pract*. Jan–Feb; 16(1):47–-57, 2003.
64. Caselli L. Clinical and electroretinographic study on activity of anthocyanosides, *Arch Med Inst*. 37: 29–35, 1985.
65. Passariello N, Bisesti V and Sgambato S. Influence of anthocyanosides on the microcirculation and lipid picture in diabetic and dyslipidic subjects, *Gazz Med Ital*. 138:563–566, 1979.
66. Coget JM, Merlen JF. Anthocyanosides and microcirculation, *J Mal Vasc*. 5:43–46, 1980.
67. Schweizer J, Hautmann C. Comparison of two dosages of ginkgo biloba extract EGb 761 in patients with peripheral arterial occlusive disease Fontaine's stage IIb. A randomized, double-blind, multicentric clinical trial, *Arzneimittelforschung* 49(11):900–904, 1999.
68. Lanthony P, Cosson JP. The course of color vision in early diabetic retinopathy treated with Ginkgo biloba extract. A preliminary double-blind vs. placebo study, *J Fr Ophtalmol*. 11(10):671–674, 1988.
69. Doly M, Droy–Lefaix MT, Bonhomme B, Braquet P. Effect of Ginkgo biloba extract on the electrophysiology of the isolated retina from a diabetic rat, *Presse Med*. Sep 25; 15(31):1480–1483, 1986.
70. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis, *Eur J Clin Pharmacol*. 46(6):517–522, 1994.
71. Forst T, Pohlmann T, Kunt T, Goitom K, Schulz G, Lobig M, Engelbach M, Beyer J, Pfutzner A. The influence of local capsaicin treatment on small nerve fiber function and neurovascular control in symptomatic diabetic neuropathy, *Acta Diabetol*. Apr; 39(1):1–6, 2002.
72. No authors listed. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group, *Diabetes Care* Feb; 15(2):159–165, 1992.
73. Biesbroeck R, Bril V, Hollander P, Kabadi U, Schwartz S, Singh SP, Ward WK, Bernstein JE. A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy, *Adv Ther*. Mar–Apr; 12(2):111–120, 1995.
74. Burkitt D, Trowell H. *Western Diseases: Their Emergence and Prevention*, Harvard Univ Press, Cambridge, MA, 1981.
75. National Research Council; Diet and Health. Implications for Reducing Chronic Disease Risk, National Academy Press, Washington DC, 1989.
76. Kristal, HJ and Haig JM. Diabetes, Cancer and Weight: A Metabolic Typing Survey. *Townsend Lett*. Feb/March, 2003.
77. Anderson JW, Ward K. High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus, *Am J Clin Nutr*. Nov; 32(11):2312–2321, 1979.
78. Kay RM, Grobin W, Trace N. Diets rich in natural fiber improve carbohydrate tolerance in maturity onset, non-insulin dependent diabetics, *Diabetologia* 20:12–23, 1981.
79. Simpson HC, Simpson RW, Lousley S et al. A high carbohydrate leguminous fiber diet improves all aspects of diabetic control, *Lancet* Jan 3; 1(8210):1–5, 1981.

80. Jenkins DJA, Wolever TMS, Bacon S et al. Diabetic diets: high carbohydrate combined with high fiber, *Am J Clin Nutr.* 33:1729–1733, 1980.
81. Jenkins DJ, Leeds AR, Gassull MA et al; Unabsorbable carbohydrates and diabetes: decreased postprandial hyperglycemia, *Lancet* Jul 24; 2(7978):172–174, 1976.
82. Chandalia M, Garg A, Luthohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial effects of a high dietary fiber intake in patients with type 2 diabetes, *N Engl J Med.* 342:1392–1398, 2000.
83. Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of NIDDM in men, *Diabetes Care* 20:545–550, 1997.
84. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women, *JAMA* 277:472–477, 1997.
85. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. A prospective study of dietary glycemic load, carbohydrate intake and risk of coronary heart disease in U.S. women, *Am J Clin Nutr.* 71:1455–1461, 2000.
86. Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J. Beneficial effects of chromium for people with diabetes, *Diabetes* 46:1786–1791, 1997.
87. Cheng N, Zhu X, Shi H, Wu W, Chi J, Cheng J, Anderson RA. Follow-up survey of people in China with type 2 diabetes mellitus consuming supplemental chromium, *J Trace Elem Exp Med.* 12:55–60, 1999.
88. Ravina A, Slezak L, Rubal A, Mirsky N. Clinical use of trace element chromium (III) in the treatment of diabetes mellitus, *J Trace Elem Exp Med.* 8:183–190, 1995.
89. Davie SJ, Gould BJ, Yudkin JS. Effect of vitamin C on glycosylation of proteins, *Diabetes* 41:167–173, 1992.
90. Vinson JA et al. *In vitro* and *in vivo* reduction of erythrocyte sorbitol by ascorbic acid, *Diabetes* 38:1036–1041, 1989.
91. Pozzilli P, Browne PD, Kolb H. Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. The Nicotinamide Trialists, *Diabetes Care* Dec; 19(12):1357–1363, 1996.
92. Pociot F, Reimers JI, Andersen HU. Nicotinamide — biological actions and therapeutic potential in diabetes prevention, *Diabetologia* 36:574–576, 1993.
93. Cleary JP. Vitamin B3 in the treatment of diabetes mellitus: case reports and review of the literature, *J Nutr Med.* 1: 217–225, 1990.
94. Pozzilli P, Andreani D. The potential role of nicotinamide in the secondary prevention of IDDM, *Diabetes Metabol Rev.* 9: 219–230, 1993.
95. Mandrup–Poulsen T, Reimers JI, Andersen HU et al. Nicotinamide treatment in the prevention of insulin-dependent diabetes mellitus, *Diabetes Metab Rev.* 9(4):295–309, 1993.
96. Andersen HU et al. Nicotinamide prevents interleukin-1 effects on accumulated insulin release and nitric oxide production in rat islets of langerhans, *Diabetes* 43:770–777, 1994.
97. McCarty MF. High-dose biotin, an inducer of glucokinase expression, may synergize with chromium picolinate to enable a definitive nutritional therapy for type II diabetes, *Med Hypotheses* May; 52(5):401–406, 1999.
98. Reddi A, DeAngelis B, Frank O et al. Biotin supplementation improves glucose and insulin tolerances in genetically diabetic KK mice, *Life Sci.* 42:1323–13-30, 1988.
99. Maebashi M, Makino Y, Furukawa Y et al. Therapeutic evaluation of the effect of biotin on hyperglycemia in patients with non-insulin-dependent diabetes mellitus, *J Clin Biochem Nutr.* 14:211–218, 1993.
100. Solomon LR, Cohen K. Erythrocyte O2 transport and metabolism and effects of vitamin B6 therapy in type II diabetes mellitus, *Diabetes* 38:881–886, 1989.
101. Coelingh–Bennink HJ, Schreurs WH. Improvement of oral glucose tolerance in gestational diabetes, *Br Med J.* 3:13–15, 1975.
102. Paolisso G, D'Amore A, Giugliano D, Ceriello A, Varricchio M, D'Onofrio F. Pharmacologic doses of vitamin E improve insulin action in healthy subjects and on insulin-dependent diabetic patients, *J Clin Nutr.* May; 57(5):650–656, 1993.
103. Paolisso G et al. Daily vitamin E supplements improve metabolic control but not insulin secretion in elderly type II diabetic patients, *Diabetes Care* 16:1433–1437, 1993.

104. Manning PJ, Sutherland WH, Walker RJ et al. Effect of high-dose vitamin E on insulin resistance and associated parameters in overweight subjects, *Diabetes Care* Sep; 27(9):2166–2171, 2004.
105. Kahler W, Kuklinski B, Ruhlmann C, Plotz C. Diabetes mellitus — a free radical-associated disease. Results of adjuvant antioxidant supplementation, *Z Gesamte Inn Med*. May; 48(5):223–232, 1993.
106. White JR, Campbell RK. Magnesium and diabetes: a review, *Ann Pharmacother*. 27: 775–780, 1993.
107. Wimhurst JM, Manchester KL. Comparison of ability of Mg and Mn to activate the key enzymes of glycolysis, *FEBS Lett*. 27:321–326, 1972.
108. Editorial. Manganese and glucose tolerance, *Nutr Rev*. 26:207–210, 1968.
109. Salgueiro MJ, Krebs N, Zubillaga MB et al. Zinc and diabetes mellitus: is there a need of zinc supplementation in diabetes mellitus patients? *Biol Trace Elem Res*. Sep; 81(3):215–228, 2001.
110. Mooradian AD, Morley JE. Micronutrient status in diabetes mellitus, *Am J Clin Nutr*. 45:877–895, 1987.
111. Cody V, Middleton E, Harborne JB. *Plant Flavonoids in Biology and Medicine — Biochemical, Pharmacological, and Structure–Activity Relationships*, Alan R. Liss, New York, 1986.
112. Kuhnau J. The flavonoids: a class of semiessential food components: their role in human nutrition, *Wld Rev Nutr Diet* 24:117–119, 1976.
113. Trepel F. Dietary fiber: more than a matter of dietetics. II. Preventative and therapeutic uses, *Wien Klin Wochenschr*. Aug 31; 116(15–16):511–522, 2004.
114. Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence, *J Am Coll Nutr*. Feb; 23(1):5–17, 2004.
115. Cohen N, Halberstam M, Shlimovich P et al. Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with non-insulin-dependent diabetes mellitus, *J Clin Invest*. 95:2501–2509, 1995.
116. Halberstam M, Cohen N, Shlimovich P et al. Oral vanadyl sulfate improves insulin sensitivity in NIDDM but not in obese nondiabetic subjects, *Diabetes* 45:659–666, 1996.
117. Goldfine A, Simonson D, Folli F, Patti ME, Kahn R. Metabolic effects of sodium metavanadate in humans with insulin-dependent and non-insulin-dependent diabetes mellitus *in vivo* and *in vitro* studies, *J Clin Endocrinol Metab*. 80:3311–3320, 1995.
118. Verma S, Cam MC, McNeill JH. Nutritional factors which can favorably influence the glucose, insulin system: vanadium, *J Am Coll Nutr*. 17:11–18, 1998.
119. Boden G, Chen X, Ruiz J, vanRossum GD, Turco S. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus, *Metabolism* 45:1130–1135, 1996.
120. Ranic M, Berger M. Exercise and diabetes mellitus, *Diabetes*, 28:147–163, 1979.
121. Koivisto VA, DeFronzo RA. Exercise in the treatment of type II diabetes, *Act Endocrin Suppl*. 262:107–111, 1984.
122. Selby JV, Newman B, King MC et al. Environmental and behavioral determinants of fasting plasma glucose in women. A matched co-twin analysis, *Am J Epidem*. 125: 979–988, 1987.
123. Pollack ML, Wilmore JH, Fox SM. *Exercise in Health and Disease*, WB Saunders, Philadelphia PA, 1984.

8 Native American Medicine

Robert H. Cichewicz and Laura J. Clifford

CONTENTS

INTRODUCTION

Diabetes is a term given to an assemblage of medical disorders characterized by a state of altered metabolism. Type 2 diabetes mellitus, typified by insulin resistance or deficiency, is the most prevalent form of this disease in North America. Within the last several decades, the number of individuals in North America suffering from type 2 diabetes has risen markedly[1,2]; a disproportionate increase has been observed among Native American populations.[3–5] Several pharmaceutical agents have been developed to help diabetic patients cope with the disease, but all of these products produce a variety of undesirable side effects. It is essential that new therapeutic agents are identified to help deal with this disease.

Humans have long used the plant kingdom as a reservoir of medicinal agents to treat all manner of diseases, including diabetes. Ethnobotanical studies in North America have identified a variety of plants traditionally employed by Native Americans for treating diabetes, despite the fact that diabetes was rarely encountered among these populations prior to European acculturation. Today, however, traditional Native American antidiabetic plants represent only a subset of all the plants used throughout North America for treating diabetes. For example, new reputed antidiabetic plants have been introduced into North American markets from other traditional medical systems such as Ayurvedic and Chinese herbal medicine. Furthermore, modern North American herbalists have adopted the use of some new plants into the American *materia medica* that exhibit promising antidiabetic effects. As a result, a complex amalgamation of antidiabetic plants that represent modern North American, traditional Native American, and other traditional medical systems can be found today throughout continental North America. Together, these plants warrant further investigation as leads in the development of new pharmaceutical entities.

The role of plants in the prevention and treatment of diabetes is not strictly limited to medicinal applications. A significant body of literature has emerged that links the increased prevalence of diabetes in North America, especially among Native Americans, to a decrease in the quantity of vegetative matter consumed in the diet. The mechanisms behind the health-conveying benefits associated with plant consumption in the diet are unclear; however, it could be linked to the rich array of phytoceuticals present in plant tissues.

This chapter addresses the history of the development and current status of type 2 diabetes among Native American populations with particular regard to dietary changes within the last

century. The use of plants under traditional Native American and contemporary North American cultural systems for treating diabetes will also be discussed. A review of Native American ethnographic literature has provided a list of many reputed antidiabetic plants that warrant further investigation. The names, parts used, and cultural affiliations of these plants are provided. In addition, a short list of some plants recently adopted by American herbal practitioners for treating diabetes is presented. The modern use of these plants may represent the beginning of a new tradition in treatment of diabetes in North America as they continue to gain wider popular acceptance from herbalists and diabetics.

RISE IN PREVALENCE OF TYPE 2 DIABETES AMONG NATIVE AMERICANS: HISTORIC EVIDENCE AND MODERN TRENDS

The occurrence of type 2 diabetes in North America is increasing at a significant rate among the general population. Results from a survey conducted from 1990 to 1998 noted that the incidence of diabetes increased from 4.9% in 1990 to 6.5% in 1998.[2] These figures pale in comparison to the epidemic proportion of type 2 diabetes witnessed among Native American populations in the past 50 years; the incidence in that group is reported to range as high as 20 to 30%.[6] Among some populations, the prevalence of the disease is staggering. For example, among the Pima Indians of Arizona and surrounding regions, approximately 50% of adults over 35 years of age suffer from type 2 diabetes.[7]

Several factors have been suggested as playing a potentiating role in the surge of clinical type 2 diabetes among Native Americans. It has been postulated that a "thrifty gene" may be partly responsible for the variation in the incidence of diabetes between Native Americans and the rest of the North American population.[8] The thrifty gene hypothesis suggests that early Native Americans had to contend with frequent interruptions in food supplies and, as a result, selective pressure favored individuals who were capable of efficient fat storage. In recent times, this efficiency has proven to be highly detrimental in light of the abundance of available food.

Although this idea is intriguing, evidence supporting this hypothesis is lacking. It has also been suggested that the recent increase in longevity of Native Americans has simply revealed a genetic predisposition toward this disease; however, epidemiological data refute this claim as well.[4] A fetal-origin model for type 2 diabetes implicates fetal malnutrition as leading to the development of this disease, which is consequently propagated to the following generation.[9] This theory has not gained support in the research community.

Instead, recent changes in dietary and exercise patterns linked with a concatenate increase in obesity among Native Americans are likely the root cause behind the incredible rise in type 2 diabetes. Diet plays a significant role in the development of type 2 diabetes mellitus, particularly with regard to the change from a traditional diet to a high-fat, low-fiber diet (Table 8.1). In addition

TABLE 8.1
Characterization of Dietary Intake of Four Food Groups by Native Americans in Traditional and Modern Lifestyles

Lifestyle	Carbohydrate	Fat	Protein	Fiber
Traditional: hunting–gathering	Low	Moderate to low	High to moderate	Low
Traditional: agricultural	High	Low	Moderate to low	High
Modern	High	High to moderate	Moderate	Low

Source: Ritenbaugh C. and Goodby C.-S., *Med. Anthropol.*, 11, 227, 1989.

to these gross qualitative dietary changes, it is also important to account for the quantitative alterations in food availability and consumption that coincided with decreased energy expenditure.

Despite the presence of these mitigating factors, several studies have now demonstrated the strong positive impact that changes in diet, including the reincorporation of traditional dietary patterns, can have on the reduction of diabetes. In a study of a Northern Ontario remote aboriginal community in which the age-adjusted prevalence rate of type 2 diabetes was 26%, 728 of 1018 residents were examined using an oral glucose tolerance test and questioned in regard to previous 24-h dietary intake. Fiber intake was found to be quite low. Statistical analysis adjusted for age, sex, and body mass index indicated that an increase of fiber intake reduced the risk of diabetes by 39%, and an equivalent increase in protein increased the risk by 38%.[10]

Other factors also believed to be influential in preventing the development of diabetes include increasing exercise,[11] reducing caloric intake,[12] and incorporating traditional vegetable food in the diet.[12] It is possible that many traditional plant foods not only are highly nutritious, but may also contain a complex assemblage of phytochemicals that could provide some degree of protection from diabetes.[13,14] For example, it has been demonstrated that several edible plants used in traditional diets may possess hypoglycemic properties.[15]

PLANTS USED FOR THE TREATMENT OF DIABETES IN NORTH AMERICA

A number of Native Americans still consult native healers alone or in conjunction with Western medical practitioners for advice regarding the treatment of diabetes.[16] In a survey of 300 Navajo patients interviewed in a rural clinic, 62% had sought advice from native healers and 39% used native healers regularly. Many of these respondents reported consulting the native healers about treating their diabetes.[17]

Information about plants used to treat diabetes has also been transmitted by oral traditions. For example, Seneca Indians have reported knowledge of medicinal plants for preventing diabetes.[18] Despite the prevalence of diabetes among Native Americans today, relatively few plants are reported as having been used traditionally to treat this disease (Table 8.2). A number of potential reasons for this discrepancy are possible; however, it is likely that the very low incidence of diabetes prior to European acculturation may account for this phenomenon. The 30 plants listed in Table 8.2 can be characterized by extreme taxonomic diversity including gymnosperms, vascular cryptograms, monocotyledons, and dicotyledons. A number of Native American cultural groups are included that represent a widespread geographic range across the entire North American continent. Most of the listed plants are native to North America; however, a few were reportedly used following European introduction.

Today, many Native and non-Native North Americans still use plants as an adjunct in the treatment of diabetes. However, many of the plants used currently do not have an established pedigree for treating diabetes in North America.[16] Some plants have been adopted from other traditional medical systems, such as *Gymnema sylvestre* Retz. Schultes (gurmar or gymnema), *Momordica charantia* L. (bitter melon or karela), and *Ocimum sanctum* L. (holy basil)[42] (Table 8.3). It is conceivable that some of these antidiabetic plants, novel to the North American *materia medica*, might one day become established as new traditional medicines in this region. A listing of some of these potential new antidiabetic plants is provided in Table 8.3. Although the listed plants represent a wide range of geographic and cultural affinities, it is interesting to note the strong influence that traditional Asian cultures, particularly Ayurvedic and Chinese traditional systems, have had on North American herbal medicine.[37,42]

Few of the traditional Native American antidiabetic plants reported in Table 8.2 have been studied in any detail to determine their therapeutic potential. One notable exception is the genus *Opuntia*, members of which have been reported to possess promising potential for the treatment

TABLE 8.2
Plants Used by Native Americans for the Treatment of Diabetes in North America[a]

Plant	Common Name	Part Used	Cultural Affiliation	Ref.
Acer glabrum Torr. (Aceraceae)	Rocky Mountain maple, vine maple	Decoction of bark	Saanich and Cowichan Coast Salish	19
Acorus calmus L. (Acoraceae)	Calmus, sweet cane, sweet flag, sweet root	Infusion of roots	Lakota	20
Anemopsis californica (Nutt.) Hook. & Arn. (Saururaceae)	Lizard tail, swamp root, yerba mansa	Decoction of roots	Kawaiisu	21
Aralia nudicaulis L. (Araliaceae)	Sarsaparilla, spikenard, wild liquorice, wild sarsaparilla	Whole plant	Iroquois	22
Aralia racemosa L. (Araliaceae)	American spikenard, Indian spikenard, spikenard	Infusion of roots	Algonquin	23
Arbutus menziesii Pursh (Ericaceae)	Arbutus, Pacific madrone	Infusion of bark	Cowichan	24
Armoracia rusticana (Lam.) P. Gaertn., B. Mey. & Scherb. (Brassicaceae) (not native to North America)	Creole mustard, German mustard, horse-reddish root, horseradish, red horseradish	Not specified	Iroquois	25
Artemisia alaskana Rydb., *Artemisia arctica* Less., and *Artemisia frigida* Willd. (Asteraceae)	Wormwood	Decoction of unspecified part	Tanana	26
Ceanothus americanus L. (Rhamnaceae)	New Jersey tea, redroot	Decoction of plant	Iroquois	22
Cinna arundinaceae L. (Poaceae)	Stout wood reed, wood reedgrass, woodreed	Decoction of plant	Iroquois	22
Cirsium ochrocentrum Gray (Asteraceae)	Yellow-spined thistle, yellowspine thistle	Infusion of fresh or dried roots taken three times daily	Zuni	27
Clintonia borealis (Aiton.) Raf. (Convallariaceae)	Bead-lily, bluebeard lily, Clinton's lily, yellow bluebeadlily	Decoction of smashed whole plant	Iroquois	22
Cypripedium acaule Aiton. (Orchidaceae)	Lady-slipper, lady's slipper, moccasin-flower, nerve root, pink lady's slipper	Infusion of unspecified part	Cherokee	28
Cypripedium calceolus var. *parviflorum* (Salisb.) Fern. (Orchidaceae)	Lady slipper, lady's slipper, nerve root, yellow lady's slipper	Infusion of unspecified part	Cherokee	28
Daucus carota L. (Apiaceae) (not native to North America)	Bee's nest, bird's nest, Queen Anne's lace, wild carrot	Infusion of blossoms	Delaware, Mohegan, and Oklahoma	29–31
Equisetum arvense L. (Equisetaceae)	Field horsetail, common horsetail	Not specified	Iroquois	25

TABLE 8.2 (CONTINUED)
Plants Used by Native Americans for the Treatment of Diabetes in North America[a]

Plant	Common Name	Part Used	Cultural Affiliation	Ref.
Euphorbia sp. (Euphorbiaceae)	Spurge	Infusion of leaves	Algonquin	23
Juniperus scopulorum Sarg. (Cupressaceae)	Juniper, Rocky Mountain juniper	Infusion of unspecified part	Kutenai	32
Lewisia rediviva Pursh. (Portulacaceae)	Bitter-root, Oregon bitterroot	Eat dried or fresh roots	Okanagan–Colville	33
Oplopanax horridus (J. E. Smith) Miq. (Araliaceae)	Devil's club	Infusion of roots, bark used in unspecified manner	Gitksan, Haisla, Thompson, and Wet'suwet'en	34, 35
Opuntia spp. (Cactaceae)	Beavertail cactus, nopal, prickly pear, tuna	Juice of stems, fresh or cooked stems and fruits	Various groups throughout southwestern North America	36, 37
Peniocereus greggii var. *greggii* (Engelmann) Britton & Rose (Cactaceae)	Chaparral cactus, deer-horn cactus, night-blooming cereus, queen of the night, sweet potato cactus	Decoction of roots	Pima	38
Pinus strobes L. (Pinaceae)	White pine	Not specified	Iroquois	25
Prunella vulgaris L. (Lamiaceae)	All-heal, heal all, self-heal	Whole plant used in unspecified manner	Iroquois	22
Quercus ilicifolia Wang. (Fagaceae)	Bear oak, scrub oak	Not specified	Iroquois	25
Rhus sp. (Anacardiaceae)	Sumac	Decoction of berries	Iroquois	22
Sassafras albidum (Nutt.) Nees (Lauraceae)	Sassafras	Tea of unspecified part	Iroquois	25
Vaccinium ovatum Pursh (Ericaceae)	Black huckleberry, California huckleberry, evergreen blueberry, evergreen huckleberry, roundleaf blueberry	Decoction of leaves	Pomo and Kahaya	39
Vitis vulpina L. (Vitaceae)	Chicken grape, frost grape, grape, river-bank grape	Infusion of roots	Chippewa	40
Yucca filamentosa L. (Agavaceae)	Adam's needle, bear grass, bear's grass, soap root, yucca	Infusion of unspecified part	Cherokee	28

[a] Data taken in part from Moerman D., http://www.umd.umich.edu/cgi-bin/herb/ (accessed 1 August 2001).

of diabetes and its symptoms in humans. The stems and the fruits of *Opuntia* have long been consumed in Southwestern North America as a traditional food. Today, the use of *Opuntia* has spread across the continent where it can be purchased from many local grocers.

Several studies using human and animal models have been performed on *Opuntia* in order to test its potential as an antidiabetic agent and evaluate its hypoglycemic activity. Normal and pancreatectomized rabbits orally administered fresh, liquidified *Opuntia* stems exhibited significant hypoglycemic responses.[46] Similar effects were observed in rabbits treated with a semipurified *Opuntia* extract.[47] Further trials were conducted in which a limited number of normal, diabetic, and obese human subjects were fed whole cooked *Opuntia* stems prior to each meal.[48] Changes were noted for a number of blood chemistry parameters in each group; however, the most significant

TABLE 8.3
Some Popular Nontraditional Plants Now Used in North America for Treatment of Diabetes

Plant	Common Name	Notes	Ref.
Brickellia spp. (Asteraceae)	Brickellbush, hamula	Infusion of leaves used in North America	37
Cacalia decomposita A. Gray (Asteraceae)	Matarique	Tincture of root used in North America	37
Cinnamomum zeylanicum Ness. (Lauraceae)	Cinnamon	Powdered bark used in North America	37, 42
Gymnema sylvestre (Retz.) Schultes (Asclepiadaceae)	Gurmar, gymnema	Tincture of leaf used in Asia and South Africa	13, 42, 43
Momordica charantia L. (Cucurbitaceae)	Balsam-apple, bitter gourd, bitter melon, karela	Juice or decoction of fruit is used throughout Asia, Central America, and West Africa	13, 42, 44
Ocimum sanctum L. (Lamiaceae)	Holy basil	Fresh leaf used in India	42
Panax quinquefolium L. (Araliaceae)	American ginseng, ginseng, red berry	Powdered root used in Asia	13, 45
Trigonella foenum-graecum (Fabaceae) L.	Bird's foot, fenugreek, sicklefruit fenugreek	Defatted or powdered seeds used in Asia and Europe	13, 16, 43

results were observed in the diabetic and obese subjects in which significant decreases in triglyceride and cholesterol levels were observed. In addition, the diabetic subjects exhibited a significant decrease in fasting serum glucose levels following ingestion of *Opuntia*.

Further evidence in support of *Opuntia*'s hypoglycemic activity was obtained from tests in which type 2 diabetic patients were given broiled *Opuntia* stems. A significant reduction in serum glucose levels was noted in patients receiving the *Opuntia* as compared to controls.[49] It is interesting to note that, in experiments employing dried, powdered *Opuntia*, the antidiabetic effects of this plant are severely attenuated.[50,51] Heat-treating fresh *Opuntia* may be necessary to realize its full medicinal benefits.[52] Further studies are still needed, but the available data indicate that incorporating *Opuntia* products in the diet of diabetic patients may convey significant health benefits.

Opuntia and other plants presented in Table 8.2 require further research in order to evaluate their chemotherapeutic potential thoroughly. Relatively little is known regarding these plants' chemical constituents. Furthermore, there is a substantial lack of information about the safety of consuming these antidiabetic plants alone or in conjunction with Western drugs. As the popularity of nonconventional therapies such as herbal medicines continues to rise in the U.S.[53,54] and the rest of North America, more people will likely consume these plants. Many questions need to be addressed in order to ensure consumer safety.

CONCLUSIONS

New approaches are needed to stymie the sharp rise in the incidence of diabetes among Native Americans. Several factors have been identified as playing contributing roles in the increase of diabetes, but dietary changes appear to be the most important influence. The reincorporation of traditional plant foods into the diet may help to reduce the incidence of diabetes because they may contain a number of beneficial phytochemicals. Efforts to improve standard Western chemotherapeutic practices may be achieved through the utilization of traditional Native American herbal therapies. Also, growing evidence indicates that many non-native plants are being used for the treatment of diabetes in North America.

North America can be characterized as composed of a complex intertwining of diverse cultural and social heritages that are each represented by unique traditions. This includes the breadth of traditional knowledge about herbal preparations for treating diabetes. The marriage of these diverse traditional medical practices has yielded as its fruits the creation of a new tradition in the herbal treatment of diabetes in North America. Further research is gravely needed to evaluate the potential benefits and dangers of these herbal therapies. It is hoped that these efforts will lead to the development of new herbal therapies for the treatment of diabetes.

REFERENCES

1. Kenny, S.J., Aubert, R.E. and Geiss, L.S., Prevalence and incidence of non-insulin-dependent diabetes, in *Diabetes in America,* M.I. Harris, C.C. Cowie, M.P. Stern, E.J. Boyko, G.E. Reiber and P.H. Bennett, Eds., National Institutes of Health, Bethesda, 1995, 2nd ed.
2. Mokdad, A.H., Ford, E.S., Bowman, B.A., Nelson, D.E., Englegau, M.M., Vinicor, F. and Marks, J.S., Diabetes trends in the U.S.: 1990–1998, *Diabetes Care*, 23, 1278, 2000.
3. West, K.M., Diabetes in American Indians, *Adv. Metab. Disorders*, 9, 29, 1978.
4. Gohdes, D., Diabetes in North American Indians and Alaska natives, in *Diabetes in America,* M.I. Harris, C.C. Cowie, M.P. Stern, E.J. Boyko, G.E. Reiber and P.H. Bennett, Eds., National Institutes of Health, Bethesda, 1995, 2nd ed.
5. Burrows, N.R., Geiss, L.S., Englegau, M.M. and Acton, K.J., Prevalence of diabetes among Native Americans and Alaska natives, 1990–1997: an increasing burden, *Diabetes Care*, 23, 1786, 2000.
6. Weiss, K.M., Ulbrecht, J.S., Cavanagh, P.R. and Buchanan, A.V., Diabetes mellitus in American Indians: characteristics, origins and preventive health care implications, *Med. Anthropol.*, 11, 283, 1989.
7. Knowler, W.C., Bennett, P.H., Hammon, R.H. and Miller, M., Diabetes incidence and prevalence in Pima Indians: a 19-fold greater incidence than in Rochester, Minnesota, *Am. J. Epidemiol.*, 108, 497, 1978.
8. Ritenbaugh, C. and Goodby, C.-S., Beyond the thrifty gene: metabolic implications of prehistoric migration into the New World, *Med. Anthropol.*, 11, 227, 1989.
9. Benyshek, D.C., Martin, J.F. and Johnston, C.S., A reconsideration of the origins of the type 2 diabetes epidemic among Native Americans and the implication for intervention policy, *Med. Anthropol.*, 20, 25–64, 2001.
10. Wolever, T.M.S., Hamad, S., Gittelsohn, J., Gao, J., Hanley, A.J.G., Harris, S.B. and Zinman, B., Low dietary fiber and high protein intakes associated with newly diagnosed diabetes in a remote aboriginal community, *Am. J. Clin. Nutr.*, 66, 1470, 1997.
11. Ravussin, E., Valencia, M.E., Esparza, J., Bennett, P.H. and Schulz, L.O., Effects of a traditional lifestyle on obesity in Pima Indians, *Diabetes Care*, 17, 1067, 1994.
12. Boyce, V.L. and Swinburn, B.A., The traditional Pima Indian diet, *Diabetes Care*, 16 (suppl. 1), 369, 1993.
13. Bailey, C.J. and Day, C., Traditional plant medicines as treatment for diabetes, *Diabetes Care*, 12, 553, 1989.
14. Day, C., Traditional plant treatments for diabetes mellitus: pharmaceutical foods, *Br. J. Nutr.*, 80, 5, 1989.
15. Roman–Ramos, R., Flores–Saenz, J.L. and Alarcon–Aguilar, F.J. Antihyperglycemic effect of some edible plants, *J. Ethnopharmacol.*, 48, 25, 1995.
16. Berman, B.M., Swyers, J.P. and Kaczmarczyk, J., Complementary and alternative medicine: herbal therapies for diabetes, *J. Assoc. Acad. Minority Physicians*, 10, 10, 1999.
17. Kim, C. and Kwok, Y.S., Navajo use of native healers, *Arch. Intern. Med.*, 158, 2245, 1998.
18. Judkins, R.A., American Indian medicine and contemporary health problems. IV. Diabetes and perception of diabetes among Seneca Indians, *N.Y. State J. Med.*, 1320, 1978.
19. Turner, N.J. and Hebda, R.J., Contemporary use of bark for medicine by two Salishan native elders of Southeast Vancouver Island, Canada, *J. Ethnopharmacol.*, 29, 59, 1990.
20. Kraft, S.K., Recent changes in the ethnobotany of Standing Rock Indian Reservation, unpublished thesis, University of North Dakota, 1990.

21. Zigmond, M., *Kawaiisu Ethnobotany*, University of Utah Press, Salt Lake City, 1981.
22. Herrick, J.W., Iroquois medical botany, unpublished thesis, State University of New York, Albany, 1977.
23. Black, M.J., *Algonquin Ethnobotany: an Interpretation of Aboriginal Adaptation in South Western Quebec*, Series #65, National Museums of Canada, Ottawa, 1980.
24. Turner, N.C. and Bell, M.A.M., The ethnobotany of the Coast Salish Indians of Vancouver Island, I and II, *Econ. Bot.*, 25, 63, 1971.
25. Herrick, J.W., *Iroquois Medical Botany*, Syracuse University Press, Syracuse, 1995.
26. Kari, P.R., *Upper Tanana Ethnobotany*, Alaska Historic Commission, Anchorage, 1985.
27. Camazine, S. and Bye, R.A., A study of the medical ethnobotany of the Zuni Indians of New Mexico, *J. Ethnobot.*, 2, 365, 1980.
28. Hamel, P.B. and Chiltoskey, M.U., *Cherokee Plants and Their Uses — a 400 Year History*, Herald Publishing Co., Sylva, 1975.
29. Tantaquidgeon, G., Mohegan medicinal practices, weather-lore and superstitions, *SI-BAE Annu. Rep.*, 43, 264, 1928.
30. Tantaquidgeon, G., *A Study of Delaware Indian Medicine Practice and Folk Beliefs*, Pennsylvania Historical Commission, Harrisburg, 1942.
31. Tantaquidgeon, G., *Folk Medicine of the Delaware and Related Algonkian Indians*, Anthropological Papers #3, Pennsylvania Historical Commission, Harrisburg, 1972.
32. Hart, J., *Montana Native Plants and Early Peoples*, Montana Historical Society Press, Helena, 1992.
33. Turner, N., Bouchard, R. and Kennedy, D.I.D., *Ethnobotany of the Okanagan–Colville Indians of British Columbia and Washington*, British Columbia Provincial Museum, Victoria, 1980.
34. Gottesfeld, L.M.J., The importance of bark products in the aboriginal economies of Northwestern British Columbia, Canada, *Econ. Bot.*, 46, 148, 1992.
35. Turner, N.J., Thompson, L.C. and Thompson, M.T., *Thompson Ethnobotany: Knowledge and Usage of Plants by the Thompson Indians of British Columbia*, Royal British Columbia Museum, Victoria, 1990.
36. Moore, M., *Medicinal Plants of the Desert and Canyon West*, Museum of New Mexico Press, Santa Fe, 1989.
37. Yarnell, E., Southwestern and Asian botanical agents for diabetes mellitus, *Altern. Complem. Therap.*, 6, 7, 2000.
38. Curtin, L.S.M., *By the Prophet of the Earth*, San Vicente Foundation, Sante Fe, 1949.
39. Goodrich, J. and Lawson, C., *Kashaya Pomo Plants*, American Indian Studies Center, University of California, Los Angeles, 1980.
40. Densmore, F., Uses of plants by the Chippewa Indians, *SI-BAE Annu. Rep.*, 44, 273, 1928.
41. Moerman, D., Native American ethnobotany database, Dearborn: The University of Michigan-Dearborn. Online. Available http://www.umd.umich.edu/cgi-bin/herb/ (accessed 1 August 2001).
42. Broadhurst, C.L., Treating type II diabetes nutritionally, *Nutr. Sci. News*, 3, 356, 1998.
43. Miller, L.G. and Murray W.J., *Herbal Medicinals: a Clinician's Guide*, Haworth Press, New York, 1998.
44. Austin, S., Brown, D. and Lininger, S.W., Natural approaches for diabetes, *Am. J. Nat. Med.*, 5, 8, 1998.
45. Vuksan, V., Sievenpiper, J.L., Koo, V.Y.Y., Francis, T., Beljan–Zdravkovic, U., Xu, Z. and Vidgen, E., American ginseng (*Panax quinquefolius* L.) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus, *Arch. Intern. Med.*, 160, 1009, 2000.
46. Ibanez–Camacho, R. and Roman–Ramos, R., Hypoglycemic effect of *Opuntia* cactus, *Arch. Invest. Med.*, 10, 223, 1979.
47. Ibanez–Camacho, R. and Meckes–Lozoya, M., Effect of a semipurified product obtained from *Opuntia streptacantha* L. (a cactus) on glycemia and triglyceridemia of rabbit, *Arch. Invest. Med.*, 14, 437, 1983.
48. Frati–Munari, A.C., Fernandez–Harp, J.A., de la Riva, H., Ariza–Andraca, R. and del Carmen Torres, M., Effects of nopal (*Opuntia* sp.) on serum lipids, glycemia and body weight, *Arch. Invest. Med.*, 14, 117, 1983.
49. Frati–Munari, A.C., Gordillo, B.E., Altamirano, P. and Ariza, C.R., Hypoglycemic effect of *Opuntia streptacantha* Lemaire in NIDDM, *Diabetes Care*, 11, 63, 1988.

50. Frati–Munari, A.C., de Leon, C., Ariza–Andraca, R., Banales–Ham, M.B. and Lopez–Ledesma, R., Effect of a dehydrated extract of nopal (*Opuntia ficus indica* Mill) on blood glucose, *Arch. Invest. Med.*, 20, 211, 1989.
51. Frati–Munari, A.C., Vera–Lastra, O. and Ariza–Andraca, C.R., Evaluation of nopal capsules in diabetes mellitus, *Gaceta Med. Mex.*, 128, 431, 1992.
52. Frati–Munari, A.C., Altamirano–Bustamante, E., Rodriguez–Barcenas, N., Ariza–Andraca, R. and Lopez–Ledesma, R., Hypoglycemic action of *Opuntia streptacantha* Lemaire: study using raw extracts, *Arch. Invest. Med.*, 20, 321, 1989.
53. Eisenberg, D.M., Kessler, R.C., Foster, C., Norlock, F.E., Calkins, D.R. and Delbanco, T.L., Unconventional medicine in the United States: prevalence, cost, and patterns of use, *N. Engl. J. Med.*, 328, 246, 1993.
54. Eisenberg, D.M., Davis, R.B., Ettner, S.L., Appel, S., Wilkey, S., Van Rompay, M. and Kessler, R.C., Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey, *JAMA*, 280, 1569, 1998.

9 Antidiabetic Plants in Mexico and Central America

Francisco Javier Alarcon–Aguilar and Ruben Roman–Ramos

CONTENTS

INTRODUCTION

Diabetes mellitus (DM) has become a problem of public health in Mexico and Central America (CA). Barcelo and Rajpathak reported the highest prevalence rate (around 10%) of diagnosed type 2 DM among adults in Costa Rica and Mexico.[1] Because of the lack of information, the recorded prevalence in the other countries of this region is moderate (around 3 to 6%); however, "taking in account that in most populations there are many people with undiagnosed type 2 diabetes," its prevalence is increasing.[1] The number of deaths related to diabetes in Latin America and the Caribbean region, of which Mexico and Central America represent almost one fourth of the inhabitants, has been estimated at more than 400,000 per year.[2]

Thus, in spite of the availability of insulin and oral hypoglycemic agents currently used for DM control, the lack of sufficient economic resources has forced the population in this region to use plants for its medical empirical treatment. Although some programs have been carried out to improve the quality of diabetic patient care and some initiatives undertaken to support the herbal medicine, these continue to be limited; currently, there are many problems because this type of medicine is continually marginalized by the national health systems in the region.[3]

The flora of Mexico, like Central American flora, has more than 20,000 higher vascular plants; therefore, the biodiversity of Mexico and Central America is among the richest of the world. Furthermore, more than 90 ethnic groups who live in this region use the natural resources within their reach in accord with their cultural necessities. Miller et al. have reported that, in underdeveloped countries, the patients are mostly from low socioeconomic conditions. For them, the use of herbal remedies is perceived as "natural" and safe; furthermore, it promotes wellness and not just treatment of illness. Moreover, they are afraid of the side effects of conventional drugs.[4]

As a result of these facts, a lot of information is currently available about the utility and study of Mexican and Central American medicinal plants.[5–9] However, the recovery and analysis of information about plants used for DM control in this area are complicated because, in many cases, it is insufficient and confused and in others scattered (principally in Central America). Thus, no single publication compiles the ethnobotanical and pharmacological information concerning the plants used in this region, as well as in what way they should be prepared and studied for DM

control. The objective of the present work was to analyze the ethnobotanical information about Mexican and Central American medicinal plants used for DM control and the results obtained in the investigation of their hypoglycemic activity.

METHODS

The literature that deals with the use and investigation of Mexican and Central American antidiabetic plants was analyzed. The compiled information was obtained through bibliographic investigation: books, reports, and articles from specialized journals in ethnobotany. Information on the pharmacology and chemistry of Mexican and Central American medicinal plants was analyzed. A herbarium research, searching for the antidiabetic plants recorded in the *Medicinal Plants Herbarium* from the *Instituto Mexicano del Seguro Social* (IMSSM-Herbarium) was also carried out. Furthermore, some documented data in papers about various initiatives by international associations to identify the medicinal plants used in Mexico, Belize, Guatemala, Nicaragua, Panama, and Costa Rica were analyzed.

RESULTS

Table 9.1 lists the 175 antidiabetic plants most used empirically for DM control in Mexico and Central America. Some species are used in two or more countries of the region (in total, 23 species). In addition, for each plant listed, the table includes information about the botanical family, scientific name, most used popular name in Mexico and/or Central America, utilized part, manner of preparation, and number of bibliographic references indicating that each plant has potential antidiabetic effects.

Botanical families with the highest numbers of antidiabetic plant species are:

Asteraceae (21)
Leguminosae (14)
Euphorbiaceae (10)
Cactaceae (9)
Labiatae (7)
Aristolochiaceae (6)
Rubiaceae (6
Apocynaceae (5)

On the other hand, the plants most cited as antidiabetic remedies, with more than ten reports each, are various species of:

Opuntia (Cactaceae)
Tecoma stans (Bignoniaceae)
Aloe barbadensis (Liliaceae)
Cecropia obtusifolia (Moraceae)
Parmentiera edulis (Bignoniaceae)
Psacalium decompositum (Asteraceae)
Bidens pilosa (Asteraceae)
Momordica charantia (Cucurbitaceae)
Crataegus mexicana (Rosacea)
Marrubium vulgare (Labiatae)

TABLE 9.1
Mexican and Central American Plants Used Traditionally for DM Control

Family	Scientific Name	Popular Name	Country	Used Part	Preparation	No. Rep.
Acanthaceae	*Justicia spicigera* Schlecht.	Muicle	Mexico	Bark, leaves	Infusion	2
Agavaceae	*Agave lechuguilla* Torr.	Lechuguilla	Mexico	Stems	Drinking water	2
	Yucca guatemalensis Baker. syn. *Y. elephantipes*	Izote	Honduras	Leaves, flowers	Decoction	1
Anacardiaceae	*Anacardium occidentale* L.[a]	Cacaya, acuyu	Panama, Mexico	Bark	Infusion	2
	Mangifera indica L.[a]	Mango criollo	Mexico	Leaves, stems	Decoction	5
Anonaceae	*Malmea depressa* (Baill.) R. E. Fr. syn. *Guatteria leiophylla* (F.D. Sm.) Saft. Ex Standl.	Elemuy	Mexico	Roots	Decoction	1
	Rhus virens Lindh. Ex A. Gray.	Lantrisco	Mexico	Pell	Infusion	2
Apocynaceae	*Catharanthus roseous* G. Don.[a]	Guaca, Chula, Mulata, Teresita	Honduras, Mexico	Leaves, flowers	Decoction, infusion	7
	Plumeria rubra L.	Cacaloxóchitl, Flor de mayo	Mexico	Flowers	Decoction	4
	P. rubra L. var. *acutifolia* Bailey.	Gluchin	Central America	Stems	N/A	1
	Rauwolfia serpentina Benth ex. Kurz.	Sarpagande	Central America	N/A	N/A	1
	R. tetraphylla L.[a]	Paulio, paulillo	Honduras, Mexico	Leaves, roots	Decoction	2
Araceae	*Xanthosoma robustum* Schott.[a]	Mafafa blanca	Mexico	Leaves	Decoction	1
Aristolochiaceae	*Aristolochia anguicida* Jacq.	Guaco, guacolicor	Honduras	Roots	Decoction	1
	A. brevipes Benth.	Hierba del Indio	Mexico	Roots	Decoction	1
	A. maxima Jacq.	Guaco	Honduras	Roots	Decoction	1
	A. odoratissima L.	Guaco	Honduras	Roots	Decoction	1
	A. pilosa H.B.K.	Guaco	Honduras	Roots	Decoction	1
	A. sericea Benth.[a]	Guaco	Mexico	Leaves, stems	Infusion	2
Asclepiadaceae	*Cynanchum schlechtendalii* (Deche.) Standl. et Steyerm.	Xtum-ak	Mexico	Resin	Drops (decoction)	1
Asteraceae	*Acourtia thurberi* Gray.[a]	Matarique	Mexico	Roots	Decoction	3
	Artemisia mexicana Willd.[a]	Estafiate	Mexico	Whole plant	Decoction	2
	Bidens pilosa L. syn. *B. odorata* Cav.[a]	Aceitilla, Chatay	Guatemala, Mexico	Whole Plant	Decoction, infusion	11
	B. veronicaefolia (H.B.K) Gray.[a]	Hierba dorada	Mexico	Leaves	Decoction	1
	Calea integrifolia (DC.) Hemsl.	Prodigiosa	Mexico	Stems, leaves	Decoction	4
	C. urticifolia (Mill.) DC.	N/A	El Salvador	N/A	Decoction	1

TABLE 9.1 (CONTINUED)
Mexican and Central American Plants Used Traditionally for DM Control

Family	Scientific Name	Popular Name	Country	Used Part	Preparation	No. Rep.
	C. zacatechichi Schltdl.[a]	Prodigiosa	Mexico	Whole plant	Decoction	3
	Cirsium mexicanum DC.	Cardo santo	Mexico	Roots	Decoction	4
	C. rhaphilepis (Hemsl.) Petr.	Cardo santo	Mexico	Flowers	Infusion	5
	Conyza filaginoides (DC.) Hieron.	Simonillo	Mexico	Whole plant	Infusion	4
	Cynara scolymus L.	Alcachofa	Mexico	Bracts	Liquidize, infusion	4
	Lactuca sativa L. var. *romana*[a]	Lechuga romana	Mexico	Leaves	Juice	1
	Neurolaena lobata (L.) R. Br.[a]	Tres puntas, Gavilana, Mano de lagarto	Central America	Leaves	Decoction	7
	Psacalium decompositum Gray.[a] Syn. *Cacalia decomposita* Gray.	Maturi, matarique	Mexico	Roots, stems	Decoction	12
	P. palmeri (Greene) Rob. et Brett. syn. *Senecio palmeri* (Greene) Rydb.	Matarique	Mexico	Roots	Decoction	5
	P. peltatum (H.B.K.) Cass.[a] Syn. *Senecio peltiferus* Hemsl.	Matarique	Mexico	Roots	Decoction, infusion	7
	P. sinuatum (Cerv.) Rob et Brett.	Matarique	Mexico	Roots	Decoction	5
	Taraxacum officinale Weber.[a]	Arnica, Diente de león	Costa Rica, Mexico	Whole plant	Decoction	4
	Tridax procumbens L.	Hierba del toro	Guatemala	Leaf	Decoction	1
	Trixis frutescens	Chiriquí, Chucha, Diente de león,Tulán verde	Central America, Mexico	N/A	N/A	1
	T. radialis	Palo de Santamaría, Falsa árnica, plumilla, Arnica de monte	Central America, Mexico	N/A	N/A	2
Bignoniaceae	*Astianthus viminalis* H.B.K.[a]	Azuchil	Mexico	Roots, leaves	Decoction, infusion	2
	Crescentia alata (H.B.K.)	Morro	Guatemala	N/A	N/A	1
	C. cujete L.	N/A	Honduras	N/A	N/A	1
	Parmentiera edulis DC.[a] syn. *P. aculeata* (H.B.K.) Seem.	Cuajilote, Chote	Mexico	Roots, branch, fruit	Decoction, infusion, juice (fruit)	12

	Tecoma stans (L.) H.B.K.[a]	Flor de San Pedro, Huachácata Tronadora, Timboco, Tronador,	Central America, Mexico	Roots, stems, leaves, branch	Liquidize, infusion, decoction, grilled	34
Bixaceae	*Bixa orellana* L.[a]	Achiote	Guatemala, Mexico	Roots	Decoction	3
Bombacaceae	*Pachira aquatica* Aubl.	Apompo	Mexico	Roots	Infusion	3
Boraginaceae	*Cordia alliodora* (Ruiz et Pav.) Cham.	Palo de rosa	Mexico	Bark	Infusion	1
	Tournefortia hirsutissima L.[a]	Lágrimas de San Pedro	Mexico	Stems	Decoction	3
Burseraceae	*Bursera simaruba* (L.) Sarg.	Palo mulato	Mexico	Bark	Decoction	3
Cactaceae	*Aporocactus flagelliformis* (L.) Lem.	Junco	Mexico	Stems	Decoction	2
	Lamaireocereus dumortieri	Órgano	Mexico	Stems	Infusion	4
	Nopalea indica L.	Nopal	Mexico	Stems	Decoction	3
	Opuntia ficus-indica (L.) M.[a]	Nopal, Nopal de castilla	Central America, Mexico	Stems	Juice	5
	O. leucotricha DC.	Duraznillo	Mexico	Stems, roots	Infusion	1
	Opuntia megacantha Salm–Dyck.[a]	Nopal de coyote	Mexico	Stems	Juice, crude	1
	Opuntia. sp.[a]	Nopal, Taat (mixe)	Mexico	Stems, roots	Juice, grilled, crude, infusion, liquidize	47
	O. streptacantha Lemaire.[a]	Nopal, Xoconostle,	Mexico	Stems	Grilled, juice	14
	Rhipsalis baccifera (J. Mill.) Stearn.	Disciplinilla, Niguilla	Mexico	Stems	Infusion	5
Chenopodiaceae	*Spinacea oleracea* L.[a]	Espinaca	Mexico	Leaves	Juice	1
Combretaceae	Cumbretum fructicosum	Peineta	Guatemala	N/A	N/A	1
	Terminalia catappa L.	Almendra	Mexico	Leaves	Infusion	1
Convolvulaceae	*Ipomoea crassicaulis* Rob	Llinda mañana	Mexico	Bark	Decoction	1
	Turbina corymbosa (L.) Raf.	Guana	Mexico	Leaves	Infusion	1
Cruciferae	*Brassica oleracea* L.[a]	Col	Mexico	Leaves	Juice	1
	B. oleracea L. var. *botrytis*[a]	Coliflor	Mexico	Flowers	Juice	1
Cucurbitaceae	*Cucumis sativus* L.[a]	Pepino	Mexico	Fruit	Juice	2
	Cucurbita ficifolia (L.) Bouché.[a]	Chilacayote	Mexico	Fruit	Juice	7
	Ibervillea sonorae Greene.[a] syn. *Maximowiczia sonorae* S. Wats.	Wareke, Wereque	Mexico	Roots	Ground, decoction	2
	Momordica charantia L.[a]	Condeamor, Calaica, Sorosí (see Sorrow)	Central America, Mexico	Whole plant, leaves, fruits, bark, vine	Decoction, infusion	12

TABLE 9.1 (CONTINUED)
Mexican and Central American Plants Used Traditionally for DM Control

Family	Scientific Name	Popular Name	Country	Used Part	Preparation	No. Rep.
Ebenaceae	*Diospyros ebenaster* Retz. Syn. *D. Ebenum* J. König ex Retz.	Zapote de agua	Mexico	Seeds	Infusion	1
Equisetaceae	*Equisetum robustum* A. Br.	Cola de caballo	Mexico	Stems	Infusion	2
	E. myriochaetum Schltdl. & Cham.[a]	Cola de caballo	Mexico	Whole plant	Drinking water	1
Ericaceae	*Agarista mexicana*[a]	Palo santo	Mexico	Leaves	Decoction	3
Euphorbiaceae	*Cnidoscolus aconitifolius* (Mill.) I.M. Johnst.	Chaya	Mexico	Leaves	Grilled	4
	C. multilobus (Lex) L.M.[a]	Chaya	Mexico	Leaves	Decoction	2
	Croton draco Schltdl.	Sangre grado	Mexico	Bark, leaves	Infusion	8
	C. niveus Jacq.	Quina roja	Honduras	Bark	Decoction	1
	C. tonduzii Pax.	Quina	Honduras	Bark	Decoction	1
	C. xalapensis H.B.K.	Quina roja	Honduras	Bark	Decoction	1
	Euphorbia prostata Aiton.[a]	Golondrina	Mexico	Whole plant	Decoction	1
	Jatropha dioica Sessé ex Cerv.	Sangre grado	Mexico	Roots	Decoction	1
	J. gossypiifolia L.	Parroty grass	Costa Rica, Nicaragua	Leaves	Decoction	2
	Pedilanthus palmeri	Candelilla	Mexico	Bark/stems	Infusion	2
Flacourtiaceae	*Samyda yucatanensis* Standl.	Naranja ché	Mexico	Roots	Decoction	1
Fouquieriaceae	*Fouquierua splendens* Engelm.	Albardana	Mexico	Stems	Decoction	1
Gramineae	*Coix lachryma-jobi* L.[a]	Lágrima de San Pedro	Mexico	Leaves, seeds	Decoction, infusion	3
	Cynodon dactylon (L.) Pers.[a]	Grama	Mexico	Whole plant	Decoction	3
	Saccharum officinarum L.[a]	Caña de cuchi	Mexico	Roots	Drinking water	1
Julianaceae	*Amphypterygium adstringens* (Schltdl.) Schiede. syn. *Juliana adstringens* Schtdl.	Cuachalalate	Mexico	Bark	Infusion	1
Labiatae	*Lepechinia caulescens* (Ort.) Epling.[a]	Salvia	Mexico	Leaves, stems, flowers	Decoction	4
	Marrubium vulgare L.[a]	Marrubio, mastro, mastrán	Mexico, Honduras	Whole plant, roots, branch	Liquidize, infusion, decoction	11
	Mentha piperita L.[a]	Hierbabuena	Mexico	Branches, whole plant	Infusion, decoction	4
	Ocimum bacilicum L.	Albaca	Honduras	Leaves	Decoction	1

	O. campechianum Miller. syn. *O. Micrantum* Willd.	Albaca de gallina	Honduras	Leaves	Decoction	1
	Origanum vulgare L.	Orégano	Mexico	Roots, leaves	Infusion	2
	Teucrium cubense Jacq.[a]	Agrimonia	Mexico	Whole plant	Decoction	3
Lauraceae	*Persea americana* (L.) Mill.[a]	Aguacate	Mexico, Nicaragua	Seeds, bark, leaves	Infusion, decoction	5
Leguminosae	*Acacia farnesiana* (L.) Willd.	Huizache	Mexico	Branch	Infusion	1
	Bauhinia divaricata L.[a]	Pezuña de vaca	Mexico	Leaves	Decoction, infusion	3
	Cajanus cajan (L.) Millsp.[a]	Algarrobo	Panama	Leaves	Infusion	1
	Cassia alata L.	Barajo	Guatemala	Leaf	Decoction	5
	C. emarginata L. syn. *Senna bicapsularis* (L.) Roxb.	Retama, retama china	Mexico	Leaves, branch	Infusion	3
	C. occidentalis (DC.) Hemsl. syn. *Senna occidentalis* Link.	Frijolillo, tronador	Mexico	Leaves	Infusion	3
	C. reticulata Willd. syn. *Senna reticulata* (Wild.) Irwin et Barneby.	Saragundi	Costa Rica	Leaves	Decoction	1
	C. skinneri Benth. syn. *S. Skinneri* Benth.[a]	Parácata, frijolillo	Mexico	Leaves	Decoction	2
	Eysenhardtia polystachya (Ortega) Sarg.[a]	Palo dulce, rosilla	Mexico	Stems, whole plant	Tincture, infusion, decoction	3
	Haematoxylon brasiletto Karst.	Palo de Brasil	Mexico	Bark	Infusion	2
	Hymenaea courbaril L.[a] syn. *H. resinifera* Salisb.	Algarrob	Costa Rica, Panama	Leaves, bark	Infusion	3
	Phaseolus vulgaris L.[a]	Frijol, judía	Mexico	Pods	Decoction	3
	Sweetia panamensis Benth.	Huayacán, Bark de Honduras	Belize, Mexico	Bark	Decoction	4
	Trigonella foenum–graceum L.[a]	Fenugreco	Mexico	Seeds	Decoction	2
Liliaceae	*Allium sativum* L.[a]	Ajo	Mexico	Leaves, bulbs	Infusion, decoction	3
	Allium cepa L.[a]	Cebolla	Mexico	Bulbs	Decoction	2
	Aloe barbadensis Mill.[a] syn. *A. vera* L.	Zábila, Sábila	Guatemala, Mexico	Stems, flowers	Liquidize, infusion, juice	25
Lobeliaceae	*Lobelia laxiflora* H.B.K.	Arete chiquito	Mexico	Bark	Infusion	1
Loganiaceae	*Buddleia americana* L.[a]	Tepozán	Mexico	Leaves	Decoction	2
Loranthaceae	*Arceuthobium vaginatum* (Willd.) Presl.	Crameria	Mexico	Whole plant	Infusion	1
	Psittacanthus calyculatus (DC.) Don.[a]	Injerto, mal de ojo, visco, muérdago	Mexico	Branches, leaves, stems, flowers	Infusion	3
	Struthanthus densiflorus (Benth.) Standl.	Injerto, San Bartolo	Mexico	Branch	In water	3
Malvaceae	*Malvastrum coromandelianum* (L.) Garcke.	Malvavisco	Mexico	Leaves	Infusion	1
	Pavonia schiedeana Steud.[a]	Cadillo	Mexico	Leaves, stems	Infusion	2
Marantaceae	*Calathea macrosepala*[a]	Macús, Chufle	El Salvador	Roots, tubercles following flowering	N/A	1

TABLE 9.1 (CONTINUED)
Mexican and Central American Plants Used Traditionally for DM Control

Family	Scientific Name	Popular Name	Country	Used Part	Preparation	No. Rep.
Menispermaceae	*Cissampelos pareira* L.	Guaco	Mexico	Roots	Picada	3
Monimiaceae	*Peumus boldus* Molina.	Boldo	Mexico	Leaves	Infusion	1
Moraceae	*Cecropia obtusifolia* Berth.[a]	Chancarro, guarumbo, hormiguillo,	Central America, Mexico	Leaves, stems, bark	Decoction, infusion	16
	C. peltata L.	Huarumbo, Guarumbo	Mexico	Leaves, stems, bark	Infusion, drinking water	5
Musaceae	*Musa sapientum* L.[a]	Flor de plátano	Mexico	Roots, flowers	Infusion, decoction	3
Myrtaceae	*Eucalyptus globulus* Labill.[a]	Eucalipto, Alcanfor	Guatemala, Mexico	Leaves	Infusion, decoction	7
	Eugenia jambos	Pomarrosa	El Salvador	Seeds	Pulverized	1
	Psidium guajava L.[a]	Guayaba	Guatemala, Panama	Leaves, fruit	Juice	2
Nyctaginaceae	*Allionia choisyi* Standll.	Hierba de la hormiga	Mexico	Whole plant	Decoction	1
	Salpianthus arenarius (H.B.K.) G. Ortega.[a]	Catarinita, catarinilla	Mexico	Flowers	Decoction	1
	Salpianthus macrodonthus Stand.[a]	Catarinita, Catarinilla, Apatzicua	Mexico	Leaves, flowers, roots	Decoction	6
Oleaceae	*Olea europaea* L.[a]	Olivo	Mexico	Leaves	Decoction	1
Palmae	*Acrocomia mexicana* Karw.[a]	Cocoyol	Mexico	Fruit	Decoction	4
Papaveraceae	*Argemone ochroleuca* Sweet.	Chicalote	Mexico	Roots	Infusion	1
	Argemone ochroleuca Sweet ssp. *ochroleuca*	Cardo, chicalote	Mexico	Roots, stems	Infusion	7
Piperaceae	*Piper hispidum* Sw.	Cordoncillo	Mexico	Leaves	Decoction	4
	Piper sanctum (Miq.) Schltdl.	Palo santo	Mexico	Leaves	Decoction	1
Rhamnaceae	*Colubrina glomerata* (Benth.) Hemsl.	Quina	Mexico	Bark	Decoction	1
Rhizophoraceae	*Rhizophora mangle* L.[a]	Mangle, mangle rojo	Mexico	Peel, bark, stems	Decoction, infusion	6
Rosaceae	*Crataegus mexicana* Moc. & Sessé.[a] Syn. C. *pubescens* (H.B.K.) Steud.	Tecojote criollo	Mexico	Roots, leaves, branch	Infusion, decoction	11
	Eriobotrya japonica (Thunb.) Lindl.[a]	Níspero	Mexico	Leaves, flowers	Infusion, decoction	5
	Prunus armeniaca L.	Chabacano	Mexico	Roots	Decoction	2
	Rosa centifolia L.	Rosa de castilla	Mexico	Stems, leaves, flowers	Infusion	1
Rubiaceae	*Bouvardia terniflora* (Cav.) Schl.	Trompetilla	Mexico	Leaves	Decoction	1

	Coutarea latiflora Moc & Sess. syn. *Hintonia latiflora* Moc & Sess.	Campanillo, Copalche, Copalquin	Mexico	Whole plant, leaves, stems	Infusion, decoction	3
	Exostema caribaeum (Jacq.) Roem. & Schult.	Quina	Mexico	Bark	Decoction	1
	Psychotria elata (Sw.) Hammel.	Red scholars	Nicaragua	Flowers, stem, roots, leaves	Decoction	1
	P. poeppigiana Muell. Arg.	Sore mouth bush	Nicaragua	Flowers, stem, leaves	Decoction	1
	Randia echinocarpa Moc. & Sesse.[a]	Granjel	Mexico	Fruit	Decoction	2
Rutaceae	*Citrus aurantium* L.[a]	Naranja agria	Mexico	Fruit	Juice	6
	Decatropis bicolor (Zucc.) Radlk.	Ranto	Mexico	Leaves	Infusion	1
Sapindaceae	*Serjania racemosa* Schumach.	Bejuco de 3 corazones	Mexico	Stems	Infusion	6
	Serjania triquetra Radlk.[a]	Palo de 3 costillas	Mexico	Stems	Decoction	2
Saururaceae	*Anemopsis californica* Hook. & Arn.	Hierba del manso	Mexico	Roots, leaves	Infusion	1
Scrophulariaceae	*Capraria biflora* L.	Claudiosa	Mexico	Leaves	Infusion	3
Simaroubaceae	*Quassia amara* L.	Cuasia, Hombre grande, Tru	Mexico, Guatemala, Honduras	Bark, leaves	Decoction	8
Smilacaceae	*Smilax aristolochiaefolia* Mill.	Cocolmecatl	Mexico	Roots	Infusion	3
Solanaceae	*Physalis phyladelphica* Lam. syn.[a] *Physalis ixocarpa*	Tomate verde	Guatemala, Mexico	Peel	Decoction	3
	Solanum seaforthianum Andr.	Lágrimas de San Pedro	Mexico	Leaves	Infusion, decoction	1
	Solanum verbascifolium L.[a]	Malabar	Mexico	Stems	Infusion, decoction	2
Sterculiaceae	*Guazuma ulmifolia* Lam.[a]	Guácima	Mexico	Bark, leaves	Infusion, decoction	8
Turneraceae	*Turnera diffusa* Willd.[a]	Damiana	Mexico, Honduras	Whole plant, leaves	Decoction	7
Umbelliferae	*Arracacia brandegeei* Coulter & Rose.	Chuchupate	Mexico	Roots	Decoction	1
	Cuminum cyminum L.[a]	Comino	Mexico	Seeds	Decoction	1
	Ligusticum porteri Coult. & Rose.	Raíz de cochino	Mexico	Roots	Infusion	2
Urticaceae	*Urtica dioica* L.[a]	Ortiga	Guatemala, Mexico	Leaves	Decoction	3
Verbenaceae	*Vitex mollis* H.B.K.	Ahuilotes	Mexico	Roots	Infusion	1
Zingiberaceae	*Costus ruber* Griseb.[a]	Caña agria	Mexico	Stems	Decoction	1
	Zingiber officinale Roscoe.	Jenjibre	Mexico	Roots	Decoction	1
Zygophyllaceae	*Guaiacum coulteri* A. Gray.[a]	Guayacán	Mexico	Stems	Decoction	2
	Larrea tridentata (DC.) Coville.	Gobernadora	Mexico	Leaves, stems, roots	Decoction, infusion	4

Notes: No. rep.: number of reports; N/A: data not available.

[a] Scientifically studied plants.

These 10 plants have been studied in different experimental models, principally using *in vivo* techniques. Agreeing with the classification proposed by other researchers for the antibiabetic plants around the world,[10,11] Mexican and Central American antidiabetic plants also can be classified into three groups:

- Plants used as antidiabetic remedies whose pharmacological properties have not yet been investigated. Table 9.1 lists 95 plant species that have not yet been researched.
- Plants whose hypoglycemic activity has been experimentally and/or clinically researched, but whose hypoglycemic compounds have not been identified. Table 9.1 lists 80 such plant species. At the pharmacological level, the Mexican and Central American plants most extensively studied are: *Aloe barbadensis*, *Catharanthus roseous, Cecropia obtusifolia*, *Momordica charantia*, various species of *Opuntia*, *Psacalium decompositum*, *Tecoma stans,* and *Trigonella foenum-graceum*.
- Hypoglycemic plants whose active principles have been chemically characterized. These plants are[12–23]:

  Acrocomia mexicana (coyolosa)
  Agarista mexicana (triterpene 23,24 dimethyl-24-ethyl-stigmast-25-ene)
  Astianthus viminalis H.B.K. (iridoids)
  Cecropia obtusifolia (possibly isoorientin and chlorogenic acid)
  Equisetum myriochaetum (kaemferol-3-O-soforosida-4′-O-β-D-glycoside)
  Opuntia ficus-indica (polysaccharide)
  Opuntia streptacantha (polysaccharide)
  Parmentiera edulis (lactucin-8-O-methylacrylate, a guaianolide)
  Psacalium decompositum (various furoeremophylanes and an aqueous polysaccharide fraction)
  Salpianthus arenarius (saliriol)
  Brickellia veronicaefolia (5,7,3′-trihydroxi-3,6,4′-trimethoxyflavone)
  Tecoma stans (tecomine and tecostanine alkaloids)

DISCUSSION

In this work, the ethnobotanical and pharmacological information was compiled and classified in order to facilitate its analysis for new or continued experimental and clinical studies with Mexican and Central American antidiabetic plants. In some countries from this region, field, market, or bibliographic ethnobotanical investigations about the antidiabetic plants used by the population have been carried out.[24–28] One important source of information comes from the IMSS-Herbarium collection, whose heritage is the most important in Latin America, with more than 13,000 Mexican and Central American medicinal plants recorded.

In 2002, Hernandez et al. reported 82 plants used for DM control in Mexico.[29] Those 64 plants species with complete ethnobotanical data in the investigation mentioned were included in the present work. Our research also reports 23 species included in *Morton's Atlas of Medicinal Plants of Middle America* (1985), which recorded 69 antidiabetic plants of Middle America, including some plants used in Caribbean and South American countries.[5] Furthermore, information was also obtained from the ethnobotanical studies on the popular medicine in Belize, Guatemala, Nicaragua, Panama, and Costa Rica,[30–34] as well as from ethnopharmacological investigations published in different specialized journals, in which the hypoglycemic activity of around 80 Mexican antidiabetic plants was experimentally investigated.[35–43]

It is important to indicate that Mexico and Central America have a great cultural similarity, principally between inhabitants of the south of Mexico and northern Central America, whose botanical and cultural richness is a legacy of the Mayan civilization. Therefore, the population's

traditional knowledge about the utility of the plants in some cases is the same. The most popular antidiabetic plants used by both regions in question are:

Anacardium occidentale
Bidens pilosa
Bixa orellana
Catharanthus roseous
Cecropia obtusifolia
Eucalyptus globolus
Momordica charantia
Opuntia ficus-indica
Plumeria rubra
Physalis phyladelphica
Quassia amara
Swertia panamensis
Taraxacum officinale
Tecoma stans
Trixis frutescens
Trixis radialis

Similarly, in many cases it was found that various species with a reputation of antidiabetic effects belong to the same genus, probably because morphological similarities among them provoke the people to use these plants for the same therapeutic function. For example, the genus *Aristolochia* has six different species used as antidiabetic remedies, *Opuntia* and *Psacalium* have five each, and *Cassia* has four.

Although several Central American plants have been reported as antidiabetic remedies, only in some cases has the evaluation of their hypoglycemic properties been carried out.[30,31,44–46] For example, *Neurolaena lobata* (L.) R. Br. (Asteraceae) is a Panamanian plant that has shown hypoglycemic activity in healthy and alloxan-diabetic mice.[7] Sesquiterpene lactones isolated from this plant have not been pharmacologically evaluated. *Hymenaea courbaril* L. and *Cajanus cajan* are other plants used in Panama with hypoglycemic activity in normoglycemic animals.[7,47] Central American medicinal plants that have been investigated so far have been selected predominantly to assess antimicrobial, brine shrimp toxicity, and anticancer, larvicidal, and insecticidal activities, as well as against HIV and, in general, for the treatment of infectious disorders.[48–50]

On the other hand, various antidiabetic plants used in Mexico and Central America, such as *Catharanthus roseous, Momordica charantia*, and *Trigonella foenum-graceum*, have also been reputed to act as antidiabetic remedies in Asian and African countries, and they have been pharmacologically studied in other countries (from Asia and Africa) that do not belong to the region presently considered. The use of plants by people across a broad range of geographic regions supports the assumption that hypoglycemic bioactive compounds of some value may be present in these plants. Although hypoglycemic activity has been reported in the three mentioned plants (probably the antidiabetic plants most extensively studied worldwide) and several hypoglycemic agents have been proposed, it has not yet been possible to perform suitable clinical studies.

The results obtained in this survey emphasize several important facts:

- Necessity for chronic studies. The studies with antidiabetic plants carried out until now have been done on experimental animals, measuring principally acute hypoglycemic effects. However, various plants exhibit hypoglycemic activity only when evaluated in chronic studies, such as *A. barbadensis*.[51] Therefore, it is important to start chronic studies principally for those reputed antidiabetic plants that have not shown acute hypoglycemic effects, such as *Citrus aurantium* L., *Crataegus mexicana* Moc & Sessé, *Physalis*

philadelphica Lam., *Serjania triquetra* Radlk., etc. Around 40 out of the 80 antidiabetic plants studied until now in Mexico and Central America did not show acute hypoglycemic effect in different experimental models using *in vivo* techniques.[40]

- Exigency of knowing the mechanisms of the hypoglycemic action produced by these plants. The hypoglycemic plants could produce their action by a mechanism that requires the presence of functioning pancreatic β-cells and stimulating the insulin secretion like the oral hypoglycemic agents sulfonylurea type, or by extra-pancreatic mechanisms, including interference in the intestinal glucose absorption, inhibiting insulinase, and/or stimulating the insulin receptors. Furthermore, "there are many other toxicological effects of plants which may result in hypoglycemia, such as hepatotoxicity or β-adrenergic blockade."[11] However, with the results obtained to date, it is not possible to know how the Mexican and Central American antidiabetic plants act.
- The isolation and chemical characterization of hypoglycemic principles should be intensified. In Mexico, traditional preparations of these plants have been studied, but the purification and study of the active compounds or fractions obtained from hypoglycemic plants have just recently started. Hypoglycemic compounds are known in only 12 antidiabetic plants used in Mexico and Central America; this represents a level lower than the 16% reported worldwide.[11]
- Beginning toxicological and clinical studies is urgently needed. Many plants could be dangerous because they contain beneficial and toxic substances together. For example, *Psacalium decompositum* (syn. *Cacalia decomposita*) is one of the most used and studied plants in Mexico for DM control, and it has been determined to contain hypoglycemic compounds and pyrrolizidine alkaloids, which are considered potent hepatotoxic, carcinogenic, and mutagenic agents.[15,16,52] Although immature fruits of *Cucurbita ficifolia* have shown hypoglycemic activity on type 2 diabetic patients,[53] some evidence indicates that the mature fruits of the same plants also produce hypoglycemic activity in experimental models, but with associated toxicological effects.[41,54] Thus, because the traditional preparations are complex mixtures of unknown substances, it is considered urgent to begin toxicological studies, principally with the plants most extensively used by the population, and to determine which plants are innocuous. No suitable toxicological information about Mexican and Central American hypoglycemic plants is available.
  - In addition to *C. ficifolia*, two other edible plants have been clinically studied: *Opuntia ficus-indica* and *Opuntia streptacantha*.[55] The lack of clinical studies is due to ethical impediments to performing studies in human beings in the absence of previous knowledge about toxicological effects of these hypoglycemic plants. However, in Mexico and Central America, many edible plants with hypoglycemic activity, such as *Cucumis sativus*, *Cucurbita ficifolia*, *Phaseolus vulgaris*, *Spinaceae oleraceae*, etc., could be studied in human beings.[38] In accordance with Ernst, clinical investigation should be rigorous, preferably through randomized controlled trials.[56] However, without knowledge about dosing, drug interaction, and toxic effects and due to ethical considerations, this too seems complicated.

CONCLUSIONS

DM is a serious health problem in Mexico and Central America. The lack of sufficient economic resources has forced the population in this region to use plants for its medical empirical treatment. Thus, the use of antidiabetic plants in the region is currently much diffused among its inhabitants. The present work lists the ethnobotanical data of 175 Mexican and Central American antidiabetic plants; however, people in this region likely use more than 300 different species. For more than 80 of these plants, experimental studies have been carried out and hypoglycemic effects have been detected in around 50%.

Aloe barbadensis, *Anacardium occidentale*, *Bidens pilosa*, *Cecropia obtusifolia*, *Eucalyptus globolus*, *Momordica charantia*, various species of *Opuntia*, *Parmentiera edulis*, various species of *Psacalium*, and *Tecoma stans* are the antidiabetic plants most used, and they are also some of the more studied hypoglycemic plants. However, their medicinal potential has not been chronically or clinically studied. Furthermore, chemical and pharmacological screening looking for the hypoglycemic principles in plants should be intensified because, so far, only a few promising hypoglycemic agents have been isolated and chemically characterized.

Taking into account the socioeconomic problems and the cultural circumstances in which Mexican and Central American people live, and in view of the number of species without experimental data as revealed by this literature review, we recommend that further experiments be conducted with these plants to develop new medicines and phytomedicines to treat diabetes and reduce the economic and social cost of medicine for this condition and its complications.

REFERENCES

1. Barcelo, A. and Rajpathak, S., Incidence and prevalence of diabetes mellitus in the Americas, *Pan Am. J. Pub. Health.*, 10, 300, 2001.
2. Barcelo, A. and Vovides, Y., The Pan American health organization and world diabetes day, *Pan Am. J. Pub. Health.*, 10, 297, 2001.
3. Nigenda, G. et al., The practice of traditional medicine in Latin America and the Caribbean: the dilemma between regulations and tolerance, *Salud Publica Mexico*, 43, 1, 2001.
4. Miller, K.L. et al., Complementary and alternative medicine in cardiovascular disease: a review of biologically bases approaches, *Am. Heart J.*, 47, 401, 2004.
5. Morton, F.J., *Atlas of Medicinal Plants of Middle America. Bahamas to Yucatan*, Charles C. Thomas Publisher, Springfield, IL, 1981, 1420.
6. Martinez, M., *Las Plantas Medicinales de Mexico*, Botas, México, 1989.
7. Gupta, M.P., Plants and traditional medicine. Case of Panama, in *Economic and Medicinal Plant Research*, Vol. 4, Wagner, H. and Farnsworth, N.R., Eds., London, Academic Press, 1990.
8. Aguilar, C.A. et al., *Herbario Medicinal del Instituto Mexicano del Seguro Social. Información Etnobotánica*, Instituto Mexicano del Seguro Social, Mexico, 1994, 253.
9. Aguilar, C.A. et al., *Plantas Medicinales del Herbario IMSS: su Distribucion por Enfermedades*. Instituto Mexicano del Seguro Social, Mexico, 1998, 119.
10. Bailey, J. and Day, C., Traditional plant medicines as treatments for diabetes, *Diabetes Care*, 12, 553, 1989.
11. Marles, R.J. and Farnsworth, R., Plants as sources of antidiabetic agents, in *Economic and Medicinal Plants Research 6,* Wagner, H. and Farnsworth, N.R., Eds., London, Academic Press, 1994, 149.
12. Hammouda, Y. and Amer, S.M., Antidiabetic effect of tecomine and tecostanine, *J. Pharm.* Sci., 55, 1452, 1960.
13. Hammouda, Y., Kader, R.A., and Samir, A.M., Hipoglycemic propierties of tecomine and tecostanine, *J. Pharm. Pharmacol.*, 16, 833, 1964.
14. Perez, R.M., Actividad hipoglucemiante de *Salpianthus arenarius*, *Acrocomia mexicana*, *Agarista mexicana* y *Verbesina persicifolia*, Ph.D. thesis, Universidad Autonoma Metropolitana Iztapalapa, Mexico, 1997.
15. Inman, W.D. et al., Antihyperglycemic sesquiterpenes from *Psacalium decompositum, J. Nat. Prod.*, 62, 1088, 1999.
16. Alarcon, A.F. et al., Hypoglycemic activity of root water decoction, sesquiterpenoids, and one polysaccharide fraction from *Psacalium decompositum* in mice, *J. Ethnopharmacol.*, 69, 207, 2000.
17. Andrade–Cetto, A. et al., Hypoglycemic effect of *Equisetum myriochaetum* aerial parts on streptozocin diabetic rats, *J. Ethnopharmacol.*, 72, 129, 2000.
18. Perez, R.M. et al., Hypoglycemic effects of lactucin-8-*O*-methylacrylate of *Parmentiera edulis* fruit, *J. Ethnopharmacol.*, 71, 391, 2000.
19. Perez, R.M. et al., Isolation and hypoglycemic activity of 5, 7,3′-trihydroxy-3,6,4′-trimethoxyflavone from *Brickellia veronicaefolia*, *Phytomedicine*, 7, 25, 2000.

20. Andrade–Cetto, A. and Wiedenfeld, H., Hypoglycemic effect of *Cecropia obstusifolia* on streptozocin diabetic rats, *J. Ethnopharmacol.*, 78, 145, 2001.
21. Meckes, M. et al., Iridoides adicionales de la planta medicinal *Astianthus viminalis* y su actividad hipoglucemiante y antihiperglucemiante, *Rev. Soc. Quim. Mex.*, 45, 195, 2001.
22. Perez, R.M. and Vargas, S.R., Triterpenes from *Agarista mexicana* as potencial antidiabetic agents, *Phytother. Res.,* 16, 55, 2002.
23. Alarcon, A.F.J. et al., Hypoglycaemic activity of two polysaccharides isolated of *Opuntia streptacantha* and *O. ficus indica*, *Proc. West. Pharmacol. Soc.*, 46, 139, 2003.
24. Linares, E., Bye, R., and Flores, B., *Tés curativos de México (Cuaderno 7)*, Instituto de Biología, UNAM. Mexico, 1990.
25. Martinez, I., Etnobotánica mexicana de plantas popularmente usadas para el tratamiento de la diabetes en algunos mercados de Mexico, thesis, Instituto de Biología, Universidad Nacional Autonoma de Mexico. Mexico, 1980.
26. Legorreta, I., Estudio comparativo de las plantas usadas para el tratamiento de diabetes en algunos mercados de México, thesis, Instituto de Biología, Universidad Nacional Autonoma de Mexico, Mexico, 1989.
27. Sabine, A. *Yucate Mayan Medicinal Plants: Ethnobotany, Biological Evaluation and Phytochemical Study of* Crossopetalum gaumeri, Swiss Federal Institute of Technology, Zurich, 2000.
28. Lorena–Porras, C., Medicinal plants of Guatemala with hypoglycemic effects, *Rev. Lat. Quim.*, 29 (Supl), 26, 2001.
29. Hernandez, G.E. et al., Studies on hypoglycemic activity of Mexican medicinal plants, *Proc. West. Pharmacol. Soc.,* 45, 118, 2002.
30. Arnason, T. et al., Maya medicinal plants of San José Succotz, Belize, *J. Ethnopharmacol.*, 2, 345, 1980.
31. Hirschhorn, H.H., Botanical remedies of South and Central America and the Caribbean: an archival analysis. Part I, *J. Ethnopharmacol.*, 4, 129, 1981.
32. Joly, L.G. et al., Ethnobotanical inventory of medicinal plants used by the Guaymi Indians in Western Panama. Part II, *J. Ethnopharmacol.*, 28, 191, 1990.
33. Giron, M.L. et al., Ethnobotanical survey of the medicinal flora used by the Caribs of Guatemala, *J. Ethnopharmacol.*, 34, 173, 1991.
34. Coe, F.G. and Anderson, J.G., Screening of medicinal plants used by the Garífuna of Eastern Nicaragua for bioactive compounds., *J. Ethnopharmacol.*, 53, 29, 1996.
35. Perez, R.M. et al., Study of the hypoglycemic effect of some Mexican plants, *J. Ethnopharmacol.*, 12, 253, 1984.
36. Roman, R.R. et al., Experimental study of the hypoglycemic effect of some antidiabetic plants, *Arch. Invest. Med.,* 22, 87, 1991.
37. Roman, R.R. et al., Hypoglycemic effect of plants used in Mexico as antidiabetics, *Arch. Med. Res.*, 23, 59, 1992.
38. Roman, R.R., Flores, S.J.L., and Alarcon, A.F., Antihyperglycemic effect of some edible plants, *J. Ethnopharmacol.*, 48, 25, 1995.
39. Alarcon, A.F.J. et al., Effects of three Mexican medicinal plants (Asteraceae) on blood glucose levels in healthy mice and rabbits, *J. Ethnopharmacol.*, 55, 171, 1977.
40. Alarcon, A.F.J. et al., Study of the antihyperglycemic effects of plants used as antidiabetics*., J. Ethnopharmacol.*, 61, 101, 1998.
41. Alarcon, A.F. et al., Evaluation of the hypoglycemic effect of *Cucurbita ficifolia* Bouché (Cucurbitaceae) in different experimental models, *J. Ethnopharmacol.*, 82, 185, 2002.
42. Alarcon, A.F.J. et al., Investigation on the hypoglycemic effects of extracts of four Mexican medicinal plants in normal and alloxan-diabetic mice. *Phytother. Res.,* 16, 383, 2002.
43. Alarcon, A.F.J. et al., Hypoglycemic activity of *Ibervillea sonorae* roots in healthy and diabetic mice and rats. *Pharm. Biol.*, 40, 570, 2002.
44. Hirschhorn, H.H., Botanical remedies of South and Central America, and the Caribbean: an archival analysis. Part II, *J. Ethnopharmacol.*, 5,163, 1982.
45. Epstein, N. and Yaquinto, M., *Sastun. My Apprenticeship with a Maya Healer. Rosita Arrigo*, Harper San Francisco, New York, 1994, 153.

46. House, P.R. et al., *Plantas Medicinales Comunes de Honduras*. Tegucijalpa-MDC, Honduras, CA, UNAH. CIMN-H. CID/CIIR.GTZ, 504, 1995.
47. Gupta, M.P. et al., Hypoglycemic activity of *Neurolaena lobata* (L.), *J. Ethnopharmacol.*, 10, 323, 1984.
48. Gupta, M.P. (Ed.) *270 Plantas Medicinales Iberoamericanas*, Colombia: CYTED SECAB, Convenio Andres Bello, SECAB Ciencia y Tecnología No. 55. 617, 1995.
49. Solis, N.P. and Gupta, M.P., Evaluation of Panamanian as a source of bioactive molecules: results of a natural foundation project, presented at 42nd Annual Meeting of the American Society of Pharmacognosy, Mexico, July, 2001.
50. Solis, N.P. et al., Bioprospecting in Central America: results from a multinational OAS project, presented at 42nd Annual Meeting of the American Society of Pharmacognosy, Mexico, July, 2001.
51. Ali, A.M., Effect of aloes on blood glucose levels in normal and alloxan diabetic mice, *J. Ethnopharmacol.*, 28, 215, 1990.
52. Sullivan, G., Detection of pyrrolizidine alkaloids in matarique *(Cacalia decomposita*), *Vet. Hum. Toxicol.*, 23, 6, 1981.
53. Acosta-Patiño, J.L. et al., Hypoglycemic action of *Cucurbita ficifolia* on type 2 diabetic patients with moderately high blood glucose levels, *J. Ethnopharmacol.*, 77, 99, 2001.
54. Hernandez, G.E. et al., Acute toxicological study of *Cucurbita ficifolia* juice in mice. *Proc. West. Pharmacol. Soc.*, 45, 42, 2002.
55. Frati–Munari, A. et al., Influence of nopal intake upon fasting glycemia in type II and healthy subjects, *Arch. Invest. Med.,* 22, 51, 1991.
56. Ernst, E., Plants with hypoglycemic activity in humans, *Phytomedicine,* 4, 73, 1997.

10 Antidiabetic Plants in the Caribbean

Compton E. Seaforth

CONTENTS

INTRODUCTION

The Caribbean region comprises one of the most diverse archipelagos in the world. Its natural vegetation is predominantly tropical forest, including an estimated 20,000 vascular plant species; about 7000 of these are endemic, mostly in Cuba, Hispaniola, and Jamaica. More than 10% of these plants are naturalized, including several medicinal species brought in — especially since the 17th century — from Europe, Africa, and India (Davis et al. 1997).

Knowledge of the Caribbean herbs and their uses originated with the slaves from Africa and with the Caribs and other Amerindians who were the first inhabitants. This knowledge was handed down from generation to generation by the oral tradition, changing as new uses were discovered and also blending with the customs and beliefs of the post-Columbian colonizers who came from Europe and later from India. The documentation of this folk knowledge is rather scarce and is scattered across the breadth of the natural and social sciences (Honychurch 1980; Morton 1981; Seaforth et al. 1982).

Traditional plant remedies in the Caribbean are known as "bushteas" or "bushmedicines," and they abound especially in communities with limited access to formal healthcare. Most medicinal plants in the region occur widely dispersed as weeds and are known, mainly, by the local common names preserved by the oral tradition. Thus, confusion can arise in attempting to identify them and when the same name is given to two or more different plants. Also, misidentification can occur when the specific plant is given different common names, sometimes as a consequence of the varying influences of West Africa and India on the English, French, or Spanish version of the name. For instance, *Catharanthus roseus*, which is traditionally used to treat diabetes, is known in some Caribbean islands as periwinkle; however, it is much better known as old maid (in Grenada), caca poule (in the Commonwealth of Dominica), cangrejera (in the Dominican Republic), vicaria (in Cuba), and ramgoat rose (in Jamaica).

The incidence of diabetes mellitus has been increasing for several decades in the Caribbean, and today this condition has become a major cause of disability and hospitalization and a serious financial burden. The estimated cost of medication and treatment in hospital for amputations, eye disease, and other related services for diabetics was reported in 2001 as in excess of U.S. $30 million annually (Henry 2001a).

In official circles, "diabetes and hypertension: twin trouble" have become the significant themes for chronic noncommunicable diseases (Morrison 2000) and they are not confined to upper socio-economic classes in the region. The prevalence of hypertension and diabetes mellitus (mainly of the type 2) is estimated at about 30 and 20%, respectively, in the adult population (Henry 2001a). Both disease conditions have been treated traditionally by means of the same herbal remedy. This folk remedy may be a decoction made from any one of the following plants: *Aristolochia trilobata* (leaf), *Gomphrena globosa* (leaf), *Mangifera indica* (leaf), *Passiflora quadrangularis* (leaf), *Caesalpinia bonduc* (seed) (Morton 1981; Biswas et al. 1997; Swarup 1997), or, especially, *Momordica charantia* (herb) (Morton 1981; Seaforth et al. 1982)

The International Diabetes Institute estimated that there were over one million cases of diabetes in the Caribbean in 1994. Projections were that 380,000 new cases would be found over the next 5-year period. Even higher figures have been achieved indicating that this disease is a common and growing public health concern in the region (Sargeant et al. 2001). The Caribbean Food and Nutrition Institute has recommended that, with type 1 and type 2 diabetes, diet is the cornerstone to successful treatment; there appears to be a constant need to re-emphasize that an appropriate diet and good nutrition are not an adjunct to diabetes management, but rather, in fact, are central to it (Henry 2001b).

DIETARY ASPECTS

The pattern of food consumption in the Caribbean over the past 40 years has moved toward that of North America. During this period, although undernutrition rates declined substantially, nutrition-related chronic diseases emerged to epidemic proportions (Editorial 2000). However, the extent to which changes in the diet caused this phenomenon in the Caribbean countries is not known. This possibility has prompted consideration as to whether aspects of the traditional Caribbean diets should be retained, or even encouraged, in the management of diabetes (Wolever and Ramdath 1997).

Nutrition is an area of medicine conducive to home remedies and these often are supported by users' testimonies. Therefore, people have tended to maintain the tradition of consuming certain plant foods to manage diabetes mellitus, such as *Momordica charantia* (fruit), *Sechium edule* (fruit), *Zingiber officinalis* (Jamaican ginger root) (Alleyne and Cruickshank 1990), and *Coriandrum sativum* (fruit) (Morton 1981). *Momordica charantia* is known by different names across the Caribbean, such as caraili, cerassee, maiden apple, pomme coolie, and sorrow seed. Various extracts from its fruit and from the vine have demonstrated hypoglycemic and also antihyperglycemic effects in tests with a diverse array of animal models, as described in hundreds of publications. Evidence has indicated insulin secretagogue and insulin mimetic activity in the fruit (Grover et al. 2002). *Coriandrum sativum,* which is known as coriander or cilantro, is a popular spice that has shown antihyperglycaemic effects in streptozotocin diabetic mice (Gray and Flatt 1999).

The expectation persists globally that increasing the consumption of fruits, vegetables, and starchy roots and tubers (e.g., *Ipomoea batatas*) would have the potential to protect against a range of chronic diseases. *Sechium edule* (fruit), called Jamaican cho-cho, has demonstrated significant antihypertensive effects (Gordon et al. 2000). In Japan, a glycoprotein component isolated from the cortex of white-skinned sweet potato (*Ipomoea batatas*) has showed antidiabetic activity in streptozotocin-induced diabetic rats and genetically diabetic models of mice and rats (Kusano et al. 2001). It is possible that certain culinary plants play a role in the treatment of diabetes (Day 1998; Broadhurst et al. 2000).

As is the case for many tropical plants, the composition of most Caribbean plant foods still requires scientific evaluation (Magnus 1993; Wolever and Ramdath 1997). Consider ackee (*Blighia sapida*), the national fruit of Jamaica, which is a remarkable case. Eating the unripe fruit has been associated with bouts of severe vomiting, central depression, convulsions, and profound hypoglycemia; blood glucose levels down to 3 mg per deciliter, especially for undernourished consumers,

have been found. Treatment of these effects is symptomatic, involving infusions of dextrose solution and management of the vomiting accomplished with antiemetics. However, the mechanisms underlying the vomiting and neurological disorders have not been properly established (Kean 1988). Ackee-induced poisoning has been attributed to two water-soluble hypoglycemic constituents: hypoglycin A (3-methylenecyclopropylalanine) in the edible arillus of the fruit and hypoglycin B (gamma-glutamylhypoglycin A), which, together with hypoglycin A, is present in the seeds. The unripe fruit has a much higher concentration of hypoglycin A than that of the ripe arillus, which is a safe food after boiling and the aqueous extract is discarded. Neither hypoglycin A nor hypoglycin B has been found suitable for drug development (Bressler et al. 1969; Golden et al. 2002).

THE HERBAL REMEDIES

Little scientific communication about the traditional herbal remedies has taken place among health care professionals in the Caribbean region. This has been dominated in a significant way from the outside by Spanish, Dutch, British, French, and American influences, so much technical information has stayed within the spheres of interest of these non-Caribbean nations.

TRAMIL (Traditional Medicine in the Islands) is an applied research project on the medicinal uses of plants in the Caribbean region (Robineau and Soejarto 1996). During the last few decades, ethnobotanical surveys, including the work of the TRAMIL group, have shown that folkloric medicinal plants are used to treat mainly self-limiting conditions, like colds and gastrointestinal disorders, and only to a lesser extent for such ailments as hypertension and diabetes (Hernandez et al. 1984; Seaforth 1987; Robineau 1997). The findings show that it will probably be impossible and perhaps undesirable to attempt officially to reduce the use of herbal medicines in the Caribbean region, except for those known to be toxic preparations.

The leaders of another French-sponsored project (ACCT 1985) reported that the traditional remedies for diabetes in the Commonwealth of Dominica are infusions or decoctions made from *Catharanthus roseus* (leaf), *Pluchea symphytifolia* (root), *Stachytarpheta jamaicensis* (leaf), or *Chaptalia nutans* (leaf). Generally, the recipe consists of five leaves per glass of water, from which the dose is one tablespoonful of the "bushtea" taken thrice daily.

The important guidebook by Morton (1981) describes comprehensively a number of plants used traditionally to treat diabetes in the Caribbean. Among them are the following, which are not mentioned elsewhere in this chapter: *Ageratum conyzoides* (root), *Bixa orellana* (root), *Borreria verticillata* (whole plant), *Cassia fruticosa* (flower), *Eryngium foetidum* (whole plant), *Chromolaena odorata* (flowers), *Malachra alceifolia* (leaf), and *Scoparia dulcis* (whole plant).

The popularity of herbal folk remedies to treat diabetes mellitus among patients attending government health centers has been reported in Jamaica by Alleyne and Cruickshank (1990) and in Trinidad and Tobago by Mahabir and Gulliford (1997). In the latter country, *Momordica charantia* (leaf and fruit) and, to a lesser extent, *Neurolaena lobata* (leaf) were among the preferred plant sources for diabetes treatment.

In Cuba, plants used traditionally to treat diabetes (Roig 1988) include *Lepidium virginicum* (whole plant), *Ocimum sanctum* (aerial parts), *Phyllanthus swartzii* (seed and leaf), *Syzygium cuminii* (fruit), and *Tecoma stans* (leaf and flowers). Oral administration of *Syzygium cumini* (synonym *Eugenia jambolana* Lam.) fruit extracts to normoglycemic and streptozotocin-induced diabetic rats showed hypoglycemic action possibly mediated by insulin secretion (Grover et al. 2002).

The traditional herbal remedies found in other tropical regions are also favored among Caribbean people. In Fiji and in Trinidad, for instance, the leaf extracts of certain edible fruit plants are used to treat diabetes, including *Momordica charantia* (caraili), *Mangifera indica* (mango), *Tamarindus indica* (tamarind), and *Carica papaya* (pawpaw) (Mahabir and Gulliford 1997). *Mangifera indica* (leaf) is also a folk remedy for diabetes in Nigeria and its antihyperglycemic effects have been demonstrated in glucose-fed rats (Aderigbe et al. 1999). *Momordica charantia* continues to

be the subject of study all over the world (Raman and Lau 1996; Ahmed et al. 2001; Vikrant et al. 2001; Muira et al. 2001; Grover et al. 2002). Antihyperglycemic extracts have been obtained from the weedy *Bidens pilosa* (Ubillas et al. 2000; Dimo et al. 2001), and from the holy basil, *Ocimum sanctum* (Vats et al. 2002). The ethanolic leaf extract of *Ocimum sanctum* significantly reduced blood glucose levels in normal, glucose-fed hyperglycemic and streptozotocin-induced diabetic rats (Grover et al. 2002).

Testing of *Catharanthus roseus* as a Jamaican antidiabetic folk medicine in the 1950s led to the fortuitous discovery by Eli Lilly Co. in the U.S. of the effectiveness of two of its many alkaloids — vincaleukoblastine and leurocristine — against leukemia and certain tumors. The potentially hypoglycemic extracts of this plant currently remain under investigation (Chattopadhyay 1999; Singh et al. 2001). Will such bioactivity in the plant extracts be proven as the effect of synergy among some of the constituents?

Within the Caribbean region, some preliminary work continues to seek mainly to compare the blood sugar-lowering activities of *Bixa orellana* and other plant extracts (Morrison and West 1982; Tolan et al. 2001). However, the available technological infrastructure, pharmaceutical expertise, and financial resources are not sufficient to support sustained in-depth studies of traditional medicinal plants as well as the processes likely to lead to new single-chemical-entity drug development.

FUTURE DIRECTIONS

Cecropia peltata L. (leaf) is abundantly known as a traditional Caribbean remedy for diabetes. Its sister species, *C. obtusifolia* Bertol, has a similar reputation in Mexico and neighboring lands (Morton 1981). In light of the demonstrated hypoglycemic effect of extracts from *Cecropia obtusifolia* on streptozotocin-diabetic rats (Andrade–Cetto and Wiedenfeld 2001), the leaf extracts of *Cecropia peltata* (Seaforth 1987) now appear to be deserving of more systematic research. Other candidates recommended for further study are *Syzygium cuminii* Skeels (synonym *Eugenia jambolana* Lam.) (Grover et al. 2001) and *Tecoma stans* (Meckes–Lozoya and Mellado–Campos 1985).

Neurolaena lobata is a herb that yields a very bitter leaf decoction popularly used for a variety of conditions, including malaria and diabetes; research has demonstrated antiprotozoal activity in the plant extracts (Berger et al. 2001). Although ethanolic extracts of the leaves produced hypoglycemia in preliminary tests on rats, no antidiabetic agents have been isolated so far (Gupta et al. 1984). The challenge remains for further investigations of this plant, at least through preliminary clinical observation. By local tradition, bitter-tasting bush-teas often are assumed to be antidiabetic, so *Momordica charantia* and *Neurolaena lobata* are significant candidate species for possible development into modern antidiabetic phytomedicines.

Current studies generally encourage further serious evaluation of the herbal folk remedies as they continue to play a significant role alongside orthodox medical practices in the treatment of diabetes mellitus in the Caribbean (Michie 1992).

Table 10.1 is a summary of the plants mentioned in this chapter.

TABLE 10.1
Antidiabetic Plants in the Caribbean

Plant (Family)	Common Name	Part Used — Ref.
Ageratum conyzoides L. (Compositae)	Zeb-a-fam	Root — Morton 1981
Aristolochia trilobata L. (Aristolochiaceae)	Tref	Leaf — Morton 1981
Bidens pilosa L. (Compositae)	Railway daisy	Whole plant[a] — Dimo et al. 2001
Bixa orellana L. (Bixaceae)	Roucou	Root — Morton 1981
Blighia sapida Kon. (Sapindaceae)	Ackee	Fruit[a] — Kean 1988
Borreria verticillata (L.) G.F.W. Mey (Rubiaceae)	White head broom	Whole plant — Morton 1981
Caesalpinia bonduc Roxb. (Leguminosae)	Nicker	Seed — Morton 1981
Carica papaya L. (Caricaceae)	Pawpaw	Fruit — Mahabir and Gulliford 1997
Cassia fruticosa Mill. (Leguminosae)	Cockrico	Flower; bush — Morton 1981
Catharanthus roseus G. Don (Apocynaceae)	Periwinkle	Leaf[a] — Singh et al. 2001
Cecropia obtusifolia Bertol. (Moraceae)	Guarumo	Leaf[a] — Andrade–Cetto and Wiedenfeld 2001
Cecropia peltata L. (Moraceae)	Bois canon	Leaf — Seaforth 1987
Chaptalia nutans Polak. (Compositae)	Dandelion, whiteback	Whole plant — ACCT 1985
Chromolaena odorata King & Robinson (Compositae)	Christmas bush	Flower — Morton 1981
Coriandrum sativum L. (Umbelliferae)	Culantro	Fruit[a] — Gray and Flatt 1999
Eryngium foetidum L. (Umbelliferae)	Shadobeni	Whole plant — Morton 1981
Gomphrena globosa L. (Amaranthaceae)	Bachelor button	Leaf — Morton 1981
Ipomoea batatas (L.) Lam. (Convolvulaceae)	Sweet potato	Root[a] — Kusano et al. 2001
Lepidium virginicum L. (Cruciferae)	Mastuerzo	Whole plant — Roig 1988
Malachra alceifolia Jacq. (Malvaceae)	Guimauve	Leaf — Morton 1981
Mangifera indica L. (Anacardiaceae)	Mango	Leaf[a] — Grover et al. 2002
Momordica charantia L. (Cucurbitaceae)	Caraili	Various parts[a] — Grover et al. 2002
Neurolaena lobata R. Br. (Compositae)	Zeb-a-pique	Leaf — Berger et al. 2001
Ocimum sanctum L. (Labiatae)	Albahaca morada	Aerial parts[a] — Grover et al. 2002
Passiflora quadrangularis L. (Passifloraceae)	Barbadine	Leaf — Morton 1981
Phyllanthus swartzii Kostel syn. *P. microphyllus* Kth. (Euphorbiaceae)	Yerba de la nina	Aerial parts — Roig 1988
Pluchea symphytifolia (Mill.) Gillis (Compositae)	Tabac zombi	Root — ACCT 1985
Scoparia dulcis L. (Scrophulariaceae)	Sweet broom	Whole plant — Morton 1981
Sechium edule Sw. (Cucurbitaceae)	Cho-cho	Fruit — Gordon et al. 2000
Stachytarpheta jamaicensis Vahl (Verbenaceae)	Vervine	Leaf — ACCT 1985
Syzygium cuminii Skeels (Myrtaceae)	Jambolan	Fruit[a]— Grover et al. 2002
Tamarindus indica L. (Leguminosae)	Tamarind	Fruit and leaf — Mahabir and Gulliford 1997
Tecoma stans (L) H.B.K. (Bignoniaceae)	Sauco amarillo	Aerial parts — Roig 1988
Zingiber officinalis Rosc. (Zingiberaceae)	Ginger	Root — Alleyne and Cruickshank 1990

[a] Diabetes-related effects shown in the scientific study.

REFERENCES

ACCT. (1985) Medecine Traditionnnelle et Pharmacopee. Contribution aux Etudes Ethnobotaniques et FLoristiques a la Dominique (The Commonwealth of Dominica), Paris: Agence de Cooperation Culturelle et Technique (ACCT).

Aderigbe, A.O., Emudianughe, T.S. and Lawal, B.A. (1999) Antihyperglycemic effect of *Mangifera indica* in rat, *Phytother. Res*., 13: 504–507.

Ahmed, I., Lakhami, M.S., Gillett, M., John, A. and Raza, H. (2001) Hypotriglyceridemic and hypocholesterolemic effects of antidiabetic *Momordica charantia* (karela) fruit extract in streptozotocin-induced diabetic rats, *Diabetes Res. Clin. Pract*., 51: 155–161.

Alleyne, S. and Cruickshank, J.K. (1990) The use of informal medication - particularly bushteas - in Jamaican patients with diabetes, *Cajanus. Caribbean Food Nutr. Inst. Q*., 23: 57–67.

Andrade-Cetto, A. and Wiedenfeld, H. (2001) Hypoglycemic effect of *Cecropia obtusifolia* on streptozotocin diabetic rats, *J. Ethnopharmacol*., 78: 145–149.

Berger, I., Passreiter, C.M., Caceres, A. and Kubelka, W. (2001) Antiprotozoal activity of *Neurolaena lobata*, *Phytother. Res*., 15: 327–330.

Biswas,T.K., Bandyopadhyay, S., Biswapati, M., Bhaswar, M. and Sengupta, B.R. (1997) Oral hypoglycemic effect of *Caesalpinia bonducella*, *Int. J. Pharmacognosy*, 35: 261–264.

Bressler, R., Corredor, C. and Brendel, K. (1969) Hypoglycin and hypoglycin-like compounds, *Pharmacol. Rev*., 21: 105–130.

Broadhurst, C.L., Polansky, M.M. and Anderson, R.A. (2000) Insulin-like biological activity of culinary and medicinal plant aqueous extracts *in vitro*, *J. Agric. Food Chem*., 48: 849–852.

Chattopadhyay, R.R. (1999) A comparative evaluation of some blood sugar lowering agents of plant origin, *J. Ethnopharmacol*., 67: 367–372.

Davis, S.D., Heywood, V.H., Herrera–MacBryde, O., Villa–Lobos, J. and Hamilton, A.C. (Eds) (1997) *Centres of Plant Diversity. Volume 3. The Americas*, Cambridge: WWF/IUCN.

Day, C. (1998) Traditional plant treatments for diabetes mellitus: pharmaceutical foods, *Br. J. Nutr*., 80: 5–6.

Dimo, T., Azay, J., Tan, P.V., Pellecuer, J., Cros, G., Bopelet, M. and Serrano, J.J. (2001) Effects of the aqueous and methylene chloride extracts of *Bidens pilosa* leaf on fructose-hypertensive rats, *J. Ethnopharmacol*., 76: 215–221.

Editorial. (2000) Food consumption issues and trends in the Caribbean, *Cajanus. Caribbean Food Nutr. Inst. Q*., 33: 1–3.

Golden, K.D., Williams, D.J. and Bailey–Shaw, Y. (2002) High–performance liquid chromatographic analyses of amino acids in ackee fruit with emphasis on the toxic amino acid hypoglycin A, *J. Chromatogr. Sci*., 40: 441–446.

Gordon, E.A., Guppy, L.J. and Nelson, M. (2000) The antihypertensive effects of the Jamaican cho-cho (*Sechium edule*), *W. Indian Med. J*., 49: 27–31.

Gray, A.M. and Flatt, P.R. (1999) Insulin-releasing and insulin-like activity of the traditional antidiabetic plant *Coriandrum sativum* (coriander), *Br. J. Nutr*., 81: 203–209.

Grover, J.K., Vats, V., Rathi, S.S. and Dawar, R. (2001) Traditional Indian antidiabetic plants attenuate progression of renal damage in streptozotocin-induced diabetic mice, *J. Ethnopharmacol*., 76: 233–238.

Grover, J.K., Yadav, V. and Vats, V. (2002) Medicinal plants of India with antidiabetic potential, *J. Ethnopharmacol*., 81: 81–100.

Gupta, M.P., Solis, N.G., Avella, M.E. and Sanchez, C. (1984) Hypoglycemic activity of *Neurolaena lobata* (L.) R. Br., *J. Ethnopharmacol*., 10: 323–327.

Henry, F.J. (2001a) Health sector reform in the Caribbean: the nutrition factor, *Cajanus. Caribbean Food Nutr. Inst. Q*., 34: 2–37.

Henry, F.J. (2001b) Obesity-related mortality, morbidity and behavior in the Caribbean, *Cajanus. Caribbean Food Nutr. Inst. Q*., 34: 62–72.

Hernandez, L., Munoz, R.A., Miro, G., Martinez, M., Silva–Parra, J. and Chavez, P.I. (1984) Use of medicinal plants by ambulatory patients in Puerto Rico, *Am. J. Hosp. Pharm*., 41: 2060–2064.

Honychurch, P.N. (1980) *Caribbean Wild Plants and Their Uses,* Barbados: Letchworth Press.

Kean, E.A. (1988) Commentary on a review of the mechanism of ackee-induced vomiting sickness, *W. Indian Med. J*., 37: 139–142.

Kusano, S., Abe, H. and Tamura, H. (2001) Isolation of antidiabetic components from white-skinned sweet potato (*Ipomoea batatas* L.), *Biosci., Biotechnol. Biochem.*, 65: 109–114.

Magnus, M. (1993) Caribbean fruits, vegetables and ground provisions, *Cajanus. Caribbean Food Nutr. Inst. Q.*, 26: 146–175.

Mahabir, D. and Gulliford, M.C. (1997) Use of medicinal plants for diabetes in Trinidad and Tobago, *Pan Am. J. Public Health*, 1: 174–179.

Meckes–Lozoya, M. and Mellado–Campos, V. (1985) Is the *Tecoma stans* infusion an antidiabetic remedy? *J. Ethnopharmacol.*, 14: 1–9.

Michie, C.A. (1992) The use of herbal remedies in Jamaica, *Ann. Trop. Paediatr.,* 12: 31–36.

Morrison, E.Y. and West, M. (1982) A preliminary study of the effects of some West Indian medicinal plants on blood-sugar levels in the dog, *W. Indian Med. J.*, 31: 194–197.

Morrison, E.Y. (2000) Diabetes and hypertension: twin trouble, *Cajanus. Caribbean Food Nutr. Inst. Q.*, 33: 61–63.

Morton, J.F. (1981) *Atlas of Medicinal Plants of Middle America: Bahamas to Yucatan*, Springfield, IL: Charles C. Thomas.

Muira, T., Hoh, C., Iwamoto, N., Kato, M., Kawai, M., Park, S.R. and Suzuki, I. (2001) Hypoglycemic activity of the fruit of the *Momordica charantia* in type 2 diabetic mice, *J. Nutr. Sci. Vitaminol. (Tokyo)*, 47: 340–344.

Raman, A. and Lau, C. (1996) Antidiabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae), *Phytomedicine*, 2: 349–362.

Robineau, L. and Soejarto, D.D. (1996) TRAMIL: a research project on the medicinal resources of the Caribbean, in M.J. Balick, E. Elizabetski and S.A. Laird (Eds) *Medicinal Resources of the Tropical Forest* (*Biodiversity and its Importance to Human Health*), New York: Columbia University Press.

Robineau, L. (Ed) (1997) *Farmacopea Caribena*, Martinique: Ediciones Emile Desormeau.

Roig, J.T. (1988) *Plantas Medicinales*, *Aromaticas o Venenosas de Cuba*, La Habana: Editorial Cientifico-Tecnica.

Sargeant, L.A., Willis, R.J. and Forrester, T.E. (2001) Chronic diseases-facing a public health challenge, *W. Indian Med. J.*, 50 Suppl. 4: 27–31.

Seaforth, C.E. (1987) Medicinal and poisonous plants in the West Indies, in A.J.M. Leeuwenberg (Ed) *Medicinal and Poisonous Plants of the Tropics*, Wageningen: Pudoc Press.

Seaforth, C.E., Adams, C.D. and Sylvester, Y. (1982) *A Guide to the Medicinal Plants of Trinidad and Tobago*, London: Commonwealth Secretariat.

Singh, S.V., Vats, P., Suri, S., Shyam, R., Kuniria, M.M., Ranganathan, S. and Sridharan, K. (2001) Effects of an antidiabetic extract of *Catharanthus roseus* on enzymic activities in streptozotocin-induced diabetic rats, *J. Ethnopharmacol.*, 76: 269–277.

Swarup, D. (1997) Hypoglycemic, antihyperglycemic and hypolipidemic activities of *Caesalpinia bonducella* seeds in rats, *J. Ethnopharmacol.*, 58: 39–44.

Tolan, I., Ragoobirsingh, D. and Morrison, E.Y. (2001) The effect of capsaicin on blood glucose, plasma insulin levels and insulin-binding in dog models, *Phytother. Res.*, 15: 391–394.

Ubillas, R.P., Mendez, C.D., Jolad, S.D., Luo, J., King, S.R., Carlson, T.J. and Fort, D.M. (2000) Antihyperglycemic acetylenic glucosides from *Bidens pilosa*, *Planta Med.*, 66: 82–83.

Vats, V., Grover, J.K. and Rathi, S.S. (2002) Evaluation of antihyperglycemic and hypoglycemic effect of *Trigonella foenum-graecum* Linn, *Ocimum sanctum* Linn and *Pterocarpus marsupium* Linn. in normal and alloxanized diabetic rats, *J. Ethnopharmacol.*, 79: 95–100.

Vikrant, V., Grover, J.K., Tandon, N., Rathi, S.S. and Gupta, N. (2001) Treatment with extracts of *Momordica charantia* and *Eugenia jambolana* prevents hyperglycemia and hyperinsulinemia in fructose fed rats, *J. Ethnopharmacol.*, 76: 139–143.

Wolever, T. and Ramdath, D. (1997) The use of Caribbean foods in the management of diabetes mellitus, *Cajanus. Caribbean Food Nutr. Inst. Q.*, 30: 101–106.

11 Management of Diabetes in African Traditional Medicine

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CONTENTS

INTRODUCTION

African traditional medicine is generally recognized as being organized into three levels of specialty (Chavunduka, 1994). These areas, which may overlap in some cases, are divination, herbalism, and spiritualism.

The spiritualist (or medium) is generally identified with a political role and public health duties; the diviner (disparagingly called "witch-doctor" by the missionaries from Europe) and herbalist are more involved with health delivery to the individual in traditional society. The diviner uses magical or supernatural powers to diagnose and treat disease with the aid of ancestral spirits who endow amulets, animal parts, or herbs with the power to heal or drive away evil. The herbalist, on the other hand, applies knowledge attained by empirical observation or passed on through

generations. He or she relies exclusively on herbs to treat illness diagnosed by observation, regardless of any purported supernatural cause. In general, herbalists are elderly members of society who derive their livelihood by means other than healing. Their pharmacopoeia remains relevant and of interest to ethnopharmacologists and phytochemists and is a potential source of new drugs.

The concept of disease in African society is different from allopathic Western medicine. It is probably closer to the aboriginal view. Illness is believed to be of natural or cultural or social origin (Ayenzu, 1983). Cultural or social illness is thought to be related to a supernatural cause — e.g., angered spirits, witchcraft, or alien spirits. Conditions that have been previously unknown and poorly understood in African society, including cardiomyopathies, hypertension, and diabetes, are attributed to "natural" causes. It is not known whether these diseases existed in precolonial Africa. If they did, they were not recognized or were misdiagnosed and would certainly have led to sudden death attributable to some unknown or mysterious agent. This is largely because the correct diagnosis of these conditions relies on clinical observations and/or biochemical measurements. Traditional healers generally have no problem diagnosing external and gross anatomical complaints, but the diagnosis of more complex conditions is understandably vague and unreliable (Marston and Hostettman, 1987).

Diabetes mellitus (DM) is not very difficult to diagnose because of the universal classical symptoms of polyuria (frequent copious urination), glucosuria (appearance of glucose in the urine), and polydipsia (frequent thirsting and water intake). Apparently, traditional healers use the attraction of ants to a person's urine (due to its sweetness) as confirmation of this diagnosis (Iwu, 1993).

In light of this, it is not surprising to find that treatments used by traditional healers for diabetes are many and varied. NAPRALERT lists DM as the 26th most important medical condition. At least 514 plant species have been used to treat DM worldwide (Farnsworth, 1988). Whether these treatments can be traced back to historic times or are of more recent origin is not known. However, many of them continue to be used in modern African society as an adjunct to prescribed pharmaceuticals. The use of the herbal potions is supported almost exclusively by anecdotal evidence and some animal studies, which generally show them to be hypoglycemic. Information on the phytochemical nature of the active compounds is scanty and few clinical studies support the use of these plants as stand-alone therapeutic agents. Because the diagnosis and evaluation are relatively straightforward, the probability of efficacy is relatively high.

DIETARY APPROACHES

As elsewhere in the developing world, the prevalence of DM in Africa appears to be growing due to the increasing adoption of a Western diet of processed foods rich in saturated fat and simple sugars. The African thus understands the disease, as Native Americans do, as resulting from "too much sugar in the body" (Garro, 1995). There is no name given to it which can be traced to precolonial times and it is variously known as *chirwere cheshuka* (Shona), *suikersiekte* (Afrikaans), *isifo sikashukela* (Swazi/Zulu), and *lefo latswikiri* (Sotho/Tswana). This may explain why DM is viewed by many African people as a "white man's disease": its emergence appears to be linked to the loss of a more traditional way of life coinciding with colonization. On the plains of eastern and southern Africa, cattle would have been plentiful but these were more a symbol of wealth and used for paying the bride price, compensation, draught power, and, occasionally, for religious sacrifices rather than as a food source (Bourdillon, 1987).

The diet of Africans before they became urbanized and westernized would have consisted of foods low in sugar and salt and high in fiber. This diet would have included bushmeats, which are generally lean and devoid of fat, fruit of the forest, roots, and tubers as well as whole grains. Studies on vegetables such as cabbage (*Brassica* spp.), green leafy vegetables, beans, and tubers, e.g., onions (*Allium* spp.), have shown the beneficial hypoglycemic influence in experimental animals and humans (Platel and Srinivasan, 1997; Roman–Ramos et al., 1995).

Alcohol, one of the aggravating factors of hyperglycemic incidents, was, at least at a high concentration, not readily available. Consumption of alcohol in precolonial African society was restricted to occasional ceremonies and festivals revolving around ancestral worship and rainmaking. It was generally discouraged by traditional doctors by use of taboos when they prescribed their medicines and came as a general recommendation aimed at improving personal discipline and thus compliance (Chavunduka, 1994).

Having outlined the foregoing, it should be said that once one is diagnosed with DM, there is apparently no known traditional intervention to modify the diet in contemporary society apart from a recommendation to reduce foods considered to have a lot of sugar and to increase vegetable intake. In truth, there is hardly any promotion of a wholesome diet consisting of traditional foods in diabetic patients.

ETHNOMEDICINAL APPROACHES

Many plants are used to manage DM in African traditional medicine, but little phytochemical information is available on the active constituents of many of these plants. Much of the scientific information available is drawn from *in vitro* bioassays on crude extracts of the various plants. The ethnomedicinal information remains largely unvalidated and appears to rely on much anecdotal evidence or case studies.

The discussion that follows encompasses plants that have been widely used in traditional medicine and screened for pharmacological activity. The information has been collated mainly from Iwu (1993), Watt and Breyer–Brandwijk (1962), Oliver–Bever (1986), and van Wyk et al. (1997). This review concentrates on species indigenous to sub-Saharan Africa, but also includes introduced species used in African traditional medical practice.

Acanthaceae Family

Hygrophila auriculata (Schumach.) Heine
Synonyms: *Asteracantha longifolia* (L.) Nees, *Barleria longifolia* L., *H. spinosa* T. Anders
African names: *Kinyarwanda*: ngangabukari, *Kirundi*: buganga; *Tigrinya*: balawarante
Description and distribution: Small-leaved herbaceous aquatic plant that grows well immersed and submersed. The leaves are broadly lanceolate with rounded tips and borne in opposite pairs on thin stems.
Pharmacognosy: The whole plant is used in West Africa. The root and seeds contain phytosterols. The leaves contain the alkaloid vasicine. Oral hypoglycemic activity has been shown in cats and rabbits (Oliver–Bever, 1986).
Hygrophila longifolia, a related species, may exert hypoglycemic action by mechanisms similar to those of the sulphonylureas (Fernando et al., 1998). The plant extract had no effect on the gluconeogenic capacity of the kidney or intestinal glucose absorption.

Anarcadiaceae Family

The species of family Anacardiaceae is mostly trees and shrubs; some are of economic importance because of their fruits, e.g., mango, cashew nuts, and marula.

Anacardium occidentale L.
Common names: cashew, cashew apple/nut
African names: *Shambala*: mganju, *Swahili*: mbiba
Description and distribution: the cashew nut was introduced from tropical America into Africa. It is an economically important crop in Mozambique and West Africa.

Pharmacognosy: the leaves are used in traditional medicine. Quercetin and kaempferol glycosides have been shown to normalize glycemia (Oliver–Bever, 1986).

Sclerocarya birrea (Rich.) Hochst.
Synonym: *S. caffra* Sond.
Common name: marula
African names: *Afrikaans*: maroela; *Shona*: mupfura, mutsomo; *Ndebele*: umganu; *Swahili*: roluwo; *Wolof*: beri; *Hausa*: donya
Description and distribution: it is a medium-sized tree occurring in medium to low altitude in open woodland and bush. The trees are highly valued by the cultures of the areas where they grow in tropical southern Africa, northern Nigeria, Ghana, Gambia, and Senegal.
Pharmacognosy: the many traditional rituals that involve this tree in southern Africa indicate its importance in the lives of the various ethnic groups resident in the subregion. A decoction of the bark is used for dysentery and diarrhea; this may be due to the tannin content. The bark decoction has also been used prophylactically and curatively in malaria. However, this has not been proven experimentally. A decoction of the leaves has high hypoglycemic activity when administered by mouth or intraperitoneally (Oliver–Bever, 1986). The effect is thought to be directly on the glycemia-regulating system and peripheral assimilation of glucose, especially by the muscular tissue.

Apocynaceae Family

Catharanthus roseus (L.) G. Don
Synonyms: *Lochnera rosea* Reichb, *Vinca rosea* L.
Common names: Madagascan periwinkle, pink periwinkle
African names: *Afrikaans:* maandrosies; *Zulu:* isisushlungu
Description and distribution: a popular garden plant or weed, the plant is a perennial herb with white or pink flowers. Originally from Madagascar, it has naturalized in the tropics and subtropics all over Africa and beyond.
Pharmacognosy: the plant has been used for treatment of diabetes in traditional medicine (Watt and Breyer–Brandwijk, 1962) and commercialized in France and England (Marles and Farnsworth, 1995; Bruneton, 1995). The discovery of the antineoplastic alkaloids vincristine and vinblastine was a serendipitous discovery during an investigation of the plant for antidiabetic activity (Oliver–Bever, 1986). The hypoglycemic effects are attributed to other alkaloids — namely, catharanthine, lochnerine, tetrahydroalstonine, leurosine, vindoline, and vindolinine (Marles and Farnsworth, 1995; Oliver–Bever, 1986). The onset of hypoglycemia is slow but long lasting. The roots are considered toxic due to the presence of the binary vinca alkaloids, which have found use as potent antitumor agents.

Asteraceae Family

Artemisia afra Jacq. Ex Willd.
Common names: wild wormwood, African wormwood
African names: *Afrikaans*: wilde als; *Kisambaa*: fivi; *Kinyakyusa*: lusanje; *Kisafwa*: luyanga; *Swati/Xhosa/Zulu*: umhlonyane; *Tswana*: lengana, iliongana; *Sukuma*: ushemeli; *Amaringa*: ariti
Description and distribution: the plant is a perennial herb less than 2 m high with alternately arranged feathery gray–green leaves and inconspicuous yellow flowers. It exudes a strong characteristic wormwood scent. It flowers between March and July and produces seeds from August to November. It is found in the highland areas (alt. 1500 to 3000 m) of eastern and southern Africa in volcanic, sandy, or loamy soils.

Pharmacognosy: it is widely used in folk medicines in southern Africa for coughs, colds, and flu as well as intestinal worms, gout, and malaria. When used for bronchial complaints, it is prepared as a syrupy decoction. It is a source of monoterpenes, e.g., 1,8-cineole, camphor, and thujone as well as glaucolide, guaianolide, eudesmadiene, and germacratien-type terpenoids (Jakupovic et al., 1988). Its use in DM remains unsubstantiated, but Watt and Breyer–Brandwijk (1962) cite its use in Zimbabwe to treat glucosuria.

Cnicus benedictus L
Synonym: *Centaurea benedictus*
Common names: bitter thistle, holy thistle
African name: *Afrikaans*: karmedik
Description and distribution: this is an annual with indented and spiny leaves and yellow flowers in a terminal flower head. It is widely distributed in Asia and the Mediterranean region. It was introduced to southern Africa and is found as a weed in the Cape and elsewhere in the highlands of the subcontinent.
Pharmacognosy: brandy tinctures have been used for internal cancers as well as diabetes and arthritis (Bruneton, 1995; Watt and Breyer–Brandwijk, 1962). It has emetic, diuretic, and sudorific effects. Guaianolide-type sesquiterpenoid lactone, cnicin, and bitter lignan lactones have been isolated (Vanhaelen–Fastre, 1972; Picman, 1986). It is thought that these lignans stimulate the secretion of gastric juices, resulting in increased appetite because of their bitterness. It may be postulated that this stimulus may also lead to the release of insulin. Tannins have also been isolated.
The related species, *Centaurea perrottetti* (= *C. calcitrapa*) contains a bitter principle, calcitrapin, that may be related to cnicin (Watt and Breyer–Brandwijk, 1962). The peptide fraction of this species was found to be hypoglycemic in rabbits (Oliver–Bever, 1986).

Vernonia oligocephala (DC.) Sch. Bip. Ex Walp.
Synonym: *V. kraussi* Sch. Bip. Ex Walp.
Common name: silver-haired vernonia
African names: *Afrikaans*: groenamarabossie, bitterbossie; *Shona*: chiwanika; *Kinyarwanda*: umuvumo
Description and distribution: an herbaceous perennial with erect purple flowering branches and silver-backed leaves. It is widespread in the grasslands of southern Africa.
Pharmacognosy: it has been used for the treatment of arthritis, dysentery, and diabetes. Its use is said to reduce glucosuria. Several sesquiterpenoid lactones including germacranolides and glaucolides have been isolated (Bohlman et al., 1983).

Vigna unguiculata (L.) Walp. Subsp *unguiculata*
Synonyms: *Dolichos sinensis* L., *Dolichos unguiculatus* L., *V. triloba* (Thunb.) Walp.
Common names: cowpea, asparagus bean, black-eye bean
African names: *Afrikaans*: boontjie; *Ndebele*: dinawa; *Shona*: muriwo wenyemba; *Tonga*: mbawen nyangana; *Zulu*: isihlumaya
Description and distribution: an annual or perennial, erect, trailing or climbing herb. The leaves are trifoliate and the fruit is in an erect pod that is smooth or slightly warty. It is distributed throughout southern Africa.
Pharmacognosy: the leaves and fruit are an important indigenous food. The old leaves and ripe fruit have a thermostable hypoglycemic principle that is not toxic at high doses (Oliver–Bever, 1986). Unguilin, a cyclophilin-like protein, has been isolated.

Bignoniaceae Family

Tecoma stans (L.) H.B.K.
Synonym: *Tecoma mollis*
Common names: yellow bells, yellow trumpet flower, yellow elder
African names: *Lunda*: kapapati; *Nyanja:* ulembe
Description and distribution: a tall decorative shrub that can grow into a small tree of up to 10 m with small yellow flowers. It is a native of tropical America that has become a serious invasive alien in the hot and sunny climes of tropical and southern Africa.
Pharmacognosy: the leaves contain the alkaloids tecomine and tecostanine, which are active when given orally to alloxan-diabetic rabbits. They are thought to act by way of the β-cells of the pancreas (Oliver–Bever, 1986). Intraperitoneal administration of the total extract of *T. stans* produced hepatic glycogenolysis (Meckes–Lozoya and Ibanez–Camacho, 1985). An ethanolic extract from fruits of *Tecoma stans* has led to the isolation of two novel monoterpenic alkaloids (Lins and Felicio, 1993). Iridoid glucosides have also been isolated (Bianco et al., 1981, 1982) as well as dihydroflavonols (Srivastava and Reddy, 1995).

Combretaceae Family

Terminalia sericea Burch. ex DC.
Common names: silver cluster-leaf, yellow-wood, assegai wood, silver terminalia
African names: *Afrikaans*: vaalboom; *Chagga*: mbuko; *Kilongo*: msimira; *Shona/Venda*: mususu; *Tonga*: mugosi; *Tswana*: mogonono; *Zulu*: amangwe
Description and distribution: this is a small- to medium-sized tree with a gray to pale brown, coarsely fissured bark. The leaves are silver-haired with cream-colored flowers and the fruit is winged and pink to rose–red when matured. It is widely distributed in Zimbabwe, Namibia, and northern South Africa as well as in Mozambique.
Pharmacognosy: root decoctions are used for stomach disorders and diarrhea. The bark is used for diabetes and is taken in mealie meal porridge. Several triterpenoids — e.g., sericic acid — have been isolated from the roots. Nerifolin, a cardioactive glucoside, has also been isolated along with many tannins (Bruneton, 1995).

Cruciferae Family

Brassica oleracea L
Common names: common cabbage, heading cabbage, Savoy cabbage, rape (var. *capitata*), kale (var. *acephala*), broccoli, cauliflower (var. *botrytis*)
African names: *Afrikaans*: kool, blomkool
Description and distribution: the cabbage is usually a tight cluster of leaves forming in a compact "head" with a few loose outer leaves around the base. In the summer, due to longer days, it flowers by splitting open and giving birth to a stalk that uncurls as it forces the split head farther open. The stalk grows 5 to 10 cm tall, then branches and develops numerous small, four-petaled, cross-shaped yellow flowers that eventually develop into elongated seedpods. Hundreds of cultivars of cabbage are cultivated for food everywhere that plants can be grown. The earliest records of cabbage being cultivated for food come from the Greeks around 600 B.C. Wild cabbage (*Brassica oleracea* ssp. *oleracea*) grows along the coasts in Europe and North Africa. Cabbage leaves are eaten raw in salads and coleslaw or steamed, boiled, stir-fried, and pickled. It may be fermented to make German sauerkraut and Korean kimshi.

Pharmacognosy: *Brassica oleracea* showed a significant decrease in the hyperglycemic peak of healthy rabbits when administered subcutaneously once a week (Roman–Ramos et al., 1995). It contains organic sulphur compounds (thioglycosides), which may inactivate compounds that compete with insulin in the same manner as allyl propyl disulphide (APDS) in *Allium* spp. (Oliver–Bever, 1986). This leads to an insulin-sparing effect.

Coumarins and various phenolics also contribute to the beneficial effects of eating cabbage, which is also said to be beneficial in DM due to a mild diuretic effect. However, the brassicas contain substances called goitrins that can interfere with the body's uptake of iodine and lead to goiter formation in persons who have persistent iodine deficiency (Sauer, 1993).

Cucurbitaceae Family

The cucurbits are mostly prostrate or climbing herbaceous annuals comprising about 90 genera with 700 species. They have five-sided stems and coiled tendrils and alternating leaves. The fruit is called a pepo.

Citrullus lanatus (Thunb.) Matsumura & Nakai

Synonyms: *Citrullus vulgaris* Schrad. Ex Eckl. & Zeyh., *Colocynthis citrullus* (L.) Kuntze, *Mormodica lanata* Thunb.

Common names: bitter melon, desert melon, wild watermelon

African names: *Afrikaans*: karkoer; *Shona*: manwiwa; *Ndebele*: ibotola; *Tswana*: Kgengwe; *Zulu*: ibece; *Hausa*: guna; *Yoruba*: asunwon

Description and distribution: a prostrate spreading annual with herbaceous stout stems and tendrils bifid in axils of the leaves. The fruit is globose or ellipsoid and pale green to grayish-green and mottled. It is indigenous to Southwest Asia and grows all over Africa, cultivated or semiwild.

Pharmacognosy: infusions of *Citrullus colocynthis* fruits have been traditionally used as antidiabetic medication in North Africa (Nmila et al., 2000; Ziyyat et al., 1997). Infusions have *in vitro* insulinotropic action. The bitter principles, cucurbitacins (some of which are toxic to man and beast as well as piscicidal), are typical of the genus (Watt and Breyer–Brandwijk, 1962). *Colocynthis vulgaris* Schrad. have powerful purgative constituents. A novel hydroxyl radical scavenger, citrulline, was isolated in the leaves of the wild melon exposed to drought conditions (Akashi et al., 2001). It was thought to contribute to oxidative stress tolerance.

Momordica charantia L.

Common names: balsam pear, African cucumber, bitter gourd, bitter melon

African names: *Ganda*: luyula; *Zulu*: intshungu; *Masai*: ol amboshi

Description and distribution: species of *Momordica* are distributed throughout the Tropics. They are fast-growing, trailing or climbing vines with thin stems and tendrils

Pharmacognosy: *Momordica charantia* is used in West Africa as a bitter stomachic for the treatment of jaundice and liver disease as well as an emetic and drastic purgative. The fruit or seed may be used as an abortifacient and for treating urethral discharge. It has been used as an antidiabetic in Puerto Rico (Watt and Breyer–Brandwijk, 1962). A polypeptide, p-insulin, has been shown to be the active compound and induces hypoglycemia in humans and animals on subcutaneous injection. Raman and Lau (1996) have done an extensive review of *M. charantia*.

Charantin, a mixture of the phytosterolins and the pyrimidine nucleoside vicine has also been found to be hypoglycemic (Oliver–Bever, 1986). Charantin has demonstrated more

potency than tolbutamide in equivalent doses and possesses pancreatic and extrapancreatic action (Oliver–Bever, 1986).

Aqueous extracts of the fruit of *Momordica charantia* L. reduce the blood glucose of mice with NIDDM 3 weeks after oral administration (Miura et al., 2001). It is thought to act, at least in part, by increasing the muscle content of facilitative glucose transporter isoform 4 (GLUT4) protein. The consequence is a decrease in insulin resistance. An aqueous extract of *M. cymbalaria* has shown similar effects (Rao et al., 2001).

Coccinia grandis L. Voigt

Common names: ivy gourd, African vine

Description and distribution: a perennial climber herb native to Africa, India, and Asia, it is considered invasive in Hawaii and the South Pacific. It bears flowers and fruit throughout the year. The leaves and cucumber-like fruit are eaten raw, boiled, or fried.

Pharmacognosy: the hypoglycemic fraction is found in alcoholic and aqueous extracts. It contains cucurbitacins and may effect action in the same way as related species.

Ebenaceae Family

Euclea crispa (Thunb.) Sonder ex Gürke

Common names: blue guarri, blue-leaved euclea

African names: *Afrikaans*: bloughwarrie; *Ndebele*: umtshekesane; *Shona*: madziyire; *Ronga*: magitamus; *Xhosa*: umkaza; *Zulu*: usahlulamanye

Description and distribution: it is a shrub or small, evergreen tree with a dense, leafy crown that is widely distributed in southern, central, and eastern Africa. The leaves are often an attractive blue–green, with a hard, papery texture and somewhat wavy margin.

Pharmacognosy: the bark and fruit are widely used in traditional medicine as a purgative, to prevent rheumatism, and for diabetes (Gelfand et al., 1985). Little is known about the chemistry or therapeutic potential of this species in the management of DM.

Euphorbiaceae Family

Securinega virosa (Roxb. Ex Willd.)

Synonyms: *Flueggea virosa* (Roxb. Ex Willd.), *Flueggea microcarpa* Blume

Common names: white-berry bush, snowberry tree

African names: *Afrikaans*: witbessiebos; *Kirundi*: umubwiga; *Wolof* : keng; *Bambara*: tene

Description and distribution: it is usually a many stemmed, small, bushy shrub with reddish-brown bark and is found growing at forest margins, rocky outcrops, and termite mounds in south-central Africa in Namibia, Botswana, Zimbabwe, and Mozambique. It bears small, white, fleshy, edible fruits.

Pharmacognosy: it is widely used in southern Africa for a great many conditions ranging from malaria, abdominal pains, and avoidance of abortion to snake bite antidote, backache, and bronchitis (Gelfand et al., 1985). The alcoholic and aqueous extracts of the seeds showed hypoglycemic activity in cats and rabbits (Oliver–Bever, 1986). Several alkaloids have been isolated, including fluggeine, securinine, norsecurinine, and virosine. Virosecurinine and viroallosecurinine were isolated as two cytotoxic alkaloids from the leaves of *Securinega virosa* (Tatematsu et al., 1991).

Bridelia ferruginea Benth

African names: *Fulani*: kisni; *Bambara*: nakourougo; *Eton*: ibag; *Yoruba*: ira

Description and distribution: it is a tree distributed in most of eastern and southern Africa as well as in West Africa.

Pharmacognosy: oral or intraperitoneal administration has shown a significant reduction in the fasting blood sugar in albino rats (Oliver–Bever, 1986). A 25-mg/kg tablet of B. ferruginea lowered the blood glucose level of normal healthy rabbits by about 40% (Onunkwo, 1996). Human patients have derived some benefit from using a leaf extract of this plant species. Flavonoids and biflavonoids and their glycosides as well as lignans have been isolated from the methanolic extract of this plant (Rashid et al., 2000).

Fabaceae Family

Phaseolus vulgaris L.

Common names: bush bean, Cape pea, French bean, kidney bean

African names: *Afrikaans*: boontjie; *Pedi*: monaoa, nawa; *Shi*: cishimbo

Description and distribution: an annual that may be climbing or erect. The flowers are small and may be white, pink, or lilac and the fruit is a long, narrow, smooth pod that is seeded. Cultivated throughout the world, it originated from tropical America.

Pharmacognosy: bean husks have been shown to reduce hyperglycemia in mild diabetics (Oliver–Bever, 1986). Olean-12-ene-type triterpene oligoglycosides, named sandosaponins A and B, were isolated from the seed of *Phaseolus vulgaris* L., together with three known saponins, soyasaponins I and V, and dehydrosoyasaponin I (Yoshikawa et al., 1997). Hydrocyanic acid poisoning has been reported from insufficiently cooked bean (Watt and Breyer–Brandwijk, 1962).

Trigonella foenum graecum L.

Common names: fenugreek, Greek hay

African names: *Tigrinya*: abacham; *Galinya*: sunko

Description and distribution: a fast growing annual of Mediterranean origin and found mainly in North Africa in field verges, uncultivated ground, dry grasslands and hillsides.

Pharmacognosy: Al-Habori and Raman (1998) have reviewed the antidiabetic and hypocholesterolemic effects. The seeds contain N-methylnicotinic acid (trigonelline), coumarins, and nicotinic acid. It is used in Israel as an insulin substitute. Trigonelline counteracts cortisone-induced hyperglycemia; nicotinic acid and coumarin have been shown to have hypoglycemic activity in alloxan-diabetic rats and in diabetic patients (Oliver–Bever, 1986). The aqueous extract of *Trigonella foenum-graecum* leaves given orally and intraperitoneally possesses a hypoglycemic effect in normoglycemic and alloxan-induced hyperglycemic rats (Abdel–Barry et al., 1997).

The presence of hypoglycemic activity in aqueous and methanolic extracts indicates that the active compounds are polar in nature (Zia et al., 2001). Various kaempferol and quercetin glycosides were isolated from the stems of *T. foenum-graecum* (Han, 2001). Furostanol-type steroid saponins called trigoneosides were isolated from the seeds of the Egyptian variety (Murakami, 2000).

Lupinus tassilicus Marie

Common name: lupine

African name: *Afrikaans:* lupien

Description and distribution: lupines are attractive plants bearing pea-like flowers in whorls upon long graceful spikes. About 200 annual and perennial species are native to the Americas and Mediterranean Europe through to the highlands of eastern Africa. The four species found growing in southern Africa were introduced and naturalized. *Lupinus*

tassilicus is an herbaceous species endemic to the Sahara Desert in the Algerian region of Tassili. It is considered endangered.

Pharmacognosy: the seeds contain quinolizidine alkaloids that have moderate hypoglycemic effects on alloxan-diabetic rats but not normal rats. The effect is short lasting and has been attributed to sparteine and lupanine (Oliver–Bever, 1986).

Debittered seeds of *Lupinus albus* L. are generally considered to have antidiabetic properties and are even prescribed by some physicians to counter hyperglycemia (Pereira et al., 2001). It is thought that the seeds contain water-soluble substances capable of potentiating glucose-induced insulin release. The lupine extract appears to contain at least two active principles; one of them causes Ca^{2+} release from intracellular stores and the other a reduction in β-cell K^+ permeability, presumably via inhibition of ATP-sensitive K^+ channels (Pereira et al., 2001). The presence of alkaloids such as lupinine, anagyrine, sparteine, and hydroxylupanine makes the lupines potentially toxic when ingested in large amounts, possibly due to the induction of hypoglycemia.

Sutherlandia spp. R. Br. Ex Ait. f.

Common names: cancer bush, cancer wort

African names: *Afrikaans*: kankerbossie; *Sotho*: musapelo; *Zulu*: unwele

Description and distribution: it is a small attractive shrub that grows to about 1 m in height. The large red flowers precede bladder-like pods. The plant grows almost exclusively in the Cape Province of South Africa; the six species of this genus are frequently lumped together because of the difficulty in distinguishing them.

Pharmacognosy: *Sutherlandia* spp. has been touted as the tonic for all ills and used for coughs and colds, chicken-pox, varicose veins, piles, diabetes, backache, liver problems, and general maintenance of good health, among many other uses in South Africa. In North Africa, the leaf is used as a bitter tonic and for indigestion and dysentery. Its cancer-protecting and combating properties have given it the English and Afrikaans names. Clinical trials for the reputed anticancer properties have proved negative in the past (Watt and Breyer–Brandwijk, 1962). In more recent times, it has proved popular for palliation in HIV patients, but clinical trials are still in progress. L-canavanine, pinitol, GABA, and asparagine are thought to be responsible for some of the medicinal efficacy (van Wyk et al., 1997). Pinitol has documented antidiabetic activity and is likely to be at least one of the phytochemical compounds useful for antidiabetic therapy with *Sutherlandia* species.

Liliaceae Family *sensu lato*

Allium cepa L.

Common names: common onion, shallot, potato onion

African names: *Afrikaans*: ui; *Kamba/Swahili*: kitungu; *Shona/Zulu*: hanyanisi; *Swahili*: matungulu; *Kinyarwanda*: igitunguri; *Mende*: yawe

Description and distribution: it is a perennial herb that is probably the most important of the vegetable bulb crops. First introduced to the West Indies by the Spanish, its cultivation and use spread from there to the rest of the world. It thrives under a wide variety of soils and climatic conditions. It is universally used for its culinary purposes. The leaves are tubular and smooth and the bulbs range from oblate to oval in shape. It is a cultivated crop in all parts of Africa and has been used by the ancient Egyptians.

Pharmacognosy: the onion is toxic in cattle and horses, producing gastroenteritis, vomiting, anemia, and icterus (Watt and Breyer–Brandjiwk, 1962). Oral administration in rabbits and pancreatectomized dogs lowered the blood sugar level over 1 to 5 hours. The effect is invariably lost upon storage and may be linked to the presence of an alkaloid (yet to be identified) and disulphides (Oliver–Bever, 1986). When administered subcutaneously

in healthy rabbits weekly, the hyperglycemic peak decreases (Roman–Ramos et al., 1995). It would appear that dietary onion has a beneficial effect on diabetic nephropathy, which may be exerted through its ability to reduce blood cholesterol levels and lipid peroxidation (Babu and Srinivasan, 1999).

The effects are attributed to cyclo-alliin, quercetin, and some sulphur-containing hydrocarbons (allyl propyl disulphide [APDS] and diallyl disulphide oxide [allicin]), which have been isolated (Oliver–Bever, 1986).

The related species, *Allium sativum* (garlic) also contains organic sulphur compounds. Though indigenous to Asia, it is now cultivated in many parts of Africa and is an important culinary cultivar. It is used in the preparation of diabetic tonics. The oil extracted from garlic prevents hypercholesterolemia and hyperlipidemia and produced marked hypoglycemic activity (Iwu, 1993). However, its use may lead to allergenicity and prolonged bleeding in patients on anticoagulant medication.

Bulbine natalensis Bak

Synonyms: *B. narcissifolia* Salm–Dyck, *B. latifolia* (L.f.) Roem. & Schult.

African names: *Afrikaans*: rooiwortel, *Zulu*: ibhucu

Description and distribution: aloe-like herb with fleshy, smooth leaves set in a rosette and thin flowering stems that bears yellow flowers. It has many closely related species growing in the Eastern Cape province of South Africa.

Pharmacognosy: the leaf sap is used to treat wounds, burns, rashes, and ringworm (Watt & Breyer–Brandwijk, 1962). *Bulbine capitata* is used by the Basotho of southern Africa as a mild purgative and to cure gonorrhea infections (Qhotsokoane–Lusunzi and Karuso, 2001). The powdered root has been found to be rich in anthraquinones, which would explain the reported laxative effects. The root is used in the management of diabetes. *B. asphodeloides* R. and S. is said to be diuretic and is used in uremia and in diabetes (Watt and Breyer–Brandwijk, 1962).

Aloe species

Common names: Cape aloe, aloe *(A. ferox* Mill. FP) curacao aloe (*A. barbadensis = Aloe vera*)

African names: *Afrikaans*: aalwyn; *Arabic*: sabr; *Ndebele*: incena; *Swahili*: shubiri; *Shona*: gavakava; *Xhosa*/*Zulu*/*Sotho*: umhlaba; *Kinyarwanda*: igikakarubamba kizungu; *Kirundi*: ingarigari

Description and distribution: the genus includes herbs, shrubs, and trees that bear white, yellow, or red flowers on spikes and large fleshy thorny leaves (Iwu, 1993; Van Wyk et al., 1997). It grows in subtropical Africa. The main species in Africa is *Aloe ferox* (Cape aloe), which is a robust plant with broad fleshy leaves and dark brown spines (van Wyk et al., 1997) and *Aloe marlothii* (flat flowered aloe).

Pharmacognosy: it is a source of the hydroxymethylanthraquinones used as stimulant laxatives. It has been reportedly used for management of arthritis, eczema, and conjunctivitis (Bruce, 1975). Bitter extracts of the Cape aloe have been exported from South Africa for centuries to Germany, where it is widely used in the manufacture of many phytomedicines.

The reports on the hypoglycemic activity of the Aloe species have been largely equivocal (Okyar et al., 2001). This may be due to the use of different plant parts and diabetes models. *A. vera* leaf pulp extract was shown to lower blood sugar in rats with type 1 (insulin-dependent) and type 2 (non-insulin-dependent) DM. Controlled clinical trials have shown that *A. vera* would be a useful adjunct for lowering blood glucose in diabetics as well as blood lipid levels in hyperlipidemia (Vogler and Ernst, 1999; Yongchaiyudha et al., 1996).

In contrast, the leaf gel extract was actually hyperglycemic in NIDDM rats (Koo, 1994) and this distinction seems to be one cause of the controversy. Components from the leaf

of *A. arborescens* were shown to cause direct hypoglyceration and also to activate β-cells (Beppu et al., 1993). The mode of action has also been partly attributed to decreased hepatic gluconeogenesis as seen in reduced gluconeogenesis in isolated hepatocytes as well as reduced activity of pyruvate carboxylase (PC) and phosphoenol-pyruvate carboxykinase (PEPCK), two key gluconeogenic enzymes (Al-Awadi et al., 1991). Acetylated mannans, which have immunomodulatory activity and glycoproteins, have been isolated from *A. vera* and *A. arborescens* (Reynolds and Dweck, 1999). Topical application of *A. vera* gel on wounds in diabetic rats enhances healing (Chithra et al., 1998).

Andrographis paniculata (Burm. F.) Wall. Ex Nees

Description and distribution: an erect herb, chiefly found in tropical Asia from where it spread to Africa, the West Indies, and the Americas. It is found on plains, hill slopes, wastelands, farms, dry or wet lands, seashores, and even on roadsides.

Pharmacognosy: a dose-dependent reduction of the serum blood glucose level in streptozotocin-diabetic rats has been demonstrated with an ethanolic extract of *A. paniculata* (Zhang and Tan, 2000). The activity was partly attributed to increased glucose metabolism and the reduced activity of hepatic glucose-6-phosphatase (G-6-Phase) and compared favorably with metformin. The extract also effected hypotriglyceridemia, which is beneficial in the management of diabetes.

Leaf extracts affect spermatogenesis by preventing cytokinesis of the dividing spermatogenic cells lines (Akbarsha and Murugaian, 2000). This antifertility property has been attributed to andrographolide, one of the major constituents isolated from the leaf. This compound has also been shown to inhibit HIV-induced cell cycle dysregulation resulting in a rise in CD4 (+) lymphocyte levels in infected individuals (Calabrese et al., 2000). Terpenoids and flavonoids have been isolated from this species (Gupta et al., 1996; Jantan and Waterman, 1994).

Menispermaceae Family

Cissampelos capensis L.

Synonym: *Antizoma capensis* Diels.

African names: *Afrikaans*: dawidjiewortel; *Masai*: ol egesikon; *Pedi*: lepeta; *Swahili*: mlagalaga

Description and distribution: this is a perennial climbing shrub with twining stems and rounded, bright green leaves that can be found growing in the Western Cape province of South Africa.

Pharmacognosy: it is widely used in traditional African medicine as a blood purifier and for boils, syphilis, diarrhea, and cholera. Fresh or dry rhizomes are chewed or taken as infusions or tinctures. Bioactive alkaloids of the bisbenzyltetrahydroisoquinoline type have been isolated from related species. These show sedating, antispasmodic, and antitumor activity. Nothing is known about *C. capensis* in particular.

Moraceae Family

Morus spp. L.

Common name: *M. mesozygia* (African mulberry)

African names: *Afrikaans*: moerbei; *Zinza*: mukimbu; *Zulu*: umduli; *Kinyarwanda*: iboberi

Description and distribution: mulberry trees are deciduous, long-lived, and capable of rejuvenating themselves. They thrive in moist areas with long, hot summers. They are not commercially grown for their fruit, which is too soft and insipid for transporting to the market. However domestic consumption of the fruit fresh or made into jams is widespread.

Commercial farming of mulberry trees is for their leaves, which are important in rearing silkworms in Eastern Asia and Southern Europe. Of the three main species, *M. nigra* (black mulberry) grows from 7 to 12 m high, forms a compact crown, and produces dark red fruit that appear to be black. *M. rubra* (red mulberry) is the largest of all the mulberries and grows to 20 m; *M. alba* (white mulberry) grows up to 15 m high and produces extremely sweet, pinkish, white, or purplish berries. The African mulberry (*M. mesozygia*) is widely distributed in tropical Africa.

M. mesozygia Stapf is a monoecious or dioecious tree growing up to 30 m in height with a tall, erect stem and dense crown. The fruits are small and globose and grouped into short fleshy mulberries and normally eaten in their natural state. It occurs throughout tropical Africa.

Pharmacognosy: *M. alba* and *M. nigra* possess hypoglycemic activity and increase glycosuria (Oliver–Bever, 1986). "Mulberry therapy" exhibits potential hypoglycemic and hypolipidemic effects in diabetic patients (Andallu et al., 2001).

Cyanidin and delphinidin glucosides, rutin, quercetin triglycoside, and phytosterols have been isolated from many mulberry species (Oliver–Bever, 1986). The flavonoids, dihydromorin and dihydrokaempferol, have been isolated from *M. lactea* Mildr (Watt and Breyer–Brandwijk, 1962). Polyhydroxyalkaloids occur in the root, bark, and fruits of *M. alba* (Asano et al., 2001). These water-soluble compounds, which generally occur in small quantities, are of interest because of their antidiabetic, antitumor, and antiviral actions (Nash et al., 1997). It is, however, doubtful whether the hypoglycemic activity seen in extracts of the mulberry is attributable solely to the presence of these compounds, which occur in very small amounts.

Musaceae Family

Musa paradisiaca L.

Synonym: *Musa sapientum* L.

Common names: cooking banana, plantain

African names: *Afrikaans:* piesangboom; *Chewa*: ntochi; *Ndebele*: isikova; *Shona*: hobo, hova; *Kinyarwanda/Kirundi*: igitoki/igitoke.

Description and distribution: a tree 6 to 12 m high with large shiny leaves that grows in most of tropical Africa. It originated from Southeast Asia and is now grown in most of Africa for food.

Pharmacognosy: the extract of the flowers exhibits hypoglycemic activity in fasting rabbits (Oliver–Bever, 1986). It also has slight antispasmodic and hypotensive action. In Zimbabwe, parts of the banana have been used for "heart pains" and to prevent lightning (Gelfand et al., 1985). Musarin, an alkaloid with antifungal activity, has been isolated from the fruit pulp and skin (Watt and Breyer–Brandwijk, 1962).

Myrtaceae Family

Psidium guajava L.

Common name: guava

African name: *Afrikaans*: koejawel

Description and distribution: it is a shrub or small tree that has become naturalized in many parts of the world, including Africa; it was introduced from tropical America. It flowers in the early summer and subsequently produces round or pear-shaped, many seeded fruit of commercial value.

Pharmacognosy: the leaves are commonly used for respiratory tract complaints (e.g., coughs and fever) and have also been reported for use in the treatment of malaria and diabetes. The hypoglycemic properties have been documented and may result from quercetin. However, an extract of the guava leaf showed an insignificant decrease in the hyperglycemic peak of healthy rabbits when administered subcutaneously once a week (Roman–Ramos et al., 1995). Numerous tannins have been isolated, which would explain its efficacy in the management of diarrhea. Flavonoids and some ursolic, oleanolic, crategolic, and guaijavolic triterpenoids — including psidiolic acid, a cadinylic sesquiterpene — have also been isolated (Watt and Breyer–Brandwijk, 1962).

Syzygium cumini L.
Synonym: *Eugenia cumini* (L.) Druce
Common names: Java plum, jambolan plum, water berry
African names: *Afrikaans*: waterbessie; *Bemba*: musafwa namunsi; *Lozi*: katoya; *Ndebele*: umdoni, *Shona*: mukute, muwototo; *Xhosa*: umdoni, umswi; *Kinyarwanda*: umugote.
Description and distribution: an evergreen, water-loving tree of 8 to 15 m with a dense, spreading rounded crown. The ovoid berries are red to purplish-black and occur in clusters. It is found in swamps and alongside stream banks from northeast Africa going southward to Botswana, Mozambique, and northern South Africa.
Pharmacognosy: the hypoglycemic agent has been identified as the glycoside, antimellin. The alkaloid jambosine, isorhamnetin 3-O-rutinoside, and tannins have been isolated (Vaishnava and Gupta, 1990). An alcoholic fraction is active in cats and rabbits, and a single dose of the aqueous fraction reduces blood glucose considerably (Oliver–Bever, 1986).
A tea of the leaves of *S. cumini* is popular with diabetic patients in Brazil (Teixeira et al., 2000). An investigation on the hypoglycemic activity of this tea failed to substantiate the effect. This may imply that the active fraction does not partition into water.

Oxalidaceae Family

Biophytum sensitivum (L.) DC and *B. petersianum* Klotzsch
African name: *Shona*: katsamwetsamwe (*B. petersianum*)
Description and distribution: a perennial that bears yellow–pink flowers in the summer months. It grows in tropical Africa and Asia.
Pharmacognosy: *Biophytum sensitivum* is used in traditional Nepalese folk medicine for the treatment of diabetic patients (Puri, 2001). *B. petersianum* Klotzsch is used in Zimbabwe to treat wasting (Gelfand et al., 1985), which may be a symptom of non-insulin-dependent DM. Serum insulin levels were shown to rise significantly in nondiabetic animals suggesting that the extract of *B. sensitivum* exerts an insulinotropic effect by possible stimulation of the synthesis/release of insulin from the β-cells of the islets of Langerhans.

Tiliaceae Family

Corchorus olitorius L.
Common names: jute, Jew's mallow, bush okra
African names: *Swahili*: kala; *Shona*: gwisha; nyenje; *Ndebele*: idelele
Description and distribution: a tall, erect, many branched annual weed found in the tropics and subtropics. Though it is considered a weed of pantropic distribution, attempts have been made to cultivate it in West Africa. The flowers are yellow and the fruits are short-stalked, cylindrical capsules that split into five parts.

Pharmacognosy: it is a tonic used in East Africa and is also eaten as a vegetable. The plant is an effective galactogogue and purgative (Watt and Breyer–Brandwijk, 1962). It is also used for rheumatism by application into incisions (Gelfand et al., 1984). An aqueous extract decreases hyperglycemia in mice, guinea pigs, and rabbits only in the presence of a functional pancreas. Furthermore, it appears to promote the breakdown of glucose *in vitro* (Oliver–Bever, 1986). Corchorin, a bitter principle identical to the cardenolide strophanthidin, has been isolated; this implies that the plant is potentially cardiotoxic. Strophanthidin glycosides (erysimoside and olitoriside) and digitoxigenin glycosides (corroloside and glucoevatromonoside) have been reported (Matsufuji et al., 2001); quercetin glycosides were identified from the leaves (Azuma et al., 1999).

Miscellaneous Families

Other plants have been cited in texts as being used in Africa for the treatment and management of diabetes mellitus; however, no literature could be found to support their use.

Alisma plantago-aquatica L. (Alismataceae)

Protostane-type triterpenoids as well as an acetylated sitisterol glucoside have been isolated from *A. plantago-aquatica* (the American waterplantain) (Fukuyama et al., 1988; Geng et al., 1988a, b).

Alstonia macrophylla Wall. ex G. Don. (Apocynaceae)

The methanolic crude and methanol-aqueous extract of *Alstonia macrophylla* leaves showed antimicrobial activity against various bacteria and fungi including *Staphylococcus* sp., *E. coli, Trichophyton rubrum, T. mentagrophytes,* and *Microsporum gypseum* (Chattopadhyay et al., 2001). Phytochemical screening indicated the presence of tannins, flavonoids, saponins, sterols, triterpene, and reducing sugars. Macroline-type oxindole alkaloids, including several with novel structural features, have been reported from the Malayan *A. macrophylla* (Kam and Choo, 2000).

Harpagophytum procumbens DC (Pedaliaceae)

This is a weedy perennial with creeping stems spreading from a tuberous fleshy rootstock and hooked fruit, which gives it the name devil's claw. The plant is popularly used for arthritis, as a general health bitter tonic, and as an analgesic during pregnancy and labor (van Wyk et al., 1997). When ingested, it produces purgation (Watt and Breyer–Brandwijk, 1962). Various phytosterols, triterpenoids, iridoids, and flavonoids have been isolated from this plant. No evidence supports the use of this plant in DM.

Kedrostis nana Cogn. (Cucurbitaceae)

This is a severe irritant leading to poisoning in sheep and rabbit (Watt and Breyer–Brandwijk, 1962). The root has been used as an emetic; an infusion in wine or brandy is purgative.

Leonotis ocymifolia (Burm. f.) (Labiatae)

L. leonurus Ait. F. (lion's ear) is a strong purgative and emmenagogue (Watt and Breyer–Brandwijk, 1962). It produces some narcotic effect, which is why it is called wild dagga in South Africa. *L. nepetaefolia* has been used as a tapeworm remedy and for dysmenorrhea associated with frequent abortion.

CONCLUSION

The NAPRALERT database has over 1200 plant species used worldwide for their antidiabetic activity. Many of these have yet to be extensively investigated. Of the most popular ones growing in Asia and Africa, *Gymnema sylvestre* and *Momordica* species have been found in various studies to be of benefit when used as adjunct therapy in non-insulin-dependent DM. Of particular interest in this review are the hypoglycemic potential of edible plants and their role in controlling DM. In most cases, these plants are cheap and easily accessible and should be promoted as part of the global strategy to combat DM once additional data supporting their use are available. Their safety profile appears to be unquestionable. These foods could become an important source for nutraceutical products.

REFERENCES

Abdel–Barry JA, Abel–Hassan IA, Al-Hakiem MHH (1997). Hypoglycaemic and antihyperglycaemic effects of *Trigonella foenum-graecum* leaf in normal and alloxan induced diabetic rats. *J. Ethnopharmacol.* 58(3):149–155.

Akashi K, Miyake C, Yokota A (2001). Citrulline, a novel compatible solute in drought-tolerant wild watermelon leaves, is an efficient hydroxyl radical scavenger. *FEBS Lett.* 508(3):438–442.

Akbarsha MA, Murugaian P (2000). Aspects of the male reproductive toxicity/male antifertility property of andrographolide in albino rats: effect on the testis and the *cauda epididymidal* spermatozoa. *Phytother. Res.* 14(6):432–435.

Al-Awadi F, Fatania H, Shamte U (1991). The effect of a plants mixture extract on liver gluconeogenesis in streptozotocin induced diabetic rats. *Diabetes Res. Clin. Exp.* 18(4):163–168.

Al-Habori M, Raman A (1998). Review: antidiabetic and hypocholesterolaemic effects of fenugreek. *Phytother. Res.* 12:233–242.

Andallu B, Suryakantham V, Srikanthi BL, Reddy GK (2001). Effect of mulberry (*Morus indica* L.) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes. *Clin. Chim. Acta* 314(1–2):47–53.

Asano N, Yamashita T, Yasuda K, Ikeda K, Kizu H, Kameda Y, Kato A, Nash RJ, Lee HS, Ryu KS (2001). Polyhydroxylated alkaloids isolated from mulberry trees (*Morus alba* L.) and silkworms (*Bombyx mori* L.). *J. Agric. Food Chem.* 49(9):4208–4213.

Ayenzu ES (1983). The healing plants. *Unasylva: Int. J. Forestry Forest Ind.*, CXXXV, cxlix: 2–6.

Azuma K, Nakayama M, Koshioka M, Ippoushi K, Yamaguchi Y, Kohata K, Yamauchi Y, Ito H, Higashio H (1999). Phenolic antioxidants from the leaves of *Corchorus olitorius* L. *J. Agric. Food Chem.* 47(10):3963–3966.

Babu PS, Srinivasan K (1999). Renal lesions in streptozotocin-induced diabetic rats maintained on onion and capsaicin containing diets. *J. Nutr. Biochem.* 10(8):477–483.

Beppu H, Nagamura Y, Fujita K (1993). Hypoglycemic and antidiabetic effects in mice of *Aloe arborescens* Miller var *natalensis* Berger. *Phytother. Res.* 7/spec. iss:S37–S42.

Bianco A, Massa M, Oguakwa JU, Passacantilli P (1981). Iridoids in equatorial and tropical flora. 2. 5-deoxystansioside, an iridoid glucoside from *Tecoma stans*. *Phytochemistry* 20(8):1871–1873.

Bianco A, Guiso M, Iavarone C, Massa M, Trogolo C, Oguakwa JU, Francesconi A (1982). Isolation of stansioside, a new iridoid glucoside from *Tecoma stans*, and reassignment of the stereochemistry of the C(8) center of tecomoside. *Gazz. Chim. Ital.* 112(5–6):227–229.

Bohlman F, Ates N, Jakupovic J (1983). Hirsutinolides from South African *Vernonia* species. *Phytochemistry* 22:1159–1162.

Bourdillon MFC (1987). *The Shona People: Ethnography of the Contemporary Shona*, Mambo Press, Gweru, Zimbabwe.

Bruce WGG (1975). Medicinal properties in the aloe. *Excelsa* 5:57–68.

Bruneton J. (1995). *Pharmacognosy, Phytochemistry, Medicinal Plants*. Intercept, Hampshire.

Calabrese C, Berman SH, Babish JG, Ma XF, Bunyahinto L, Dorr M, Wells K, Wenner CA, Standish LJ (2000). A phase I trial of andrographolide in HIV positive patients and normal volunteers. *Phytother. Res.* 14(5):333–338.

Chattopadhyay D, Maiti K, Kundu AP, Chakraborty MS, Bhadra R, Mandal SC, Mandal AB (2001). Antimicrobial activity of *Alstonia macrophylla*: a folklore of bay islands. *J. Ethnopharmacol*. 77(1):49–55.

Chavunduka GL (1994). *Traditional Medicine in Modern Zimbabwe*. University of Zimbabwe Publications, Harare, Zimbabwe.

Chithra P, Sajithlal GB, Chandrakasan G (1998) Influence of *Aloe vera* on the healing of dermal wounds in diabetic rats. *J. Ethnopharmacol*. 59(3):195–201.

Farnsworth NR (1988). Screening plants for new medicines. Chapter 9 in *Biodiversity*, Wilson, EO (Ed) Washington, D.C.: National Academy Press.

Fernando MR, Wickramasinghe SMDN, Thabrew MI (1998). Extra pancreatic actions of *Hygrophila longifolia*. *Pharm. Biol*. 36 (5):352–356.

Fukuyama Y, Geng PW, Wang R, Yamada T, Nakagawa K (1988). 11-Deoxyalisol C and alisol D — new protostane-type triterpenoids from *Alisma plantago-aquatica*. *Planta Med*. 54(5):445–447.

Garro LC (1995). Individual or societal responsibility? Explanations of diabetes in an Anishinaabe (Ojibway) community. *Soc. Sci. Med*. Jan; 40(1):37–46.

Gelfand M, Mavi S, Drummond RB, Ndemera B (1985). *The Traditional Medical Practitioner in Zimbabwe*. Mambo Press, Gweru, Zimbabwe.

Geng PW, Fukuyama Y, Wang R, Bao JX, Nakagawa K (1988a). An acetylated sitosterol glucoside from *Alisma plantago-aquatica*. *Phytochemistry* 27(6):1895–1896.

Geng PW, Fukuyama Y, Wang R, Bao JX, Nakagawa K (1988b). Triterpenoids from the rhizome of *Alisma plantago-aquatica*. *Phytochemistry* 27(4):1161–1164.

Gupta KK, Taneja SC, Dhar KL (1996). Flavonoid glycoside of *Andrographis paniculata*. *Indian J. Chem. Sect B-Org. Chem. Incl. Med. Chem*. 35B:512.

Han YM, Nishibe S, Noguchi Y, Jin ZX (2001). Flavonol glycosides from the stems of *Trigonella foenum-graecum*. *Phytochemistry* 58(4):577–580.

Iwu MI (1993). *Handbook of African Medicinal Plants*. CRC Press, London.

Jakupovic J, Klemeyer H, Bolhmann F, Graven EH (1988). Glaucolides and gauianolides from *Artemisia afra*. *Phytochemistry* 27(4):1129–1133.

Jantan I, Waterman PG (1994). Ent-14-beta-hydroxy-8(17), 12-labdadien-16,15-olide-3-beta,19-oxide — a diterpene from the aerial parts of *Andrographis paniculata*. *Phytochemistry* 37(5):1477–1479.

Kam TS, Choo YM (2000) Novel macroline oxindoles from a Malayan *Alstonia*. *Tetrahedron* 56:33.

Koo MWL, (1994). *Aloe vera* — antiulcer and antidiabetic effects. *Phytother. Res*. 8(8):461–464.

Lins AP, Felicio JD (1993). Monoterpenic alkaloids from *Tecoma stans* juss. *Phyto* 34(3):876–878.

Marles RJ, Farnsworth NR (1995). Antidiabetic plants and their active constituents. *Phytomedicine* 2:137–189.

Marston A, Hostettmann K (1987). Antifungal, molluscicidal and cytotoxic compounds from plants used in traditional medicine. In Hostettmann K and Lea PJ (Eds) *Biologically Active Natural Products. Proceedings of the Phytochemical Society of Europe — 27*. Oxford Science Publications.

Matsufuji H, Sakai S, Chino M, Goda Y, Toyoda M, Takeda M (2001). Relationship between cardiac glycoside contents and color of *Corchorus olitorius* seeds. *J. Health Sci*. 47(2):89–93.

Meckes–Lozoya M, Ibanez–Camacho R (1985). Hepatic glycogenolysis produced by intraperitoneal administration of total extract of *Tecoma stans* in rats. *Arch. Invest. Med*. 16 (4):387–393.

Miura T, Itoh C, Iwamoto N, Kato M, Kawai M, Park SR, Suzuki I (2001). Hypoglycemic activity of the fruit of the *Momordica charantia* in type 2 diabetic mice. *J. Nutr. Sci. Vitaminol*. 47(5):340–344.

Murakami T, Kishi A, Matsuda H, Yoshikawa M (2000). Medicinal foodstuffs. XVII. Fenugreek seed. (3): Structures of new furostanol-type steroid saponins, trigoneosides Xa, Xb, XIb, XIIa, XIIb, and XIIIa, from the seeds of Egyptian *Trigonella foenum-graecum* L. *Chem. Pharm. Bull*. 48 (7):994–1000.

Nash RJ, Watson AA, Winters AL, Fleet GWJ, Wormald MR, Dealler S, Less E, Asano N, Kizu H (1997). Novel biologically active alkaloids from British plants. In Wrigley S., Hayes M., Thomas R. and Chrystal E. (Eds) *Phytochemical Diversity: a Source of New Industrial Products*. 1st ed. RSC. U.K.

Nmila R, Gross R, Rchid H, Roye M, Manteghetti M, Petit P, Tijane M, Ribes G, Sauvaire Y (2000). Insulinotropic effect of *Citrullus colocynthis* fruit extracts. *Planta Med*. 66(5):418–423.

Okyar A, Can A, Akev N, Baktir G, Sutlupinar N (2001). Effect of *Aloe vera* leaves on blood glucose level in type I and type II diabetic rat models. *Phytother. Res*. 15(2):157–161.

Oliver–Bever BEP (1986). *Medicinal Plants in Tropical West Africa*. Cambridge University Press, Cambridge.

Onunkwo GC, Akah PA, Udeala OK (1996). Studies on *Bridelia ferruginea* leaves. 1. Stability and hypoglycemic actions of the leaf extract tablets. *Phytother. Res*. 10(5):418–420.

Pereira FC, Ouedraogo R, Lebrun P, Barbosa RM, Cunha AP, Santos RM, Rosario LM (2001). Insulinotropic action of white lupine seeds (*Lupinus albus* L.): effects on ion fluxes and insulin secretion from isolated pancreatic islets. *Biomed. Res*. 22(2):23.

Picman AK (1986). Biological activities of sesquiterpene lactones. *Biochem. Systematics Ecol*. 14(3):255–281.

Platel K, Srinivasan K (1997). Plant foods in the management of diabetes mellitus: vegetables as potential hypoglycaemic agents. *Nahrung/Food* 41(2):68–74.

Puri D (2001). The insulinotropic activity of a Nepalese medicinal plant *Biophytum sensitivum*: preliminary experimental study. *J. Ethnopharmacol*. 78(1):89–93.

Qhotsokoane–Lusunzi MA, Karuso, P (2001). Secondary metabolites from Basotho medicinal plants. II. *Bulbine capitata*. *Aust. J. Chem*. 54(7):427–430.

Raman A, Lau C (1996). Antidiabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae). *Phytomedicine* 2(4):349–362.

Rao BK, Kesavulu MM, Apparao C (2001). Antihyperglycemic activity of *Momordica cymbalaria* in alloxan diabetic rats. *J. Ethnopharmacol*. 78(1):67–71.

Rashid MA, Gustafson KR, Cardellina JH, Boyd, MR (2000). A new podophyllotoxin derivative from *Bridelia ferruginea*. *Nat. Prod. Lett*. 14(4):285–292.

Reynolds T, Dweck AC (1999). Aloe vera leaf gel: a review update. *J. Ethnopharmacol*. 68(1–3):3–37.

Roman–Ramos R, Floressaenz JL, Alarconaguilar FJ (1995). Antihyperglycemic effect of some edible plants. *J. Ethnopharmacol*. 48(1):25–32.

Sauer JD (1993). *Historical Geography of Crop Plants — a Select Roster*. CRC Press, Boca Raton, FL.

Srivastava BK, Reddy MVRK (1995). Flavonoids from the flower extract of *Tecoma stans*. *Asian J. Chem*. 7(3):679–680.

Tatematsu H, Mori M, Yang TH, Chang JJ, Lee TTY, Lee KH (1991). Cytotoxic principles of *Securinega virosa* — virosecrinine and viroallosecurinine and related derivatives. *J. Pharm. Sci*. 80(4):325–327.

Teixeira CC, Rava CA, da Silva PM, Melchior R, Argenta R, Anselmi F, Almeida CRC, Fuchs FD (2000). Absence of antihyperglycemic effect of jambolan in experimental and clinical models. *J. Ethnopharmacol*. 71(1–2):343–347.

Vaishnava MM, Gupta KR (1990). Isorhamnetin 3-O-rutinoside from *Syzygium-Cumini* L. *J. Indian Chem. Soc*. 67(9):785–786.

Vanhaelen–Fastre R (1972) Antibiotic and cytotoxic activity of cnicin isolated from *Cnicus benedictus* L. *J. Pharm. Belg*. Nov–Dec; 27(6):683–688.

van Wyk B-E, Oudtshoorn B, Gericke N (1997). *Medicinal Plants of South Africa*. Pretoria, Briza Publications.

Vogler BK, Ernst E (1999). *Aloe vera*: a systematic review of its clinical effectiveness. *Br. J. Gen. Pract*. 49(447):823–828.

Watt JM, Breyer–Brandwijk MG (1962) *The Medicinal and Poisonous Plants of Southern and Eastern Africa*. ES Livingstone, Edinburgh.

Yongchaiyudha S, Rungpitarangsi V, Bunyapraphatsara N, Chokechaijaroenporn O (1996). Antidiabetic activity of *Aloe vera* L. juice. Clinical trial in new cases of diabetes mellitus. *Phytomedicine* 3(3):245–248.

Yoshikawa M, Shimada H, Komatsu H, Sakurama T, Nishida N, Yamahara J, Shimoda H, Matsuda H, Tani T (1997). Medicinal foodstuffs. 6. Histamine release inhibitors from kidney bean, the seeds of *Phaseolus vulgaris* L: chemical structures of sandosaponins A and B. *Chem. Pharm. Bull*. 45(5):877–882.

Zhang XF, Tan BKH (2000). Antidiabetic property of ethanolic extract of *Andrographis paniculata* in streptozotocin-diabetic rats. *Acta Pharmacol. Sin*. 21(12):1157–1164.

Zia T, Hasnain SN, Hasan SK (2001). Evaluation of the oral hypoglycaemic effect of *Trigonella foenum-graecum* L. (methi) in normal mice. *J. Ethnopharmacol*. 75(2–3):191–195.

Ziyyat A, Legssyer A, Mekhfi H, Dassouli A, Serhrouchni M, Benjelloun W (1997). Phytotherapy of hypertension and diabetes in oriental Morocco. *J. Ethnopharmacol*. 58(1):45–54.

12 Antidiabetic Plants of North Africa and the Middle East

Pierre S. Haddad, Louis C. Martineau, Badiaa Lyoussi, and Phuong Mai Le

CONTENTS

INTRODUCTION

We have carried out an in-depth literature review of all the plants used for the treatment of diabetes in North Africa and the Middle East. These regions have a rich traditional antidiabetic pharmacopea that includes over 130 plant species, summarized in Table 12.1. We have selected 12 of these plants on the basis of citation frequency in book chapters and review articles. Each of these has been the object of three or more published scientific studies. The antidiabetic properties of each of these plants are summarized in the following alphabetical list.

ALLIUM CEPA AND *ALLIUM SATIVUM* (LILIACEAE FAMILY)

Onion (*Allium cepa*) and garlic (*Allium sativum*) are among the oldest vegetables used for medicinal purposes in several areas of the world, notably China, Egypt, and India. The capacity of onion to lower blood glucose has been known since the early 1920s. The hypoglycemic activity was characterized as steam volatile and ether-soluble and was later found to be unstable.[1–3] Interestingly, activity was increased when the onion juice was removed prior to extraction, leading to the hypothesis that onion juice also contains hyperglycemic agents, although this has not been confirmed experimentally. *A. cepa* extracts were as effective as the oral hypoglycemic drug tolbutamide in

TABLE 12.1
Antidiabetic Plants of North Africa and the Middle East

Family	Plant	Part Used	Country in Which Used	Ref.
Anacaediaceae	Poupartia birrea	Leaves	Africa	164–166
Apiaceae	Ammi visnaga	Fruits, inflorescence seeds	Morocco, Egypt, Israel	160, 167–170
Apocynaceae	Carissa edulis	Leaf	Egypt	171, 172
	Rhazya stricta	Leaf	U.A.E.	See text
Asclepiadaceae	Pergularia tomentosa	Aerial parts	Egypt	173
Asteraceae	Bidens pilosa	Aerial parts	Africa, Egypt	174, 175
	Conyza dioscorides	Aerial parts	Egypt	173
	Launaea nudicaulis	Aerial parts	Egypt	173
	Launaea spinosa	Aerial parts	Egypt	173
	Pulicaria incisa	Aerial parts	Egypt	173
	Jasonia montana	Aerial parts	Egypt	173
Balanitaceae	Balanites aegyptiaca	Fruit mesocarps	Egypt	176
Burseracea	Commiphora myrrh	Gum-resin	Kuwait	97, 98
Caesalpiniaceae	Cassia auriculata, Cassia fistula	Seeds, flowers, leaves, stem bark	Egypt	177, 178
	Ceratonia siliqua	Seeds	Israel	168
Capparaceae	Capparis spinosa	Fruits	Israel	168
	Cleome droserifolia	Whole plant, Leaves	Egypt, Israel	168, 179
Caryophyllaceae	Paronychia argentea	Leaves	Israel	168
	Polycarpon alsinifolium	Aerial parts	Egypt	173
	Silence succulenta	Aerial parts	Egypt	173
	Spergularia purpurea	Aerial parts	Morocco	180
Chenopodiaceae	Anabasis articulata	Aerial parts	Egypt	173
	Arthrocnemum glaucum	Aerial parts	Egypt	173
	Atriplex halimus	Leaves	Israel	See text
	Haloxylon salicornicum	Aerial parts	Egypt	173, 181
	Hammada salicornica	Whole plant	S.A.	17, 124, 147, 164, 177, 181, 182
	Spinacia oleracea		North Africa	177
	Suaeda fructicosa	Aerial parts	Morocco	183, 184
Cleomaceae	Cleomaceae amblyocarpa	Aerial parts	Egypt	173
Compositae	Achillea fragratissima	Herb	Israel	168
	Ambrosia maritime	Aerial parts	Egypt	53, 185
	Anthemis psepudocatula	Flowers	Egypt, North Africa	53, 186
	Arctium lappa Linn	Roots	North Africa	177
	Artemisia abyssinicas	Whole plant, leaves, aerial parts, bark	S.A., Egypt, U.A.E, Iraq	See text
	Artemisia arborescens			
	Artemisia herba-alba			
	Artemisia judaica			
	Atractylis gummlfera	Root	Egypt	53
	Centaurea alexandrina, Centaurea calcitrapa	Flowers, leaves	Egypt, Libya	53, 177, 186
	Chamomilla reculita	Root	Egypt	53
	Cichorium intybus	Leaves	North Africa	177
	Inula viscose	Leaves	Israel	168
	Lactuca virosal	Aerial parts, seeds	Egypt	53, 187

TABLE 12.1 (CONTINUED)
Antidiabetic Plants of North Africa and the Middle East

Family	Plant	Part Used	Country in Which Used	Ref.
	Matricaria aurea	Leaves	Israel	168
Convolvulaceae	Convulvulus althaeoides, Convulvulus lanatus	Aerial parts	Egypt	173
Crotalidae	Piscivorus piscivorus	"Snake"	Middle East	147
Cruciferae	Eruca sativa	Seeds	Egypt	188
	Farsetia aegyptia	Aerial parts	Egypt	173
	Lepidium sativum	Aerial parts	Egypt	187
	Matthiola livida	Aerial parts	Egypt	173
	Nasturtium officinale	Plant	Egypt, Morocco	186
Cucurbitaceae	Citrullus colocynthis, Citrullus colocynthis	Fruit, dried fruit pulp	Iraq, Morocco, Israel	168, 169, 189, 190
	Luffa aegyptiaca	Seeds	Egypt	171
	Momordica charantia	Fruit, seeds		See text
Ephedraceae	Ephedra alata	Aerial parts	Egypt	173
Ericaceae	Arbutus unedo	Leaves, roots	Morocco	169
Euphorbiaceae	Bridelia ferruginea	Leaves	Africa	164, 181
	Cluytia richardiana	Whole plant	S.A.	164
Fagaceae	Quercus infectoria	Galls	Iran, Iraq	
Gentianaceae	Crabcentaurium spicatum	Leaves	Egypt	53
Geraniaceae	Centaurium spicatum	Aerial parts	Egypt	173
	Geranum robetianum	Leaves	Egypt	53
Globulariaceae	Globularia alypum	Leaves, plant	Morocco, Libya	161, 186
Gramineae	Cymbopogon proximus	Entire plant	Egypt	53, 56, 57
Irvingaceae	Irvingia gabonenesis	Leaves	Africa	179, 191, 192
Juglandaceae	Juglans fallax	Leaves	Iran, Iraq, Morocco	177
	Juglans regia	Leaves, bark	Egypt, North Africa	53, 147, 169, 170, 177, 186
Labiatae	Ajuga iva	Flowers, aerial parts, whole plant	Egypt, Morocco	53, 160, 169, 186, 193, 194
	Merrubium vulgare	Leaves	Egypt, Morocco	53, 169
	Origanum syriaca	Leaves	Israel	168
	Rosmarinus officinalis	Leaves, aerial parts	Jordan, Morocco	169, 170, 195, 196
	Salvia aegyptiaca, Salvia fructicosa	Aerial parts, leaves	Egypt, Israel, Middle East	168, 173, 197
	Teucrium polium, Teucrium oliverianum	Leaves, aerial parts, whole plant	Jordan, Israel, S.A., U.A.E.	168, 164, 198
	Thymus capitatus	Aerial parts	Egypt	173
	Astragalus species	Aerial parts	Egypt	173
	Crotalaria aegyptia	Aerial parts	Egypt	173
	Lupinus albus, (Lupinus termis)	Seeds	Egypt, Libya, Israel, Morocco	See text
	Lygos raetam	Aerial parts	Egypt	173
Leguminosae	Trigonella foenum graceum	Seeds	S.A., Morocco, Ethiopia, Israel, Egypt, North Africa, Middle East	See text

TABLE 12.1 (CONTINUED)
Antidiabetic Plants of North Africa and the Middle East

Family	Plant	Part Used	Country in Which Used	Ref.
Liliaceae	Allium cepa, Allium sativum, Allium vera	Bulbs, tops, roots	S.A., Egypt, North Africa, Middle East	See text
	Aloe barbadensis, (Aloe vera)	Leaves, bulb	S.A., North Africa,	See text
	Aloe perryis Baker	Leaves	Morocco, Tunisia, Kuwait, Egypt	
Malvaceae	Gossypium herbaceum		Egypt	177
Meliaceae	Azadirachta indica		S.A.	147
Mimosaceae	Prosopis farcta	Root		168
	Acacia farnesiana	Pod	Egypt	53, 199
	Acacia nilotica	Stem, entire plant		
Moraceae	Ficus racemosa	Stem bark	Egypt	177
	Morus alba	Root bark	North Africa	177
	Morus nigra	Leaves		
Myrtaceae	Eucaluptus globulus	Leaves, fruits	Africa, Morocco	17, 169, 170, 181, 200, 201
	Myrtus communis	Leaves	Morocco, Libya	164, 169, 170, 181, 202
	Psidium guajava	Leaves, fruits	Egypt	177
Nitrariaceae	Nitraria retusa	Aerial parts	Egypt	173
Oleaceae	Olea europea	Leaves	Egypt, Morocco	See text
Orchidaceae	Orchia mascula		Egypt, Iran	203
Orobanchaceae	Cistancha tubulosa	Plant	North Africa	177
Papaveraceae	Papaver somniferum	Seeds	Egypt, Iran	177
Papilionoinaceae	Alhagi maurorum, Alhagi pseudalhagi	Plant	Iran, Iraq	177
	Cyamopsis tetragonoloba	Seed-gum	S.A.	177
	Indigofera tinctoria	Plant	Egypt	177
	Securigera securidaca	Seeds	Iraq	177
	Trifolium alexandrianum	Seeds	Egypt, Iran	177
Pistaciaceae	Pistacia leutiscus	Aerial parts	Egypt, Morocco	187
Plumbaginaceae	Limonium tubiflorum	Aerial parts	Egypt	173
Portulacaceae	Portulaca oleracea	Whole plant	Egypt, Morocco	53, 186
Ranunculaceae	Nigella sativa	Seeds, aerial parts	Morocco, Egypt, North Africa	See text
Resdaceae	Ochradenus baccatus	Aerial parts	Egypt	173
Rhamnaceae	Zizyphus spina-christi, Zizyphus lotus	Leaves, fruits	Egypt, Morocco	169, 170, 204
Rosaceae	Poterium ancistroides, Poterium spinosum	Roots	Israel	147, 181; See text
	Prunus amygdalus		Iran, Morocco	177
	Sarcopoterium spinosum	Roots	Israel	168
Rutaceae	Citrus aurantium		Egypt, Iran, Israel, Morocco	177
Scrophulariaceae	Scrophularia deserti	Aerial parts	Egypt	173
Solanaceae	Lycium shawii	Aerial parts	Egypt	173

TABLE 12.1 (CONTINUED)
Antidiabetic Plants of North Africa and the Middle East

Family	Plant	Part Used	Country in Which Used	Ref.
	Lycopersicon esculentum		Israel	177
	Nicotiana glauca	Aerial parts	Egypt	173
Umbelliferae	Cariandrum sativum	Aerial parts	Egypt, North Africa	187
	Eryngium creticum	Leaves	Israel	168
	Ferula assa-foetida		Iran	177
	Pertriselinumcrispum	Entire plant	Egypt	53
Urticaceae	Urtica dioca	Aerial parts	Morocco	169
Zygophylaceae	Fagonia arabica	Aerial parts	Egypt	173
	Peganum harmala	Seeds	Egypt, North Africa	53, 177, 186
	Zygophyllum coccineum, Zygophyllum gaetulum, Zygophyllum cornutum, Zygophyllum album	Fruit, leaves, aerial parts	Egypt, Morocco	See text

Note: S.A. = Saudi Arabia
U.A.E. = United Arab Emirates

normal[3–5] and alloxan-treated rabbits,[2,6,7] as well as in human volunteers[8] or diabetic patients.[7] Feeding streptozotocin (STZ)-treated rats the bulb, callus, seedlings, and leaves of onions for 4 days[9] or a fresh onion infusion daily for 30 days significantly reduced glycemia.[10] In a randomized crossover study, 20 type II diabetics on a diet supplemented with 3 × 20 g of fresh onion per day for 1 week experienced a small but significant decrease in fasting glycemia.[11]

The major components of the active fraction of essential oil of onion were later identified as organic disulphides and their oxides,[12,13] as well as sulfoxide amino acids. In moderately diabetic alloxan rats,[14] S-methyl cysteine sulfoxide fed daily for 45 to 60 days decreased glycemia by approximately 20%.[15,16] Liver hexokinase and glucose-6-phophatase (G-6-Pase) activities were partially normalized by the treatment.

Because these compounds are ineffective in pancreatectomized animals or in severely STZ-induced diabetes, they are believed to act by protecting insulin from thiol group attack,[17] whereas their direct action on pancreatic beta cell function has not been assessed. Indeed, they induce a rise in plasma insulin concomitantly to their hypoglycemic effect.[13] Unlike the group of Augusti,[13] Sharma et al. did not find any effect of onion juice on fasting glucose in normal subjects, but confirmed the hypoglycemic activity after a glucose load.[8] Diphenylamine was also identified in onions and found to be more efficacious than tolbutamide in glucose-fed rabbits.[18] It is most abundant in fresh onion juice; boiling and drying dramatically reduce diphenylamine content. Finally, a poorly described subfraction of the ether extract of onion was found to possess remarkable hypoglycemic activity, lasting several days following a single intravenous injection and capable of normalizing glycemia in alloxan rabbits or rats.[19]

Garlic juice and its ethyl alcohol, petroleum ether, and ethyl ether extracts also contain hypoglycemic principles.[3,4] Aqueous extracts of garlic cloves increased liver glycogen content and diminished blood glucose and triglycerides in sucrose-fed rabbits.[20] *A. sativum* chloroform extract was also recently shown to reduce dyslipidemia and the subsequent atherosclerotic lesions in STZ-treated rats.[21] As for onion, sulfoxide amino acids of garlic are potent active principles. S-allyl cysteine sulfoxide (SACS; also known as allin), a precursor of allicin, was found to exert

insulin-dependent and -independent antidiabetic actions.[22] *In vitro*, the compound stimulated insulin secretion by isolated pancreatic islets. When administered *in vivo* to STZ-treated rats, SACS enhanced lipolytic enzymes and inhibited lipogenic ones. It also caused a substantial increase in tissue glutathione, the major intracellular thiol-containing cytoprotectant, and a marginal increase in superoxide dismutase and catalase, thus explaining its potent antioxidant properties.[22]

Feeding SACS to alloxan-diabetic rats resulted in a 30% drop in glycemia and near normalization of liver G-6-Pase activity.[23] Administration of a single dose of allicin (diallyldisulphide or DADS) to mildly diabetic alloxan rabbits reduced fasting glycemia and greatly improved response to an oral glucose tolerance test (OGTT). Allicin increased basal and insulin-stimulated glucose uptake in diaphragm muscle isolated from alloxan rabbits.[24] Garlic oil, the major constituent of which is likely to be allicin,[25] fed to mildly STZ- or alloxan-diabetic guinea pigs normalized glycemia as well as the number of pancreatic beta cells per islet.[26] Similarly, when allicin was fed to mildly diabetic STZ rats maintained on a normal or a high-fat diet, glycemia was reduced significantly in both groups.[25]

Finally, *in vitro* treatment of blood obtained from human type II diabetics with SACS and DADS delayed oxidative and glycative deterioration of LDL and the loss of plasma catalase and glutathione peroxidase activities.[27] In contrast to the numerous animal studies supporting *in vivo* hypoglycemic activity, garlic was found to be ineffective at reducing glycemia or insulinemia during an OGTT in type II diabetics.[28]

ALOE VERA (LILIACEAE FAMILY)

Aloe vera, also known as *Aloe barbadensis*, is a cactus-like plant that grows in hot, dry climates such as that found in its native North Africa. It is very well known for the beneficial action of its leaf gel or sap in various dermatological conditions and is now part of many cosmetic preparations worldwide. Perhaps less known are its reported beneficial effects against diabetes.

Indeed, an Indian group reported major improvements in cardiovascular diseased states, as well as in serum glucose, total and HDL cholesterol, and triglycerides, in several thousand diabetic patients asked to consume *A. vera* "fresh flesh gelatin" twice daily alongside another plant, "husk of Isabgol," mixed into bread.[29] A Saudi team reported similar results in five diabetic patients taking *A. vera* alone in the form of the dried sap.[30] In placebo-controlled, single-blind, clinical trials on diabetic men and women, *A. vera* alone was again shown to reduce blood glucose and triglycerides without affecting appetite, body weight, or serum cholesterol. The effects were not better in patients taking the oral hypoglycemic drug glibenclamide.[31]

In animal studies, *A. vera* diminished blood glucose in a significant and persistent way in alloxan-diabetic mice.[30] A single oral dose of the dried sap of aloes was found to be without effect in normal mice, but administration over 7 days was nearly as efficient as glibenclamide at reducing fasting plasma glucose.[30] *Aloe vera* leaf gel extract nearly normalized glycemia and body weight in moderately diabetic STZ rats. Liver glycogen and liver enzymes, including hexokinase, G-6-Pase, fructose-1,6-biphosphatase, lactate dehydrogenase, glycogen synthase, and glycogen phosphorylase, were all normalized by the treatment.[32] Hypoglycemic activity has been attributed to a bitter principle obtained by ethyl acetate extraction,[33] and to crude polysaccharide fractions from combined (1:1) methanol–water and water extracts.[34] Of the latter, glycans called arborans A and B yielded significant hypoglycemic activity when injected intraperitoneally to normal and alloxan-diabetic mice.[34]

Conflicting results were reported in a study demonstrating that extracts from *A. vera* gel were ineffective at lowering blood glucose in normal rats and even caused slight hyperglycemia in type II diabetic animals.[35] In contrast, extracts from the leaf pulp were even more potent than the sulfonylurea glibenclamide in its hypoglycemic action in type II diabetic rats. Other studies on STZ-diabetic mice and rats have demonstrated the wound-healing, anti-inflammatory and analgesic

effects of *A. vera* extracts. Thus, the plant appears to be effective internally and externally to address direct and secondary consequences of diabetes, respectively.[36–38]

ARTEMISIA HERBA-ALBA (COMPOSITAE FAMILY)

The wormwood *Artemisia herba-alba* is a small perennial wooly shrub growing extensively in North African and Middle Eastern countries. Iraqi researchers have most extensively studied the plant. An Iraqi physician reported a clinical study on 15 diabetic patients who consumed a 10 g% decoction of the leaves and stems of *A. herba-alba*, with or without other treatments.[39] In 14 of the 15 patients, blood glucose diminished and diabetic symptoms improved. Most interestingly, in seven patients, the effects persisted despite withdrawal of *A. herba-alba* treatment. In a follow-up study conducted 1 year later, several patients who had relapsed were normalized again within 2 weeks after plant treatment was resumed.[40] Results in 12 additional patients were less clear because 60% of those on oral hypoglycemics did not respond well to the plant extract alone and required coadministration with drugs. Although these results are interesting, randomized placebo-controlled clinical trials are required to validate the efficacy of *A. herba-alba* in humans.

In animal studies, the decoction of *A. herba-alba* was effective in reducing blood glucose in normal and alloxan-treated rabbits of Iraqi origin.[41] A subsequent study used normal Wistar rats to show that the activity of *A. herba-alba* was found principally in the aerial parts (leaves and stem bark), rather than in the roots, and that a methanolic extract was ineffective in reducing blood sugar.[42] The same group confirmed that an aqueous extract of the aerial parts of the plant was effective in alloxan-treated Wistar rats and albino rabbits; it prevented weight loss and normalized blood glucose and glycosylated hemoglobin, as well as cholesterol, triglycerides, and phospholipids. The authors suggested that the plant may improve peripheral glucose utilization, although this remains to be tested. Acute administration of the aqueous extract of *Artemisia* panicles to normal and alloxan-diabetic rabbits gradually and significantly reduced glycemia.[43]

Finally, a careful study carried out in alloxan-treated New Zealand rabbits and albino mice revealed that a single dose of *A. herba-alba* aqueous extract induced a sustained decrease of hyperglycemia in diabetic animals but only a weak and transient hypoglycemic effect in normal animals.[44] These results contrast with those obtained with normal Iraqi albino rabbits, thereby highlighting again the importance of animal model selection. Interestingly, gastrointestinal transit time was accelerated by 50% in plant-treated animals; this can reduce glucose absorption and contribute to the antidiabetic activity.

ATRIPLEX HALIMUS (CHENOPODIACEAE FAMILY)

The sand rat *Psammomys obesus* is a rodent of semiarid regions of the Middle East and North Africa. It is well known to develop a syndrome very analogous to human type II diabetes when placed in captivity (sedentary lifestyle) and fed regular laboratory chow, which is a relatively hypercaloric diet for these animals.[45] In the search for the cause of the susceptibility of these animals to diabetes, an Israeli group discovered that the animals fed mainly on *Atriplex halimus* — a tall, shrubby saltbush found all over the Mediterranean region and in North Africa. It is particularly abundant in flooded saline land.

Aharonson et al. studied the effects of *A. halimus* leaf juice, water extract, and ash on glucose homeostasis in alloxan-treated rats.[46] They found that all three preparations could significantly diminish fed plasma glucose levels in control and alloxan-treated rats without reduction of appetite or weight loss. The fact that the ash was active suggested that the nature of the active principle might be inorganic. Shani et al. also observed that an acute administration of atriplex leaf juice to alloxan rats reduced glycemia.[47] Leaf extract was observed to maintain its hypoglycemic activity

even after heating to 700°C. This activity was associated to the content in chromium and manganese complexes, which could potentiate the effect of insulin on glucose uptake,[47] as discussed later.

However, a follow-up study in sand rats showed that *A. halimus* ash was ineffective at improving glucose tolerance, unlike what was seen in alloxan-diabetic albino rats. This highlights once again the important problem posed by the choice of the animal models in the study of antidiabetic plants in general.

A series of *in vitro* experiments later clearly demonstrated the potentiating effect of *A. halimus* ash on insulin-induced glucose oxidation in adipose tissue.[48] A strong correlation could be established with the presence of trace amounts of chromium. Indeed, chromium deficiency is known to lead to diabetes in rats[49] and chromium supplementation is helpful in human therapy of types I and II diabetes.[50] However, it appears that no studies on the potential benefits of *A. halimus* in human populations exist. Nonetheless, an Israeli group did find that they could modulate the extent of diabetes in sand rats by carefully dosing a mixture of laboratory chow and *A. halimus*.[51]

LUPINUS ALBUS (LEGUMINOSAE FAMILY)

Lupinus are species of the legume family that have been cultivated in the Mediterranean basin for over 300 years. Very nutritious, their seeds are rich in protein and soluble dietary fiber and some varieties have high oil content. Three species of lupin are found in Mediterranean regions, namely, yellow, blue, and white lupin (the latter including *L. albus* and *L. termis*).

Use of lupin for the treatment of diabetes is well known in North African/Middle Eastern folk medicine. Diabetic Palestinians, Bedouins, Yemenites, and Moroccans, among others, add lupin seeds to their diets. However, scientific evidence for their antidiabetic activity is contradictory.

Helmi et al. reported that lupin seed powder caused a profound hypoglycemic action in normal and diabetic rabbits.[52] Discussions of the mechanisms by which lupin seeds exert their antidiabetic potential revolve around the benefits of their soluble fiber content, the saponin-associated inhibition of intestinal cholesterol absorption and hepatic glucose production, and the treatment-induced increase in plasma insulin.[53] Shani et al. reported that gavage with *L. albus* seed extracts and its major alkaloids only produced a mild and transient hypoglycemic effect in alloxan-diabetic rats.[54] Similarly, Riyad et al. were unable to show a significant antidiabetic action of lupin seeds incorporated into the diet of STZ-treated rats.[55] In contrast, administration of the aqueous extract of *L. albus* to moderately diabetic alloxan rats (partial destruction of the pancreatic β-cell mass) resulted in complete normalizaton of glycemia,[56] suggesting that *L. albus* exhibits insulinotropic activity or stimulates β-cell regeneration

Also of interest are the recent studies showing that aqueous suspensions of lupin seeds had protective effects against the hepatic and renal toxicity of alloxan in rats. Indeed, *L. albus* normalized serum transaminases, as well as urea and creatinine.[57] However, it had almost no effect on phase I and II metabolic enzymes of the liver.[58] Similarly, lupin seed extracts show no toxic effects in rats; only its alkaloid, lupanine, caused a small increase in renal weight.[54] Finally, a feeding study in 14 type II diabetics failed to show a beneficial effect of lupin-derived dietary fiber.[59]

MOMORDICA CHARANTIA (CUCURBITACEAE FAMILY)

Momordica charantia is a widely used antidiabetic plant, popular in countries of the Indian subcontinent, Asia, and South America. It is one of the most extensively studied antidiabetic plants. Momordica fruit juice or extract, as well as seed extract, is consumed alone or in combination with other plants.

The hypoglycemic activity of *M. charantia* has long been known in folk medicine and has been scientifically validated in animal models of diabetes.[60–65] Momordica fruit juice restored normoglycemia in severely diabetic STZ mice,[66,67] with no hypoglycemic effect in normal mice. In normal

and alloxan-diabetic rats, glycemia was reduced respectively by 20 and 50% after oral administration of fruit juice extracts for as little as 1 week, with no histological evidence of toxicity to liver and kidney after 4 weeks. Even greater reductions of glycemia, as well as prevention of cataract formation, have been reported after prolonged administration of momordica fruit extracts in alloxan-diabetic rats.[68–70] Oral administration of momordica fruit or of its alcohol extract acutely and significantly lowered glycemia in alloxan rabbits[71] or in normal and STZ-diabetic rats,[72] respectively. The hypoglycemic activity of the aqueous extract of momordica fruit has been reported to reside in the chloroform soluble fraction.[73]

A number of human trials have also been reported. Suspension of the vegetable pulp caused a significant fall of postprandial serum glucose when ingested by 100 moderate type II diabetic subjects.[74] Ingestion of momordica fruit juice by type II diabetics also significantly reduced glycemia and area under the glycemia curve after an oral glucose load.[75,76] In contrast, fasting glycemia was not altered in 26 type II diabetic patients fed tablets made of dried momordica fruit.[77]

Momordica contains active polypeptides with insulin- or glucagon-like-activities.[78] Polypeptide-P isolated from the fruit, seeds, and tissue of *M. charantia* showed hypoglycemic effect when injected in gerbils, langurs, and humans.[79] Charantin, another peptide resembling insulin, significantly lowered blood glucose in rabbits when administered orally.[80] Other active components responsible for the antihyperglycemic activity are oleanolic acid, 3-*O*-glucuronide, and momordin Ic, which inhibit glucose transport at the level of the brush border of the small intestine.[81]

Some evidence indicates that momordica can stimulate pancreatic insulin secretion[82] and peripheral glucose metabolism, including stimulation of glucose uptake and gluconeogenesis.[83] The fruit juice was found to increase significantly the number of pancreatic β-cells in diabetic rats.[84] *In vitro*, momordica also had a cytoprotective effect on isolated pancreatic islets treated with STZ.[66] Ethanolic extract of *M. charantia* lowered blood sugar in normal and STZ-diabetic rats by a mechanism apparently involving the inhibition of gluconeogenesis and the stimulation of glucose oxidation in liver and red bloodcells.[85] Aside from improving glycemia as well as glucose and insulin tolerance, momordica fruit extract has been reported to increase the content of Glut-4 glucose transporters in the plasma membrane fraction of skeletal muscle from KK-A^y diabetic mice.[86] Momordica fruit extract increases the rate of liver glycogen synthesis by four- to fivefold.[72] Finally, it has recently been suggested that momordica may act through the AMP-activated protein kinase pathway in much the same way as metformin.[87]

NIGELLA SATIVA (RANUNCULACEAE FAMILY)

Also known as "black seed" or "black cumin," *Nigella sativa* is a spicy plant widely used in North Africa and the Middle East. It is known for its hypotensive,[88,89] immunomodulatory,[90–92] and hepatoprotective[93–95] effects.

In Kuwait, a plant mixture comprising *N. sativa*, myrrh, gum olibanum, gum asafetida, and aloe has been commonly used against diabetes. This mixture has glucose-lowering effects in normal and STZ-treated rats without affecting plasma insulin or intestinal glucose absorption.[96] A later study found that this mixture was as efficacious as the biguaninde phenformin for lowering plasma glucose in the STZ model.[97] Unlike phenformin, however, the plant mixture could reduce glucose production from lactate, alanine, or glycerol in hepatocytes isolated from diabetic animals.[97] It is noteworthy that the Kuwaiti group found that no one extract from an individual plant of the mixture could account for the improvement of glucose tolerance in the STZ-diabetic rat.[98] However, this is inconsistent with the work of several other laboratories.

Indeed, Moroccan researchers have found that a crude aqueous extract of *N. sativa* alone was very effective at restoring glucose homeostasis in the sand rat model.[99] In a similar model, the Merione shawi, they showed that an *N. sativa* decoction administered orally was able to correct diabetes and obesity.[100] The seed decoction reduced blood glucose and insulin within 1 month, as well as plasma cholesterol and triglycerides thereafter. Hot water extract of nigella seed can also

significantly decrease glycemia and protect against lipid peroxidation-induced liver damage in severely alloxan-diabetic rabbits.[101] The volatile oil of *N. sativa* seeds demonstrated hypoglycemic activity in normal and alloxan-diabetic rabbits.[102] A preliminary report found it to be as effective at lowering cholesterol as simvastatin in the obese, prediabetic sand rat.[103]

The antidiabetic properties of nigella appear to be due to a combination of pancreatic and peripheral effects, as well as cytoprotective activities. Oral or intraperitoneal treatment of mildly diabetic STZ hamsters[104] or rats[105] with nigella volatile oil extract resulted in a gradual near-normalization of glycemia. This was partly attributable to a significant increase in insulinemia, associated with improved insulin immunoreactivity in pancreatic sections.[104] Nigella volatile oil extract also exerts an important cytoprotective effect against STZ toxicity at the pancreatic level, which supports the notion that the plant may improve pancreatic function.[106] *In vitro*, the alcohol extract of defatted nigella seed exerted an insulinotropic activity.[107] Nonetheless, the *in vivo* insulin secretagogue activity of *N. sativa* remains to be confirmed.

Indeed, El-Dakhakhny et al. presented evidence for a hypoglycemic action of the volatile oil in STZ-treated rats, but neither the oil nor constituents such as thymoquinone or nigellone affected insulin secretion from isolated pancreatic islets.[108] Other experiments using *N. sativa* reported a gradual decrease in glycemia in the presence of total or nearly total destruction of pancreatic β-cells.[109] This suggests extrapancreatic effects of the plant that may result from increased peripheral insulin sensitivity or glucose utilization, or from reduced intestinal glucose absorption. A decrease in gluconeogenesis had previously been suggested by the Fararh group[104] and was recently confirmed in hepatocytes isolated from nigella-treated diabetic animals.[109] Our laboratory demonstrated that *N. sativa* enhances insulin sensitivity, as evidenced by the marked increase in insulin-stimulated p44/42 MAPK and PKB activities in hepatocytes isolated from normal rats treated *in vivo* with petroleum ether extract of seeds.[110]

Finally, a Moroccan group also showed that oral treatment of Wistar–Kyoto rats with a hexane extract of *N. sativa* seeds reduced serum cholesterol, triglycerides, and glucose, but had a negative effect on normal weight gain.[111] Our own work confirmed that a petroleum ether extract of *N. sativa* seeds significantly decreased food intake and body weight gain in normal rats.[110] Thus, although crude aqueous extracts of *N. sativa* seeds appear to be nontoxic[100,112,113] and effective against the metabolic and cardiovascular consequences of diabetes, care must be taken with organic extracts because they may have adverse actions.[92]

OLEA EUROPEA (OLEACEAE FAMILY)

The leaves of the olive tree are also known for their antidiabetic properties in Mediterranean and Middle Eastern countries. Two European studies on the variety *O. europea sativa* have demonstrated hypoglycemic and antihyperglycemic activity in normal and alloxan-treated female and male Wistar rats, respectively.[114,115] In the first study, *O. europea* decoction had no effect on intestinal glucose absorption, but significantly increased glucose uptake by skeletal muscle and insulin production by isolated pancreatic islets. These effects were closely correlated to the content of oleuropeoside, a known hypotensive agent of olive leaves. Oleuropeoside showed seasonal variation and was able, as a pure compound, to reproduce the action of the crude extract.[114]

An Italian group used an extract prepared from a glycerol-alcoholic macerate to show a transient hypoglycemic and hyperinsulinemic action of *O. europea* in normal animals, as well as an improvement of the response to an oral glucose load.[115] In contrast, alloxan-diabetic animals responded with sustained reductions in blood glucose without changes in insulinemia.[115] These authors found that extracts from shoots were more effective than those from leaves; they demonstrated a positive correlation between the hypoglycemic activity and the content in the bitter hydrosoluble glycoside, oleuropein, and a negative one with hesperidin.

Another variety of olive leaf was tested in Morocco, namely, that from *O. europea oleaster*, which is characterized by smaller leaves and inedible fruits. Researchers used the *Psammomys*

obesus sand rat model rendered hypercholesterolemic and prediabetic by feeding normal rat chow supplemented with 1% cholesterol and 3% lard for 4 months.[116] A 2-month treatment by daily gavage with an *O. europea* decoction slightly decreased fasting plasma glucose and insulin levels, improved oral glucose tolerance, and reduced blood cholesterol, atherogenous lipoproteins, and apparent lipid peroxidation.[116] Resulting microangiopathy in skin and pancreas were partly corrected, and kidney lesions were completely prevented. A follow-up study in the same model rendered obese by more prolonged hypercaloric feeding compared *O. europea* extracts with the cholesterol-lowering agent, simvastatin.[117] Results confirmed the hypoglycemic and insulin-lowering actions, but no significant effect on body weight could be seen. Plant extract was as potent as simvastatin in reducing plasma cholesterol and atherogenic lipoproteins.[117]

POTERIUM SPINOSUM (ROSACEAE FAMILY)

A small thorny shrub commonly found growing throughout the Mediterranean region, *Poterium spinosum* is known in Bedouin medicinal folklore for its potent antidiabetic properties. The root bark of the plant is boiled and then simmered for several hours before being consumed as a tea.

Studies by an Israeli group confirmed the hypoglycemic activity of aqueous extracts of the plant in normal fasting rabbits, and concentrated an active fraction by chromatography of an n-butanol extraction.[118] A follow-up study confirmed in alloxan-diabetic rats that the root bark contains the hypoglycemic activity, but the plant had no action in normal rats.[119] In contrast, Kanter et al. more recently showed that *P. spinosum* aqueous and chloroform extracts were active in diminishing the response to an oral glucose load in normal and alloxan-treated rats.[120] In the work of Shani et al., a significant hypoglycemic effect could consistently be obtained with summer root bark, but significant seasonal variations in *P. spinosum* antidiabetic activity were found.[119] Such seasonal variations are very important because they can explain intra- and interlaboratory variability.

RHAZYA STRICTA (APOCYNACEAE FAMILY)

Rhazya stricta is a small shrub found in Saudi Arabia and the United Arab Emirates. Its leaves contain several alkaloids, such as rhazizine, rhazimal, strictamine, geissochizine, and vincadline, as well as several flavonoids.[121]

R. stricta is a traditional plant treatment for diabetes in the Middle East. However, reports of its antidiabetic potential are conflicting. In STZ-treated rats, oral administration of *R. stricta* extract was found to reduce blood glucose significantly and to increase plasma insulin.[122] The alcohol extract of *R. stricta* given orally to normal mice resulted in a large and rapid, yet sustained, increase in insulinemia. When fed to severely diabetic STZ rats simultaneously with a 1-g/kg glucose load, the plant improved the response to the OGTT.[123] *R. stricta* was also observed to potentiate the effects of the oral hypoglycemic drug glibenclamide.[122] This points to a concern with all antidiabetic plants taken alongside conventional drugs, as is often the case in several countries of the Middle East and North Africa. Medical doctors and herbalists should be sensitive to such potentially dangerous drug–herb interactions.

In contrast to Ali[122] and Tanira et al.,[123] Wasfi et al., using a similar STZ-treated rat model, were unable to find any significant effect of *R. stricta* leaf decoction on glucose homeostasis, even after an OGTT.[121] Similarly, alloxan-treated mice given an aqueous extract of the plant orally showed a nonsignificant decrease in blood glucose,[124] in contrast to the onion bulb *Allium cepa*, also presented in this chapter.

TRIGONELLA FOENUM GRAECUM (LEGUMINOSAE FAMILY)

Of all the antidiabetic plants used in the Middle East and North Africa, *Trigonella foenum graecum* (fenugreek) seeds have by far received the most scientific attention. Scientific reports of the hypoglycemic properties of fenugreek date back more than 50 years.[125,126] An excellent comprehensive review of the antidiabetic and hypocholesterolemic effects of fenugreek was recently published.[127] This chapter briefly summarizes and updates the antidiabetic properties of fenugreek; readers are encouraged to consult the reviews by Al-Habori and Raman[127] and others[128] for a more detailed account.

Fenugreek seeds are included in the German Commission E monographs[129] and are indicated for internal use against loss of appetite. Diabetes is also listed as an indication, albeit as an unproven use. Nonetheless, several pilot clinical studies have demonstrated the lack of toxicity[130] and the hypoglycemic effects of fenugreek seeds in fed and fasted type I and II diabetic patients.[131–134] Raghuram et al. found that incorporation of fenugreek in the diet of type II diabetics increased glucose metabolic clearance rate as well as the number of insulin-binding sites on erythrocytes.[131] A recent double-blind placebo-controlled study in mild to moderate type II diabetics confirmed the improved glycemic control and decreased insulin resistance induced by fenugreek seed extract, although the number of patients was low.[135]

Fenugreek antidiabetic properties appear to be due to effects at the gastrointestinal, pancreatic, and peripheral levels. Single or repeated oral doses of fenugreek significantly reduced glycemia in STZ-diabetic rats[136] or severely diabetic alloxan mice[137] and normalized glycemia in severely diabetic alloxan rats[138,139] or rabbits.[140] A Canadian group recently demonstrated that feeding *T. foenum graecum* seed powder to diabetic rats normalized the activities of glycolytic and gluconeogenic enzymes in liver and in kidney.[141] Moreover, an insulinomimetic effect was observed whereby the activities of liver phosphofructokinase and glucokinase, as well as that of muscle hexokinase, were normalized.[136] A highly enriched fraction of fenugreek seed water extract also exerted effects on insulin secretion in less severe chemically induced diabetic conditions.[140]

Several of the active compounds of fenugreek have been identified. As with other leguminous plants, *T. foenum graecum* has a high content of dietary fiber, mostly in the form of galactomannans, and is a rich source of gum.[128] These properties are most probably responsible for the ability of fenugreek to delay gastric emptying, to reduce the intestinal absorption of glucose,[127] and to exert a hypoglycemic effect in various models of diabetic rats.[142] *In vitro* studies using inverted intestinal sacs from rat jejunum demonstrated that fenugreek inhibits the transepithelial transport of 3-*O*-methyl-glucose.[143] More recently, Al-Habori et al. extended these observations to show that several fenugreek seed extracts were able to inhibit sodium-dependent glucose transport in brush border membrane vesicles from rabbit intestine.[144] In addition, *T. foenum graecum* reduced the activity of enzymes involved in carbohydrate digestion, particularly α-amylase.[145,146] In this context, fenugreek resembles the commercially prescribed acarbose isolated from strains of the fungus *Actinoplanes* sp.[147]

Fenugreek seeds are also rich in steroid saponins (the most abundant are diosgenin, tigogenin, and gitogenin) and their peptide esters (fenugreekine).[128] Pharmacological studies confirmed that the saponins are responsible for stimulating appetite, which improved weight gain in STZ-diabetic rats.[148] In addition, fenugreekine was reported to have a hypoglycemic effect, although at doses significantly exceeding the normal content of the seeds.[149] Trigonelline, the *N*-methyl derivative of nicotinic acid, is a major alkaloid component of fenugreek that was initially thought to be involved in the hypoglycemic activity of fenugreek. However, studies on human diabetics in India failed to confirm this action.[150] Four major alkaloids of fenugreek — trigonelline, nicotinic acid, coumarin, and scopoletin — were tested for hypoglycemic activity in alloxan rats; coumarin was found to have the most powerful and longest lasting activity.[54]

Fenugreek, like other legumes, contains several nonmammalian amino acids. It is especially rich in 4-hydroxyisoleucine, which represents over 85% of its amino acid content[128] and is found

at a concentration of 0.56% in fenugreek seed.[151] Along with the fiber and gum mentioned earlier, it probably accounts for an important part of the improved glucose tolerance and other antidiabetic activities of the defatted seed extract. Micromolar concentrations of 4-hydroxyisoleucine have the capacity to stimulate glucose-induced insulin secretion from isolated pancreatic islets *in vitro*.[137,152,153]

The amino acid also enhances the insulin response to an OGTT in diabetic rats and dogs *in vivo*.[154] Single administration to diabetic rats partially restored insulin response, and repeated administration reduced glycemia and improved glucose tolerance.[155] Further studies confirmed that the linear major stereoisomer (2S,3R,4S) is the one responsible for the insulinotropic pancreatic response.[155] It was found that 4-hydroxyisoleucine improved insulin resistance in nutritional and genetic models of insulin resistance,[156] possibly in part due to the acute activation of muscle phosphatidylinositol-3-kinase, a key protein involved in insulin signaling and glucose transport.

Although fenugreek seeds have received the most ethnobotanical and scientific attention, fenugreek leaves also possess antidiabetic activity. The aqueous extract or powder of fenugreek leaves also exhibited significant hypoglycemic activity in alloxan- or STZ-diabetic rats.[157] In the latter case, significant improvements of hemoglobin glycosylation and liver glycogen content were noted. This was attributed to a direct effect on the pancreas, because insulinemia was markedly improved, and to peripheral effects, including significant reductions in liver and kidney hexokinase, G-6-Pase, and fructose 1,6 biphosphatase activities.[158,159]

In summary, *T. foenum graecum* exerts its antidiabetic action by interfering with carbohydrate digestion and intestinal glucose transport, by stimulating pancreatic insulin secretion in response to glucose, and by enhancing the peripheral utilization of glucose.

ZYGOPHYLLUM GAETULUM (ZYGOPHYLACEAE FAMILY)

An herbaceous plant growing in the southern regions of Morocco and Algeria, *Zygophyllum gaetulum* has long been used as a condiment and food and is among the ten most common nontoxic plants used in that area for their virtues against diabetes.[160] In normal Wistar rats, intraperitoneal or intragastric administration of *Z. gaetulum* had a transient hypoglycemic effect similar to the oral hypoglycemic drugs glibenclamide and metformin.[161] Intragastric administration of the plant extract also increased plasma insulin by 1.5 to 2 times, and intravenous injection significantly improved glucose tolerance in normal animals. In alloxan-treated rats, a single dose of *Z. gaetulum* aerial parts decoction normalized blood glucose as effectively and persistently as the oral hypoglycemic drugs. In follow-up studies, the hypoglycemic activity was found associated with a butanol-soluble fraction and with a water-insoluble precipitate.[162]

Moroccan researchers also carried out a human clinical study on newly diagnosed type II diabetics. A *Z. gaetulum* decoction was compared with the sulfonylurea glipizide and a water placebo. A single oral intake of the plant had a 30% hypoglycemic action that developed more slowly but became comparable to glipizide, as it did during a 3-week treatment, maintaining normal fasting and postprandial glycemia. Thus, *Z. gaetulum* is a promising nontoxic[160,163] antidiabetic plant whose mode of action remains to be clarified.

CONCLUSION AND PERSPECTIVES

As seen from this brief overview of 12 Middle Eastern and North African plants, much research is still needed to ascertain the antidiabetic potential of these plants, to determine their active principles, and to elucidate their modes of action. Indeed, very few active principles have been discovered, among which the most important are 4-hydroxyisoleuceine and trigonelline from fenugreek, allylpropyl disulfide from onion and garlic, and peptides and terpenoids from momordica.

The most common modes of action of several antidiabetic plants include inhibition of glucose digestion/absorption, stimulation of insulin secretion, and stimulation of peripheral glucose utilization. However, the actual cellular/molecular targets remain elusive. We have also seen that several factors may influence the outcome of scientific research on antidiabetic plants. Of importance, we note that seasonal and geographical variations can affect the activity of the plant material. Also, the choice of animal model can affect the experimental outcome. In this regard, chemically induced animal models, widely used because they are economical and well characterized, mimic type I diabetes, although type II is the most prominent form in human populations. Therefore, these models are not the most appropriate to assess beneficial effects on insulin resistance.

Bioassays using isolated cells or tissues are only beginning to be applied to research on antidiabetic plants and they offer much promise to elucidate the modes of action of active principles. Of all the plants described here, fenugreek, momordica, onion, and garlic appear to be the safest and have the most scientific evidence supporting their antidiabetic potential. Patients should nonetheless advise their physicians of their use of these plants in light of potential interaction with commonly prescribed drugs, particularly oral hypoglycemic agents.

REFERENCES

1. Bramachari, H.D. and Augusti, K.T. Hypoglycemic agent from onions. *J. Pharm.*, 14, 617, 1962.
2. Augusti, K.T. Studies on the effects of a hypoglycemic principle from *Allium cepa* Linn. *Indian J. Med. Res.*, 61, 1066, 1973.
3. Jain, R.C. et al. Hypoglycemic action of onion and garlic. *Lancet*, 29, 1491, 1973.
4. Bramachari, H.D. and Augusti, K.T. Orally effective hypoglycemic agents froms plants. *J. Pharm. Pharmacol.*, 13, 128, 1961.
5. Roman–Ramos, R. et al. Antihyperglycemic effect of some edible plants. *J. Ethnopharmacol.*, 48, 25, 1995.
6. Jain, R.C. and Vyas, C.R. Hypoglycemia action of onion on rabbits. *Br. Med. J.*, 29, 730, 1974.
7. Mathew, P.T. and Augusti, K.T. Hypoglycemic effects of onion, *Allium cepa* Linn on diabetes mellitus — a preliminary report. *Int. J. Physiol. Pharmacol.*, 19, 213, 1975.
8. Sharma, K.K. et al. Antihyperglycemic effect of onion: effect on fasting blood sugar and induced hyperglycemia in man. *Indian J. Med. Res.*, 65, 422, 1977.
9. Kelkar, S.M. et al. Determination of antidiabetic activity in *Allium cepa* (onion) tissue cultures. *Indian J. Biochem. Biophys.*, 38, 277, 2001.
10. Campos, K.E. et al. Hypoglycemic and antioxidant effects of onion, *Allium cepa*: dietary onion addition, antioxidant activity and hypoglycemic effects on diabetic rats. *Int. J. Food Sci. Nutr.*, 54, 241, 2003.
11. Tjokroprawiro, A. et al. Metabolic effects of onion and green beans on diabetic patients. *Tohoku J. Exp. Med.*, 141 Suppl, 671, 1983.
12. Augusti, K.T. Effect on alloxan diabetes of allyl propyl disulphide obtained from onion. *Naturwissenschaften*, 61, 172, 1974.
13. Augusti, K.T. and Benaim, M.E. Effect of essential oil of onion (allyl-propyl disulphide) on blood glucose, free fatty acid and insulin levels of normal subjects. *Clin. Chim. Acta*, 60, 121, 1975.
14. Sheela, C.G. et al. Antidiabetic effects of onion and garlic sulfoxide amino acids in rats. *Planta Med.*, 61, 356, 1995.
15. Kumari, K. et al. Antidiabetic and hypolipidemic effects of S-methyl cysteine sulfoxide isolated from *Allium cepa* Linn. *Indian J. Biochem. Biophys.*, 32, 49, 1995.
16. Kumari, K. and Augusti, K.T. Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (*Allium cepa* Linn) as compared to standard drugs in alloxan diabetic rats. *Indian J. Exp. Biol.*, 40, 1005, 2002.
17. Bailey, C.J. and Day, C. Traditional plant medicines as treatments for diabetes. *Diabetes Care*, 12, 553, 1989.
18. Karawya, M.S. and Wahab, S.M.A. Diphenylamine, an antihyperglycemic agent from onion and tea. *J. Nat. Prod.*, 47, 775, 1984.

19. Galal, E.E. and Gawad, M.A. Antidiabetic activity of Egyptian onion *Allium cepa* extract. *J. Egypt Med. Assoc*., 48, Suppl:14, 1965.
20. Zacharias, N.T. et al. Hypoglycemic and hypolipidaemic effects of garlic in sucrose-fed rabbits. *Indian J. Physiol. Pharmacol*., 24, 151, 1980.
21. Patumraj, S. et al. Comparative effects of garlic and aspirin on diabetic cardiovascular complications. *Drug Delivery*, 7, 91, 2000.
22. Augusti, K.T. and Sheela, C.G. Antiperoxide effect of S-allyl cysteine sulfoxide, an insulin secretagogue, in diabetic rats. *Experientia*, 52, 115, 1996.
23. Sheela, C.G. and Augusti, K.T. Antidiabetic effects of S-allyl cysteine sulphoxide isolated from garlic *Allium sativum* Linn. *Indian J. Exp. Biol*., 30, 523, 1992.
24. Mathew, P.T. and Augusti, K.T. Studies on the effect of allicin (diallyl disulphide-oxide) on alloxan diabetes. I. Hypoglycemic action and enhancement of serum insulin effect and glycogen synthesis. *Indian J. Biochem. Biophys*., 10, 209, 1973.
25. Farva, D. et al. Effects of garlic oil on streptozotocin-diabetic rats maintained on normal and high-fat diets. *Indian J. Biochem. Biophys*., 23, 24, 1986.
26. Begum, H. and Bari, M.A. Effect of garlic oil on the pancreas of experimental diabetes in guinea pigs. *Bangladesh Med. Res. Counc. Bull*., 11, 64, 1985.
27. Huang, C.N. et al. Antioxidative and antiglycative effects of six organosulfur compounds in low-density lipoprotein and plasma. *J. Agric. Food Chem*., 52, 3674, 2004.
28. Sitprija, S. et al. Garlic and diabetes mellitus phase II clinical trial. *J. Med. Assoc. Thai*., 70 Suppl 2, 223, 1987.
29. Agarwal, O.P. Prevention of atherromatous heart disease. *Angiology*, 36, 485, 1985.
30. Ghannam, N. et al. The antidiabetic activity of aloes: preliminary clinical and experimental observations. *Horm. Res*., 24, 288, 1986.
31. Vogler, B.K. *Aloe vera*: a systematic review of its clinical effectiveness. *Br. J. Gen. Pract*., October, 823, 1999.
32. Rajasekaran, S., et al. Hypoglycemic effect of *Aloe vera* gel on streptozotocin-induced diabetes in experimental rats. *J. Med. Food*, 7, 61, 2004.
33. Ajabnoor, M.A. Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. *J. Ethnopharmacol*., 28, 215, 1990.
34. Hikino, H. et al. Isolation and hypoglycemic activity of arborans A and B, glycans of *Aloe arborescens* var. natalensis leaves. *Int. J. Crude Drug Res*., 24, 183, 1986.
35. Okyar, A. et al. Effect of *Aloe vera* leaves on blood glucose level in type I and type II rat models. *Phytother. Res*., 15, 157, 2001.
36. Davis, R.H. et al. *Aloe vera*: A natural approach for treating wounds, edema and pain in diabetes. *J. Am. Pod. Med. Assoc*., 78, 60, 1988.
37. Davis, R.H. and Maro, N.P. *Aloe vera* and gibberellin. Anti-inflammatory activity in diabetes. *J. Am. Pod. Med. Assoc*., 79, 24, 1989.
38. Chithra, P. et al. Influence of *Aloe vera* on the healing on dermal wounds in diabetic rats. *J. Ethnopharmacol*., 59, 195, 1998.
39. Al-Waili, N.S.D. Treatment of diabetes mellitus by *Artemisia herba-alba* extract: preliminary study. *Clin. Exp. Pharmacol. Physiol*., 13, 569, 1986.
40. Al-Waili, N.S. *Artemisia herba-alba* Asso. in diabetes mellitus. *Clin. Exp. Pharmacol. Physiol*., 15, 497, 1988.
41. Twaij, H.A.A. and Al-Badr, A.A. Hypoglycemic activity of *Artemisia herba-alba*. *J. Ethnopharmacol*., 24, 126, 1988.
42. Al-Khazraji, S.M. et al. Hypoglycemic effect of *Artemisia herba-alba*. I. Effect of different parts and influence of the solvent on hypoglycemic activity. *J. Ethnopharmacol*., 40, 163, 1993.
43. Korkmaz, H. and Gurdal, A. Effect of *Artemisia santonicum* L. on blood glucose in normal and alloxan-induced diabetic rabbits. *Phytother. Res*., 16, 675, 2002.
44. Marrif, H.I. et al. Some pharmacological studies on *Artemisia herba-alba* (Asso.) in rabbits and mice. *J. Ethnopharmacol*., 49, 51, 1995.
45. Kalderon, B. et al. Characterization of stages in development of obesity–diabetes syndrome in sand rat (*Psammomys obesus*). *Diabetes*, 35, 717, 1986.

46. Aharonson, Z. et al. Hypoglycemic effect of the salt bush (*Atriplex halimus*) — a feeding source of the sand rat (*Psammomys obesus*). *Diabetologia*, 5, 379, 1969.
47. Shani, J. et al. Insulin-potentiating effect of salt bush (*Atriplex halimus*) ashes. *Isr. J. Med. Sci.*, 8, 757, 1972.
48. Mertz, W. et al. *In vitro* pontentiation of insulin by ash from saltbush (*Atriplex halimus*). *Arch. Int. Pharmacodyn.*, 206, 121, 1973.
49. Schroeder, H.A. Chromium deficiency in rats: a syndrome simulating diabetes mellitus with retarded growth. *J. Nutr.*, 88, 439, 1996.
50. Ravina, A. et al. Clinical use of the trace element chromium (III) in the treatment of diabetes mellitus. *J. Trace Elem. Exp. Med.*, 8, 183, 1995.
51. Adler, J.H. et al. The diabetic response of weanling sand rats (*Psammomys obesus*) to diets containing different concentrations of salt bush (*Atriplex halimus*). *Diabetes Res.*, 3, 169, 1986.
52. Helmi, R. et al. Preliminary report on the hypoglycemic effect of *Trifolium alexandrinum* and *Lupinus termis* in animal and man. *J. Egypt. Med. Assoc.*, 52, 538, 1969.
53. Eskander, E.F. and Won Jun, H. Hypoglycemic and hyperinsulinemic effects of some Egyptian herbs used for the treatment of diabetes mellitus (type II) in rats. *Egypt. J. Pharm. Sci.*, 36, 331, 1995.
54. Shani–Mishkinsky, J. et al. Hypoglycemic effect of *Trigonella foenum graecum* and *Lupinus termis* (leguminosae) seeds and their major alkaloids in alloxan-diabetic and normal rats. *Arch. Int. Pharmacodyn. Ther.*, 210, 27, 1974.
55. Riyad, M.A. et al. Effect of fenugreek and lupine seeds on the development of experimental diabetes in rats. *Planta Med.*, 54, 286, 1988.
56. Sheweita, S.A. et al. Effect of some hypoglycemic herbs on the activity of phase I and II drug-metabolizing enzymes in alloxan-induced diabetic rats. *Toxicology*, 174, 131, 2002.
57. Mansour, H.A. et al. Biochemical study on the effects of some Egyptian herbs in alloxan-induced diabetic rats. *Toxicology*, 170, 221, 2002.
58. Sheweita, S.A. et al. Effect of some hypoglycemic herbs on the activity of phase I and II drug-metabolizing enzymes in alloxan-induced diabetic rats. *Toxicology*, 174, 131, 2002.
59. Feldman, N. et al. Enrichment of an Israeli ethnic food with fibres and their effects on the glycemic and insulinemic responses in subjects with non-insulin-dependent diabetes mellitus. *Br. J. Nutr.*, 74, 681, 1995.
60. Sharma, V.N. et al. Some observations on hypoglycemic activity of *Momordica charantia*. *Indian J. Med. Res.*, 48, 471, 1960.
61. Gupta, S.S. and Seth, C.B. Effect of *Momordica charantia* Linn (Karela) on glucose tolerance in albino rats. *J. Indian Med. Assoc.*, 39, 581, 1962.
62. Jose, M.P. et al. Effect of selected indigenous drug on the blood sugar level in dogs. *Indian J. Pharmacol.*, 8, 86, 1976.
63. Vimla, D.M. et al. Hypoglycemic activity of the leaves of *Momordica charantia*. *Indian J. Pharmacol.*, 39, 167, 1977.
64. Kedar, P. and Chakrabarti, C.H. Effects of bittergourd (*Momordica charantia*) seed and glibenclamide in streptozotocin-induced diabetes mellitus. *Indian J. Exp. Biol.*, 20, 232, 1982.
65. Ali, L. et al. Studies on hypoglycemic effects of fruit pulp, seed and whole plant of *Momordica charantia* on normal and diabetic rats. *Planta Med.*, 59, 408, 1993.
66. Sitasawad, S.L. et al. Role of bittergourd fruit juice in STZ-induced diabetic state *in vivo* and *in vitro*. *J. Ethnopharmacol.*, 73, 71, 2000.
67. Virdi, J. et al. Antihyperglycemic effects of three extracts from *Momordica charantia*. *J. Ethnopharmacol.*, 88, 107, 2003.
68. Singh, N. et al. Effects of long term feeding of acetone extract of *Momordica charantia* (whole fruit powder) on alloxan-diabetic albino rats. *Indian J. Physiol. Pharmacol.*, 33, 97, 1989.
69. Rathi, S.S. et al. Prevention of experimental diabetic cataract by Indian Ayurvedic plant extracts. *Phytother. Res.*, 16, 774, 2002.
70. Rathi, S.S. et al. The effect of *Momordica charantia* and *Mucuna pruriens* in experimental diabetes and their effect on key metabolic enzymes involved in carbohydrate metabolism. *Phytother. Res.*, 16, 236, 2002.
71. Chatterjee, K.P. On the presence of an antidiabetic principle in *Momordica charantia*. *Indian J. Physiol. Pharmacol.*, 52, 240, 1963.

72. Sarkar, S. et al. Demonstration of the hypoglycemic action of *Momordica charantia* in a validated animal model of diabetes. *Pharmacol. Res.*, 33, 1, 1996.
73. Day, C. et al. Hypoglycemic effect of *Momordica charantia* extracts. *Planta Med.*, 56, 426, 1990.
74. Ahmad, N. et al. Effect of *Momordica charantia* (karela) extracts on fasting and postprandial serum glucose levels in NIDDM patients. *Bangladesh Med. Res. Counc. Bull.*, 25, 11, 1999.
75. Leatherdale, B.A. et al. Improvement in glucose tolerance due to *Momordica charantia* (karela). *Br. Med. J.*, 282, 1823, 1981.
76. Welihinda, J. et al. Effect of *Momordica charantia* on the glucose tolerance in maturity onset diabetes. J. Ethnopharmacol., 17, 277, 1986.
77. John, A.J. et al. Evaluation of the efficacy of bitter gourd (*Momordica charantia*) as an oral hypoglycemic agent — a randomized controlled clinical trial. *Indian J. Physiol. Pharmacol.*, 47, 363, 2003.
78. Qijun, L. et al. Influence of balsam pear (the fruit of *Momordica charantia* L.) on blood sugar level. *J. Traditional Chin. Med.*, 5, 99, 1985.
79. Khanna, P. et al. Hypoglycemic activity of polypeptide p from a plant source. *J. Nat. Prod.*, 44, 648, 1981.
80. Lolitkar, M.M. and Rao, M.R.R. Pharmacology of a hypoglycemic principle isolated from the fruits of *Eugenia jambolana* Linn. *Indian J. Pharm.*, 28, 129, 1966.
81. Matsuda, H. et al. Antidiabetic principles of natural medicines. III. Structure-related inhibitory activity and action mode of oleanolic acid glycosides on hypoglycemic activity. *Chem. Pharm. Bull.*, 46, 1399, 1998.
82. Rotshteyn, Y. and Zito, S.W. Application of modified *in vitro* screening procedure for identifying herbals possessing sulfonylurea-like activity. *J. Ethnopharmacol.*, 93, 337, 2004.
83. Platel, K. and Srinivasan, K. Plant foods in the management of diabetes mellitus: vegetables as potential hypoglycemic agents. *Nahrung*, 41, 68, 1997.
84. Ahmed, I. et al. Effect of *Momordica charantia* fruit juice on islet morphology in the pancreas of the streptozotocin diabetic rat. *Diabetes Res. Clin. Pract.*, 40, 145, 1998.
85. Shibib, B.A. et al. Hypoglycemic activity of *Coccinia indica* and *Momordica charantia* in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. *Biochem. J.*, 292 (pt 1), 267, 1993.
86. Miura, T. et al. Hypoglycemic activity of the fruit of the *Momordica charantia* in type 2 diabetic mice. *J. Nutr. Sci. Vit.*, 47, 340, 2001.
87. McCarty, M.F. Does bitter melon contain an activator of AMP-activated kinase? *Med. Hypotheses*, 63, 340, 2004.
88. El Tahir, K.E. et al. The cardiovascular actions of the volatile oil of the black seed (*Nigella sativa*) in rats: elucidation of the mechanism of action. *Gen. Pharmacol.*, 24, 1123, 1993.
89. Zaoui, A. et al. Effets diurétiques et hypotenseurs de *Nigella sativa* chez le rat spontanément hypertendu. *Thérapie*, 55, 379, 2000.
90. Haq, A. et al. Immunomodulatory effect of *Nigella sativa* proteins fractionated by ion exchange chromatography. *Int. J. Immunopharmacol.*, 21, 283, 1999.
91. Chakravarty, N. Inhibition of histamine release from mast cells by nigellone. *Ann. Allergy*, 70, 237, 1993.
92. Swamy, S.M. and Tan, B.K. Cytotoxic and immunomodulatory effects of ethanolic extract of *Nigella sativa* L. seeds. *J. Ethnopharmacol.*, 70, 1, 2000.
93. Daba, M.H. and Abdel–Rahman, M.S. Hepatoprotective activity of thymoquinone in isolated rat hepatocytes. *Toxicol. Lett.*, 95, 23, 1998.
94. El-Dakhakhny, M. et al. *Nigella sativa* L. oil protects against induced hepatotoxicity and improves serum lipid profile in rats. *Arzneimittelforschung*, 50, 832, 2000.
95. Mahmoud, M.R. et al. The effect of *Nigella sativa* oil against the liver damage induced by *Shistosoma mansoni* infection in mice. *J. Ethnopharmacol.*, 79, 1, 2002.
96. Al-Awadi, F.M. et al. On the mechanism of the hypoglycemic effect of a plant extract. *Diabetologia*, 28, 432, 1985.
97. Al-Awadi, F. et al. The effect of a plants mixture extract on liver gluconeogenesis in streptozotocin-induced diabetic rats. *Diabetes Res.*, 18, 168, 1991.

98. Al-Awadi, F.M. and Gumaa, K.A. Studies on the activity of the individual plants of an antidiabetic plant mixture. *Acta Diabetol. Lat.*, 24, 37, 1987.
99. Labhal, A. et al. Action antiobésité et hypocholestérolémiante de *Nigella sativa* chez le rat des sables. *Caducée*, 27, 26, 1997.
100. Labhal, A. et al. Propriétés antidiabétiques des graines de *Nigella sativa* chez le merione shawi obèse et diabétique. *Espérance Méd.*, 47, 72, 1999.
101. Meral, I. et al. Effect of *Nigella sativa* on glucose concentration, lipid peroxidation, antioxidant defense system and liver damage in experimentally induced diabetic rabbits. *J. Vet. Med. A Physiol. Pathol. Clin. Med.*, 48, 593, 2001.
102. Al-Hader, A. et al. Hypoglycemic effects of the volatile oil of *Nigella sativa* seeds. *Int. J. Pharmacognosy*, 31, 96, 1993.
103. Settaf, A. et al. Volatile oil of *Nigella sativa* lowers plasma lipids and insulin in obese hyperlipidemic sand rats (*Psammomys obesus*). *6th Int. Congr. Ethnopharmacol.*, P2A/36, 2000.
104. Fararh, K.M. et al. Isulinotropic properties of *Nigella sativa* oil in streptozotocin plus nicotinamide diabetic hamster. *Res. Vet. Sci.*, 73, 279, 2002.
105. Kanter, M. et al. Partial regeneration/proliferation of the beta-cells in the islets of Langerhans by *Nigella sativa* L. in streptozotocin-induced diabetic rats. *Tohoku J. Exp. Med.*, 201, 213, 2003.
106. Kanter, M. et al. Effects of *Nigella sativa* on oxidative stress and beta-cell damage in streptozotocin-induced diabetic rats. *Anat. Rec.*, 279A, 685, 2004.
107. Rchid, H. et al. *Nigella sativa* seed extracts enhance glucose-induced insulin release from rat-isolated Langerhans islets. *Fundam. Clin. Pharmacol.*, 18, 525, 2004.
108. El-Dakhakhny, M. et al. The hypoglycemic effect of *Nigella sativa* oil is mediated by extrapancreatic actions. *Planta Med.*, 68, 465, 2002.
109. Fararh, K.M. et al. Mechanisms of the hypoglycemic and immunopotentiating effects of *Nigella sativa* L. oil in streptozotocin-induced diabetic hamsters. *Res. Vet. Sci.*, 77, 123, 2004.
110. Le, P.M. et al. Lipid-lowering and insulin-sensitizing actions of *Nigella sativa* petroleum ether extract in the rat. *J. Ethnopharmacol.*, 94, 251, 2004.
111. Zaoui, A. et al. Effects of *Nigella sativa* fixed oil on blood homeostasis in rat. *J. Ethnopharmacol.*, 79, 23, 2002.
112. Tennekoon, K.H. et al. Possible hepatotoxicity of *Nigella sativa* seeds and *Dregea volubilis* leaves. *J. Ethnopharmacol.*, 31, 283, 1991.
113. Zaoui, A. et al. Acute and chronic toxicity of *Nigella sativa* fixed oil. *Phytomedicine*, 9, 69, 2002.
114. Gonzalez, M. et al. Hypoglycemic activity of olive leaf. *Planta Med.*, 58, 513, 1992.
115. Trovato, A. et al. Hypoglycemic activity of different extracts of *Olea europaea* L. in the rats. *Plant Med. Phytother.*, XXVI, 300, 1993.
116. Bennani–Kabchi, N. et al. Effects of *Olea europea* var. oleaster leaves in hypercholesterolemic insulin-resistant sand rats. *Thérapie*, 54, 717, 1999.
117. Bennani–Kabchi, N. et al. Effect thérapetique des feuilles d'*Olea europea* var. oleaster sur le métabolisme glucido-lipidique chez le rat des sables (*Psammomys obesus*) obèse prédiabétique. *Ann. Pharm. Fr.*, 58, 271, 2000.
118. Mishkinsky, J. et al. Hypoglycemic effect of *Poterium spinosum* L (Rosaceae). *Arch. Int. Pharmacodyn.*, 161, 306, 1966.
119. Shani, J. et al. Fluctuations in the hypoglycemic effect of *Poterium spinosum* L (Rosaceae). *Arch. Int. Pharmacodyn.*, 185, 344, 1970.
120. Kanter, Y. et al. Postprandial glucose response to extracts of *Poterium spinosum* in normal and diabetic rats. In: *Lessons from Animal Diabetes*, Shafrir, E. and Renold, A.E., Eds., London: Libbey, 1984, 627.
121. Wasfi, I.A. et al. The effect of *Rhazya strica* on glucose homeostasis in normal and streptozotocin-diabetic rats. *J. Ethnopharmacol.*, 43, 141, 1994.
122. Ali, B. The effect on plasma glucose, insulin and glucagon levels of treatment of diabetic rats with the medicinal plant *Rhazya stricta* and with glibenclamide, alone and in combination. *J. Pharm. Pharmacol.*, 49, 1003, 1997.
123. Tanira, M.O. et al. Some pharmacologic and toxicologic studies on *Rhazya stricta* decne in rats, mice and rabbits. *Gen. Pharmacol.*, 27, 1261, 1996.
124. Mossa, J.S. A study on the crude antidiabetic drugs used in Arabian folk medicine. *Int. J. Crude Drug Res.*, 23, 137, 2002.

125. Fournier, F. *Plantes Médicinales et Vénéneuses de France III*, Edition Lechevalier, 1948.
126. Nadakarnis, K.M. *Indian Materia Med.*, Bombay: Popular Book Depot, 1954.
127. Al-Habori, M. and Raman, A. Antidiabetic and hypocholesterolemic effects of fenugreek. *Phytother. Res.*, 12, 233, 1998.
128. Sauvaire, Y. et al. Chemistry and pharmacology of fenugreek. In: *Functional Foods: Herbs, Botanicals and Teas*, Mazza, G.A.O. and Lancaster, B.D., Eds., PA: Technomic Press, 2000, 107.
129. Blumenthal, M. et al. Therapeutic guide to herbal medicines. *The Complete German Commission E Monographs*. Boston: Integrative Medicine Communications, 1998, 625.
130. Sharma, R.D. et al. Toxicological evaluation of fenugreek seed: a long-term feeding experiment in diabetic patients. *Phytother. Res.*, 10, 519, 1996.
131. Raghuram, T.C. et al. Effect of fenugreek seeds on intravenous glucose disposition in non-insulin dependent diabetic patients. *Phytother. Res.*, 8, 83, 1994.
132. Madar, Z. et al. Glucose-lowering effect of fenugreek in non-insulin dependent diabetics. *Eur. J. Clin. Nutr.*, 42, 51, 1988.
133. Sharma, R.D. et al. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. *Eur. J. Clin. Nutr.*, 44, 301, 1990.
134. Bordia, A. et al. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenum-graecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. *Prostaglandins Leukot. Essent. Fatty Acids*, 56, 379, 1997.
135. Gupta, A. et al. Effect of *Trigonella foenum-graecum* (fenugreek) on glycemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. *J. Assoc. Physicians India*, 49, 1057, 2001.
136. Vats, V. et al. Effect of *T. foenum-graecum* on glycogen content of tissues and the key enzymes of carbohydrate metabolism. *J. Ethnopharmacol.*, 85, 237, 2003.
137. Ajabnoor, M.A. and Tilmisany, A.K. Effect of *Trigonella foenum graceum* on blood glucose levels in normal and alloxan-diabetic mice. *J. Ethnopharmacol.*, 22, 45, 1988.
138. Raju, J. et al. Effect of antidiabetic compounds on glyoxalase I activity in experimental diabetic rat liver. *Indian J. Exp. Biol.*, 37, 193, 1999.
139. Yadav, U.C. et al. Effects of sodium-orthovanadate and *Trigonella foenum-graecum* seeds on hepatic and renal lipogenic enzymes and lipid profile during alloxan diabetes. *J. Biosci.*, 29, 81, 2004.
140. Puri, D. et al. Mechanism of action of a hypoglycemic principle isolated from fenugreek seeds. *Indian J. Physiol. Pharmacol.*, 46, 457, 2002.
141. Raju, J. et al. *Trigonella foenum-graecum* (fenugreek) seed powder improves glucose homeostasis in alloxan-diabetic rat tissues by reversing the altered glycolytic, glyconeogenic and lipogenic enzymes. *Mol. Cell. Biochem.*, 224, 45, 2001.
142. Ali, L. et al. Characterization of the hypoglycemic effects of *Trigonella foenum graecum* seed. *Planta Med.*, 61, 358, 1995.
143. Madar, Z. Fenugreek (*Trigonella foemum-graecum*) as a means of reducing postprandial glucose level in diabetic rats. *Nutr. Rep. Int.*, 29, 1267–1273, 1984.
144. Al-Habori, M. et al. *In vitro* effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase. *A. Int. J. Exp. Diab. Res.*, 2, 91, 2001.
145. Amin, R. et al. Effect of *Trigonella foenum graecum* on intestinal absorption. *Diabetes*, 36, 211A, 1987.
146. Platel, K. and Srinivasan, K. Influence of dietary spices or their active principles on digestive enzymes of small intestinal mucosa in rats. *Int. J. Food Sci. Nutr.*, 47, 55, 1996.
147. Marles, R.J. and Farnsworth, N.R. Antidiabetic plants and their active constituents. *Phytomedicine*, 2, 137, 1995.
148. Petit, P. et al. Steroid saponins from fenugreek seeds: extraction, purification and pharmacological investigation on feeding behavior and plasma cholesterol. *Steroids*, 60, 674, 1995.
149. Ghosal, S. et al. Extractives of *Trigonella* 1. Fenugreekine, a new steroidal sapogenin-peptide ester of *Trigonella foenum graecum. Phytochemistry*, 13, 1974.
150. Nutrition, N.I.O. Annual report. Hyderabad, India: Indian Council of Medical Research, 1987, p. 11.
151. Madar, Z. and Stark, A.H. New legume sources as therapeutic agents. *Br. J. Nutr.*, 88 Suppl 3, S287, 2002.

152. Sauvaire, Y. et al. Steroid saponins from fenugreek and some of their biological properties. *Adv. Exp. Med. Biol.*, 405, 37, 1996.
153. Sauvaire, Y. et al. 4-hydroxyisoleucine: a novel amino acid potentiator of insulin secretion. *Diabetes*, 47, 206, 1998.
154. Broca, C. et al. 4-hydroxyisoleucine: experimental evidence of its insulinotropic and antidiabetic properties. *Am. J. Physiol.*, 277, E617, 1999.
155. Broca, C. et al. 4-Hydroxyisoleucine: effects of synthetic and natural analogues on insulin secretion. *Eur. J. Pharmacol.*, 390, 339, 2000.
156. Broca, C. et al. Insulinotropic agent ID-1101 (4-hydroxyisoleucine) activates insulin signaling in rat. *Am. J. Physiol. Endocrinol. Metab.*, 287, E463, 2004.
157. Abdel–Barry, J.A. et al. Hypoglycemic and antihyperglycemic effects of *Trigonella foenum-graecum* leaf in normal and alloxan induced diabetic rats. *J. Ethnopharmacol.*, 58, 149, 1997.
158. Devi, B.A. et al. Supplementation of fenugreek leaves to diabetic rats. Effect on carbohydrate metabolic enzymes in diabetic liver and kidney. *Phytother. Res.*, 17, 1231, 2003.
159. Annida, B. and Stanely Mainzen Prince, P. Supplementation of fenugreek leaves lower lipid profile in streptozotocin-induced diabetic rats. *J. Med. Food*, 7, 153, 2004.
160. Jaouhari, J.T. et al. Etude de la toxicité aiguë de dix plantes marocaines réputées hypoglycémiantes. *Thérapie*, 54, 701, 1999.
161. Skim, F. et al. Pharmacological studies of two antidiabetic plants: *Globularia alypym* and *Zygophyllum gaetulum*. *Thérapie*, 54, 711, 1999.
162. Jaouhari, J.T. et al. The hypoglycemic activity of *Zygophyllum gaetulum* extracts in alloxan-induced hyperglycemic rats. *J. Ethnopharmacol.*, 69, 17, 2000.
163. Jaouhari, J.T. et al. Hypoglycemic response to *Zygophyllum gaetulum* extracts in patients with non insulin-dependent diabetes mellitus. *J. Ethnopharmacol.*, 64, 211, 1999.
164. Ivorra, M.D. et al. A review of natural products and plants as potential antidiabetic drugs. *J. Ethnopharmacol.*, 27, 243, 1989.
165. Laurens, et al. Activité antidiabétique d'extrait de feuille de *Poupartia birrea* (Hochst) Aubr. *Ann. Pharm. Fr.*, 42, 547, 1984.
166. Laurens, et al. Activité inhibitrice de l'aldose réductase d'extrait de feuille de *Poupartia birrea* (Hochst) Aubr. *Ann. Pharm. Fr.*, 43, 23, 1985.
167. Sayed, M.D. Traditional medicine in health care. *J. Ethnopharmacol.*, 2, 19, 1980.
168. Yaniv, Z. et al. Plants used for the treatment of diabetes in Israel. *J. Ethnopharmacol.*, 19, 145, 1987.
169. Ziyyat, A. et al. Phytotherapy of hypertension and diabetes in oriental Morocco. *J. Ethnopharmacol.*, 58, 45, 1997.
170. Jouad, H. et al. Ethnobotanical survey of medicinal plants used for the treatment of diabetes, cardiac and renal diseases in the North centre region of Morocc (Fes-Boulemane). *J. Ethnopharmacol.*, 77, 175, 2001.
171. El-Fiky, F.K. et al. Effect of *Luffa aegyptiaca* (seeds) and *Carissa edulis* (leaves) extracts on blood glucose levels of normal and streptozotocin diabetic rats. *J. Ethnopharmacol.*, 50, 43, 1996.
172. Day, C. and Bailey, C.J. Hypoglycemic agents from traditional plant treatments for diabetes. *Int. Ind. Biotech.*, 8, 5, 1988.
173. Shabana, M.M. et al. Study into wild Egyptian plants of potential medicinal activity. Ninth communication: hypoglycemic activity of some selected plants in normal fasting and alloxanised rats. *Arch. Exp. Vet. Med. Leipzig*, 44, 389, 1990.
174. Ubillas, R.P. et al. Antihyperglycemic acetylenic glucosides from *Bidens pilosa*. *Planta Med.*, 66, 82, 2000.
175. Sarg, M. et al. Constituents and biological activity of *Bidens pilosa* L. grown in Egypt. *Acta Pharm. Hung.*, 61, 317, 1991.
176. Kamel, M.S. et al. Studies on *Balanites aegyptiaca* fruits, an antidiabetic Egyptian folk medicine. *Chem. Pharm. Bull.*, 39, 1229, 1991.
177. Rahman, A.U. and Zaman, K. Medicinal plants with hypoglycemic activity. *J. Ethnopharmacol.*, 26, 1, 1989.
178. Sabu, M.C. and Subburaju, T. Effect of *Cassia auriculata* Linn. on serum glucose level, glucose utilization by isolated rat hemidiaphragm. *J. Ethnopharmacol.*, 80, 203, 2002.

179. Lamba, S.S. et al. Phytochemicals as potential hypoglycemic agents. In: *Studies in Natural Products Chemistry*, Atta-Ur-Rahman, Ed. Amsterdam: Elsevier Science, 2000, p. 457.
180. Jouad, H. et al. Hypoglycemic effect of *Spergularia purpurea* in normal and streptozotocin-induced diabetic rats. *J. Ethnopharmacol.*, 71, 169, 2000.
181. Handa, S.S. et al. Hypoglycemic plants. A review. *Fitoterapia*, LX, 195, 1989.
182. Ajabnoor, M.A. et al. Antidiabetic activity of *Hammada salicornica*. *Fitoterapia*, LV, 107, 1984.
183. Bennani–Kabchi, N. et al. Effect of *Suaeda fruticosa* aqueous extract in the hypercholesterolemic and insulin-resistant sand rat. *Thérapie*, 54, 725, 1999.
184. Benwahhoud, M. et al. Hypoglycemic effect of *Suaeda fructicosa* in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.*, 76, 35, 2001.
185. Ammar, N.M. et al. The hypoglycemic effect of different extracts of *Ambrosia maritime* L. Compositae. *Egypt. J. Pharm. Sci.*, 36, 107, 1995.
186. Boulos, L. *Medicinal Plants of North Africa*. Michigan: Reference Publication Inc., 1983, 217.
187. Eskander, E.F. et al. Hypoglycemic effect of a herbal formulation in alloxan-induced diabetic rats. *Egypt. J. Pharm. Sci.*, 36, 253, 1995.
188. El-Missiry, M.A. and El-Gindy, A.M. Amelioration of alloxan induced diabetes mellitus and oxidative stress in rats by oil of *Eruca sativa*. *Ann. Nutr. Metab.*, 44, 97, 2000.
189. Abdel-Hassan, I.A. et al. The hypoglycemic and antihyperglycemic effect of *Citrullus colocynthis* fruit aqueous in normal and alloxan diabetic rabbits. *J. Ethnopharmacol.*, 71, 325, 2000.
190. Nmila, R. et al. Insulinotropic effect of *Citrullus colocynthis* fruit extracts. *Planta Med.*, 66, 418, 2000.
191. Adamson, I. et al. Erythrocyte membrane ATPases in diabetes: effect of dikanut (*Irvingia gabonensis*). *Enzyme*, 36, 212, 1986.
192. Omoruyi, F. and Adamson, I. Digestive and hepatic enzymes in streptozotocin induced diabetic fed supplements of dikanut (*Irvingia gabonensis*) and cellulose. *Ann. Nutr. Metab.*, 37, 14, 1993.
193. Bennaghmouch, L. et al. Etude pharmacologique d'*Ajuga iva*. *Ann. Pharm. Fr.*, 59, 284, 2001.
194. Hilaly, J.E. and Lyoussi, B. Hypoglycemic effect of the lyophilized aqueous extract of *Ajuga iva* in normal and streptozotocin diabetic rats. *J. Ethnopharmacol.*, 80, 109, 2002.
195. Al-Hader, A.A. et al. Hyperglycemic and insulin release inhibitory effects of *Rosmarinus officinalis*. *J. Ethnopharmacol.*, 43, 217, 1994.
196. Erenmemisoglu, A. et al. Effect of a *Rosmarinus officinalis* leaf extract on plasma glucose levels in normoglycemic and diabetic mice. *Pharmazie*, 52, 645, 1997.
197. Perfumi, M. et al. Hypoglycemic activity of *Salvia fructicosa* Mill. from Cyprus. *J. Ethnopharmacol.*, 34, 135, 1991.
198. Gharaibeh, M.N. et al. Hypoglycemic effects of *Teucrium polium*. *J. Ethnopharmacol.*, 24, 93, 1988.
199. Wassel, G.M. et al. Phytochemical examination and biological studies of *Acacia nilotia* L. Wild and *Acacia farnesiana* L. Willd growing in Egypt. *Egypt. J. Pharm. Sci.*, 33, 327, 1992.
200. Gray, A.M. and Flatt, P.R. Antihyperglycemic actions of *Eucalyptus globules* (Eucalyptus) are associated with pancreatic and extrapancreatic effects in mice. *J. Nutr.*, 128, 2319, 1998.
201. Swanston–Flatt, S.K. et al. Traditional plant treatment for diabetes. Studies in normal and streptozotocin-diabetic mice. *Diabetologia*, 33, 462, 1990.
202. Elfelliah, M.S. et al. Antihyperglycemic effect of an extract of *Myrtus communis* in streptozotocin-induced diabetes in mice. *J. Ethnopharmacol.*, 11, 275, 1984.
203. Lemela, M. et al. Effects of *Lythrum salicaria* in normoglycemic rats. *J. Ethnopharmacol.*, 14, 83, 1985.
204. Glombitza, K.W. et al. Hypoglycemic and antihyperglycemic effects of *Zizyphus spina-christi* in rats. *Planta Med.*, 60, 244, 1994.

13 Australian and New Zealand Plants with Antidiabetic Properties

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CONTENTS

INTRODUCTION

The present landmasses of Australia and New Zealand had their beginning in the fragmentation of the supercontinent Gondwanaland. The New Zealand archipelago of islands was cast adrift 80 million years ago, and Australia began its separation from India, Africa, and Antarctica 65 million years ago. During the long period of isolation of these landmasses, the great changes after that in the climate and soil saw extensive evolutionary divergence of the biota. As a consequence, the distinctive flora and fauna that developed have many unique features and a high level of endemism.[1]

In Australia, the flora evolved and diversified with little interference from immigrant species. As the island-continent maneuvered to its present position, the principal entry from other landmasses was across the tropical archipelago to the north. The effect of this limited access can be noted by the low degree of mixing of the flora with that of Asia. Some Australian groups have dispersed into Asia, e.g., *Ptilotis* (Amaranthaceae) into Indonesia and *Eucalyptus* (Myrtaceae) into the Philippines, and some tropical plant groups have moved into northern Australia. The total flora of

Australia is estimated to contain up to 25,000 species of vascular plants, 85% of which are endemic. It contains few deciduous trees, relatively few conifers, and, in the arid zone, no large succulents.[2]

Despite its small area, New Zealand comprises a distinct botanic region. The flora is not rich in species of higher plants because most of these developed on the larger continents millions of years after the formation of New Zealand. However, the vegetation is special because a high proportion of species — 85% of seed plants and 40% of ferns — is endemic. Interestingly, about 75% of New Zealand's seed plants and 85% of ferns are related to Australian genera.

INDIGENOUS PEOPLE

Australia

About 50,000 years ago, the unique and remote Australian environment became the home for the Australian Aboriginal people, a group of hunters, gatherers, and fishers that came from what is now Southeast Asia. Over time, they spread across and occupied all parts of the continent at varying densities. Australia covers a vast range of climatic regions and botanical environments: from tropical coast to rainforest, from open scrub to wet forest, from woodland to desert, and from temperate riverine to snowy alpine mountains. Most of the Aboriginal communities congregated around the more fertile coastal region, but a few occupied desert areas in central Australia. Each community (clan or language group) hunted and lived in a defined area, of which they had detailed ecological knowledge, defined by tribal law or "dreaming." These territories could be as vast as 100,000 km^2 in the desert regions or as small as 500 km^2 in the coastal country.[3]

The unique flora encountered by these ancient settlers would have posed considerable challenges. Plant materials that were edible in the raw state or could be made palatable by roasting had to be selected. In a long and hazardous process, plants with curative properties were identified, and preparation, mode of administration, and dosage of the medicine were determined. The information accumulated on useful species was transmitted orally to successive generations. Over the millennia, the Aboriginal people became astute and competent botanists with intimate knowledge of the flora that played a significant part, as food and medicine, in their survival.

New Zealand

The first human settlers in New Zealand were the Maori people who arrived from Polynesia between A.D. 800 and 1000. Although they have had much less time than the Australian Aboriginals to develop a phytopharmacopoeia, there is little doubt that they relied on indigenous plants for medicinal purposes.[2]

ABORIGINAL HEALTH

From descriptions available, it appears that the Australian Aboriginals encountered by European explorers were lean and physically fit. It was reported that they were "well formed; their limbs are straight and muscular" and that "they are capable of undergoing considerable fatigue and deprivation in their wanderings."[4] Observers commented on their great dexterity and acute eyesight. An investigation by Cleland in 1928 of all diseases recorded for Australian Aboriginals at the time included only one case of diabetes. In an update of this work in 1962, eight cases were reported.[5] As recently as the early 1960s, a study of a group of nomadic Aboriginals from the Great Sandy Desert showed them to have low body mass index with no evidence of chronic diseases.[6] Contagious and infectious diseases such as cholera, smallpox, tuberculosis, measles, and mumps were unknown until the arrival of European settlers.

Attitude to Illness

In Aboriginal society, supernatural forces were considered to be responsible for almost every event. Throughout Australia, Aboriginal people believed that serious illness and death were caused by spirits and that it was important to treat internal complaints by spiritual means through the agency of "medicine men." Therefore, it is not surprising to learn that only approximately 10% of the medicines that they prepared and used were meant to be taken for internal disorders.[7] Very few plants were used for specific purposes by nomadic groups; it was better to concentrate on plants that were relatively readily available and had a wide spectrum of curative properties.

On the other hand, the diverse variety of plant food available would have included species that were also "medicinal" in nature, i.e., medicinal food. In this context, it is interesting to note that a list of 248 food plants used by Aborigines contains 25% (53 species, identical or related) that have also been used as medicinal plants.[8]

Diabetes

It is not known whether Aboriginal people recognized diabetes as an individual disorder. Indeed, a number of symptoms — frequent urination, unusual thirst, fatigue, and abdominal cramps — might have been regarded as a general "ill-feeling" and attributed to "bad spirits." From different studies, it appears that although insulin-dependent diabetes mellitus (IDDM; type 1) occurs in Aboriginal populations, it is relatively less common than in non-Aboriginal groups.[9] The nature of the Aboriginal diet may have contributed in part to management of the disease.

Although they consumed a varied diet in which animal food was a major component, a wide variety of plant foods were part of the traditional fare. These plant foods — fruits, nuts, roots, starchy tubers, bulbs, seeds, and green vegetables — are high in fiber and contain complex carbohydrates. Food preparation, baked whole or raw, was such that nutrients were largely retained. A good knowledge of seeds containing toxic compounds and appropriate pretreatment to remove the toxins allowed them to choose from a wide range of seeds.

A detailed description of the hunter–gatherer lifestyle of the nomadic Aboriginal, groups of whom continued with this lifestyle well into the 20th century in remote parts of Australia, has been given by O'Dea.[6] Of some interest is the fact that the carbohydrates in many of the traditional foods were more slowly digested and adsorbed than those in equivalent domesticated plant food. The lower postprandial glucose and insulin levels induced may have protected these groups from developing type 2 diabetes (NIDDM), a condition to which they are susceptible when they make the transition to Western diet and lifestyle.[6,9] The high prevalence of glucose intolerance among Australian Aborigines has been rationalized by a modified "thrifty gene hypothesis."[10] The normal diet of the Aboriginal hunter–gatherers was high in protein and low in fat with a moderate intake of low glycemic index carbohydrate. In this situation, selective insulin resistance in hepatic gluconeogenesis would be an advantage for converting dietary proteins to glucose and fat. With reduced physical activity, skeletal muscle would be more insulin resistant, limiting the uptake of glucose and triglycerides. Increased consumption of carbohydrates and fats leads ultimately to NIDDM.[9,10]

The prevalence of type 2 diabetes is characterized by its early onset and has serious consequences for complications arising from diabetes: cardiovascular disease, nephropathy, neuropathy, retinopathy, and peripheral vascular disease. Among the Australian Aboriginal people, 3.5% of males and 4.7% of females suffer from diabetes. This increases to 17 and 23%, respectively, above 45 years of age. In comparison, the rates for all Australians above 45 years of age are 6.2 and 5.3%, respectively. In general, the rate for indigenous people above 15 years of age is four times higher than that found for the general population.[9,11]

A similar situation is observed for Maori, Polynesian, and Micronesian people. For people over 15 years old, the prevalence of diabetes is 3.1% in New Zealanders of European origin, 8.3% in

Maori, and 8.1% in Pacific Island people. The incidence of type 1 diabetes in Maori and Pacific Island people is 5%, but 11% in Europeans.[11,12]

AUSTRALIAN PLANTS WITH HYPOGLYCEMIC PROPERTIES

The uses of plants by Aboriginal people have been transmitted from one generation to the next entirely by word of mouth. Some of these uses were noted by early settlers and explorers, but the many sources of error for outsiders documenting this knowledge renders questionable the validity of the information.[13] In particular, the acquired indigenous knowledge of the different properties between varieties of the same species would have been appreciated only by a trained botanist, and the subtleties associated with obtaining medicinal preparations from plants would probably have been the victims of cultural differences. Moreover, it is likely that Aboriginal people would have been reluctant to disclose fully the preparation of "medicines" from plants that were considered to have spiritual significance.

Despite the recent burgeoning interest in collecting and compiling information for an Aboriginal pharmacopoeia, very little has been recorded regarding indigenous plants in the treatment of diabetes. It is useful to note that in two reviews on antidiabetic plants, Australian plants are not represented.[14,15] Two entries referring to Australasia as the location of use mention *Catharanthus roseus* (Apocynaceae) and *Momordica charantia* (Cucurbitaceae), neither of which appears to have been used by Australian Aboriginals.

In the following sections, two types of plants will be considered. First, plants included in traditional Aboriginal pharmacopoeias now known to exhibit hypoglycemic activity are considered. Second, a list of Australian plant genera related to species with proven hypoglycemic activity, but used in other parts of the world, is given.

Acacia Species (Mimosaceae)

The omnipresence of eucalypts and acacias characterizes the Australian flora. They have diversified into almost every habitat on the continent. Most of the more than 1000 Australian taxa of *Acacia* occur nowhere else in the world. They rapidly establish cover following fire, and the practice of burning by the Aborigines favored these fire-adapted species, which, because they produced a lot of seeds, naturally increased food supply.[16] *Acacia* seeds formed a staple food for the Aborigines and are rich in proteins (26%), available carbohydrate (26%), fiber (32%), and fat (9%).[17] The level of fatty acids (mostly unsaturated) is higher than in most legumes; the mean total carbohydrate content (55.8 ± 13.7%) is lower than in lentils but higher than that in soybeans.[17]

Acacia seeds are low glycemic index foods; the starch is digested and absorbed very slowly, so a sustained but small rise in blood glucose levels occurs. They are abundant even in the semiarid and arid regions of Australia and often provided 70 to 80% of total diet. Latz[7] states that, of the 60 or so species of *Acacia* in Central Australia, ~50% were, or still are, eaten by Aboriginals. Some *Acacia* seeds contain toxic compounds that can be leached out by prolonged washing and/or denatured by heating.

Some work has been carried out on *Acacia* species containing hypoglycemic compounds, although little has been done in isolating and identifying individual active components. The ethanolic extracts of the stem of *Acacia nilotica* and the pods of *A. farnesiana* have been claimed to have hypoglycemic activity.[18] Addition of gum acacia (*A. nilotica*; 20 g) to glucose (100 g) resulted in significant reduction of plasma glucose (16%) and serum insulin (11%) after 90 min.[19] Protein fractions from the seeds of *A. melanoxynol* decreased blood sugar levels by 24.4% and cholesterol levels by 27.5%, when given to young albino rats. Alloxan-diabetic rats also showed lower blood sugar (23.5%).[20] Normal rats fed a diet of powdered seeds (94%) of *A. arabica*, *A. benthami,* and *A. modesta* showed a blood sugar level 25 to 30% lower than that of rats fed a standard semipurified

casein–glucose–starch diet. No differences were observed in alloxan-diabetic animals.[21] A similar result was observed for the seeds of *A. arabica* in rabbits.[22]

It would appear that the active component(s) of the seeds stimulates the secretion of insulin by pancreatic β-cells. Flour made from *A. coaricea* seeds was used to make wheat bread (18 g/82 g wheat flour). When this was given to six healthy human subjects, the rise in plasma glucose level was significantly reduced, as were insulin values after 60 and 90 min.[23]

Some *Acacias* (e.g., *A. maidenii* and *A. confusa*) produce *N*-methyltryptamine.[24,25] It has been suggested that this compound might be an insulase inhibitor. A solution of *N*-methyltryptamine (40 mg in 20 ml *N* saline) injected intravenously in six diabetics resulted in a decrease of blood sugar levels, obvious after 30 min and reaching a minimum after 180 min. No significant change was noticed in the control group.[26]

(+)-Pinitol has been reported from the bark of *Acacia longissima*, *A. mearnsii*, *A. obtusifolia*, *A. orites*, (subgenus *Phyllodineae*), and *A. sieberiana* var. *woodi* (subgenus *Acacia*).[27,28] Pinitol enhances the action of insulin (see the section on plants related to species with known hypoglycemic properties, New Zealand).

Eucalyptus Species (Myrtaceae)

The genus *Eucalyptus* consists of about 900 taxa; all but 13 species are endemic. Eucalypts range in form from giant forest trees to mallee shrubs and can be found from snowline to shoreline, in deserts and swamps, and on floodplains. It is no surprise that eucalypts were well represented in the Aboriginal pharmacopoeia.[13] Because most species produce significant amounts of essential oils with distinct fragrances, these would have become readily available sources of simple antiseptics, analgesics, liniments, cures for coughs and colds, and "smoke treatment" of sick people.

Eucalyptus globulus (Tasmanian bluegum) is one of the better known species cultivated for eucalyptus oil and for pulp and paper production. It came into prominence when thousands of trees were planted in the malaria-infested Pontine Marshes near Rome in the belief that the oil emanating from the leaves would solve the problem.[29] The incidence of malaria decreased, but as a result of the uptake of water by the trees, which reduced the breeding sites of the carrier mosquito.

E. globulus was used by the Australian Aborigines to make poultice from gum leaves that had been bruised and heated. Leaves were used in the smoke treatment to alleviate rheumatisms, inhalation of the vapor from heated leaves was used to treat headaches, and an infusion of the leaves was drunk for colds. The use of this species in the treatment of diabetes, as a tea prepared from the leaves, appears to have begun only after its adoption in South America and Africa.

Aqueous extracts of *E. globulus* incorporated in the diet reduced the hyperglycemia and weight loss in streptozotocin-treated mice and appeared to act by modulating insulin secretion or action.[30] It enhanced 2-deoxyglucose transport by 50%, glucose oxidation by 60%, and incorporation of glucose into glycogen by 90% in mouse abdominal muscle. It evoked insulin secretion (70 to 160%) from clonal pancreatic β-cell lines. The nature of the active constituent is not known.[31]

In this context, it is useful to note that *Eucalyptus* species produce a number of metabolites that are not part of the essential oil fraction.[32] The euglobals and the macrocarpals, e.g., (1) and (2) (Figure 13.1), characterize the polar extracts of leaves of *E. globulus* and a number of other species. These compounds exhibit a range of biological activities, such as antiviral, antibacterial, and antimalarial and as inhibitors of HIV RTase.[32,33] Although they have not been tested for hypoglycemic activity, the macrocarpals inhibit aldose reductase (I_{50} 2 to 2.8 μ*M*). This enzyme is a target for the control of diabetic complications such as cataracts, retinopathy, neuropathy and nephropathy, myocardial infarction, and stroke.[34,35]

Aldose reductase (AR) is an enzyme found in many tissues, including the organs most susceptible to diabetic complications — kidney, nerve cells, the eye, and cells lining blood vessels. AR converts aldoses into alditols. In the case of glucose, sorbitol is produced in much greater amounts in hyperglycemia. Once sorbitol has been formed, it only escapes from cells slowly, with the result

that its concentration keeps rising. Because sorbitol does not easily cross cell membranes and its subsequent conversion to fructose via sorbitol dehydrogenase is slow, it accumulates inside certain cells, thus resulting in changes in osmotic pressure, alterations in the redox state of pyridine nucleotides (i.e., increased NADH/NAD^+ ratio), and depleted intracellular levels of myoinositol. These biochemical changes, which have been linked to diabetic complications, can be controlled by inhibitors of aldose reductase.[34,35]

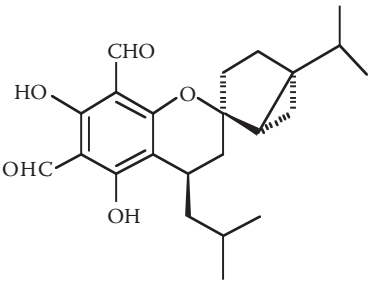
Eremophila Species (Myoporaceae)

A number of species of the genus *Eremophila* were valued for medicinal purposes by Aboriginal people in coastal and central Australia. Of these, *E. alternifolia* and *E. longifolia* had a prominent place in the Aboriginal pharmacopoeia. *E. alternifolia* was one of the few plants that they carried with them in case of need. Infusions from the leaves were taken for a variety of ailments and were said to promote a feeling of well-being.[34] Phytochemical studies have shown that both species produce the phenylethanoid verbascoside (acteoside) (3) and the iridoid geniposidic acid (4) (Figure 13.1). Both compounds cause significant but opposite changes in the Langendorff rat heart preparation. In particular, the effects induced by the two compounds are not in phase, thus exerting a stabilizing effect on heart action.[36]

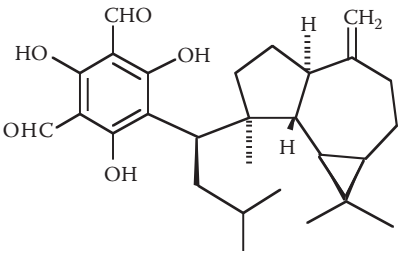
Interestingly, verbascoside has a number of other pharmacological activities. Of particular interest is the observation that verbascoside is a potent lens aldose reductase inhibitor.[37] Geniposidic acid might also contribute to the activity, but iridoids appear to be less effective as inhibitors.[37,38] On the other hand, some show hypoglycemic activity in normal and alloxan-diabetic rats.[39] The ability to lower blood glucose levels in normal rats seems to be associated with the presence of a hydroxyl group at C-6. For example, deacetyl-asperulosidic acid methyl ester (5) is active, whereas geniposide (6) (Figure 13.1) is not.[40]

OTHER PLANTS USEFUL IN TREATMENT OF DIABETES

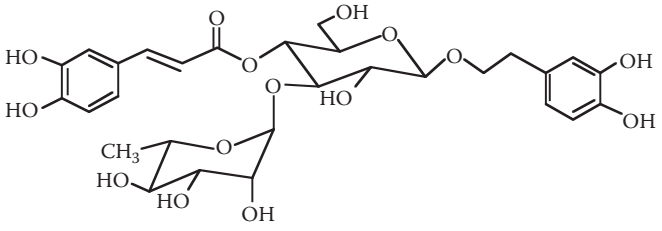
- *Lythrum salicaria* (Lythraceae). The flowers, stems, and leaves of this plant contain compounds that exhibit hypoglycemic activity in normo- and hyperglycemic rabbits,[41] rats, and mice.[42] The ethereal extract of the stems and flower induced hypoglycemia and enhanced insulin secretion in normoglycemic rats.[43] The presence of the C-glycosidic flavones vitexin (7) and orientin (8) (Figure 13.1) — as well as their isomers, isovitexin and isoorientin — has been established.[44] Vitexin is an inhibitor of AR,[45] isoorientin exhibits hypoglycemic activity,[46] and orientin has been suggested to be useful in the treatment of diabetes.[47]
- *Castanospermum australe* (Fabaceae) (Moreton Bay chestnut). The large seeds of this tree were processed to yield a flour. Because of their toxicity, the nuts were pounded and roasted or soaked in water (for up to 10 days).[8] The seed produces the alkaloid castanospermine (9) (Figure 13.1), an intestinal enzyme inhibitor with hypoglycemic activity.[48] *In vivo*, castanospermine significantly inhibited sucrase at 1 mg/kg in normal and streptozotocin-treated rats. It would be interesting to determine how efficiently castanospermine is removed in the preparation of the flour and whether subtoxic amounts of castanospermine were, in fact, ingested.
- *Euphorbia hirta* (Euphorbiaceae). A decoction of the dried herb was taken to alleviate asthma and bronchitis.[13] The plant reportedly possesses hypoglycemic activity.[49] The flavonoid quercetin has been isolated from the plant.[50] In common with a number other flavonoids, it exhibits hypoglycemic activity and is an inhibitor of aldose reductase (AR).[51]



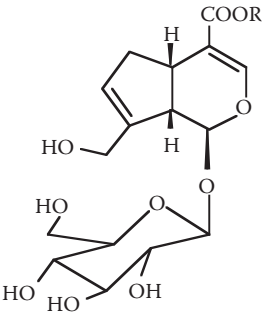
(1) Euglobal 1c



(2) Macrocarpal G

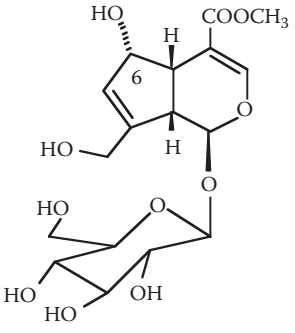


(3) Verbascoside

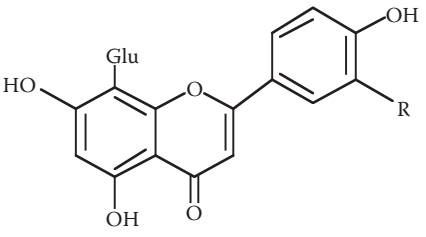


(4) **R = H** Geniposidic acid

(6) **R = CH_3** Geniposide

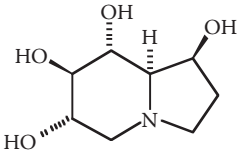


(5) Deacetylasperulosidic acid methyl ester

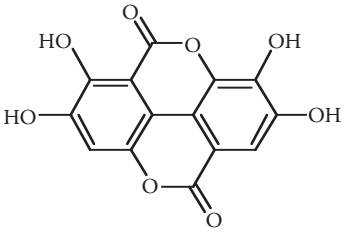


(7) **R = H** Vitexin

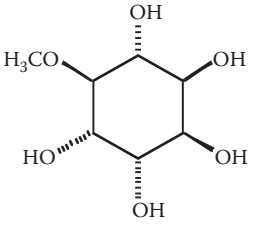
(8) **R = OH** Orientin



(9) Castanospermine



(10) Ellagic acid



(11) (+) -D-Pinitol

FIGURE 13.1 Selected plant metabolites with antidiabetic properties.

- *Goodenia ovata* (Goodeniaceae). Reported to have antidiabetic properties, this sticky erect shrub was used by the early settlers.[52] The leaves have been shown to contain ursolic acid (1 to 2% dry wt),[53] a triterpene that exhibits hypoglycemic activity in rats with streptozotocin-induced diabetes.[54]
- *Morinda citrifolia* (Combretaceae). This plant is native to Southeast Asia but has also spread to India and the Pacific Islands. The large, squashy fruit is an important medicine; it is edible, but does not have a nice taste.[8] The fruits were eaten raw or cooked, the seeds were roasted, and the young leaves were eaten as a vegetable. The plant has been widely used to treat a number of disorders, including diabetes and venereal diseases.[55] A number of anthraquinones, the iridoid asperuloside, and some disaccharides have been isolated from the fruit. Iridoid glycosides, together with the known hypoglycemic agents-β-sitosterol and ursolic acid have been obtained from the leaves.[56]
- A number of mangrove plants used in different parts of the world to treat diabetes are also found in Australia[57]:
  - *Acanthus ilicifolius* (Acanthaceae)
  - *Aegiceras corniculatum* (Myrsinaceae)
  - *Bruguiera rumphii* (Rhizophoraceae)
  - *Ceriops candolleana* (Rhizophoraceae)
  - *Lumnitzera racemosa* (Combretaceae)
  - *Nypa fruticans* (Arecaceae)
  - *Scaevola sericea* (Goodeniaceae)

  Of these, only *Aegiceras corniculatum*,[13] a *Ceriops* sp,[8] and a *Scaevola* sp[13] appear to have been used by the Aboriginal people for medicinal purposes.

PLANTS RELATED TO SPECIES WITH KNOWN HYPOGLYCEMIC PROPERTIES

Australian

Table 13.1 contains a list of Australian species used for medicinal purposes by Australian Aboriginal people, together with related species that have been used in the treatment of diabetes in other parts of the world. This is an attempt to flag Australian genera that may offer some potential as sources of phytochemicals with hypoglycemic activity. The rationale is that similar species frequently produce similar compounds. The following example, admittedly carefully selected, may serve to illustrate the point

An ethanolic extract from the bark of *Ficus bengalensis* (Moraceae) showed hypoglycemic activity in rats[58] with augmentation of insulin secretion.[43,59] Leucoanthocyanidin and leucoanthocyanin glycosides were found as active components of the extract.[60–62] The dimethyl ether (10) (Figure 13.1) showed hypoglycemic and serum insulin-raising action in normal and mildly diabetic dogs[63] and rats.[64–67]

A decoction of the leaves of *F. carica* (Moraceae) showed hypoglycemic action on diabetic rats[68] and on type 1 diabetic patients in whom it helped to control postprandial glycemia.[69] Petroleum ether extracts of the bark[70] or leaves of *F. racemosa* (*glomerata*) possess significant activity in diabetic rats.[71] Such an extract contains β-sitosterol glucoside, friedelin, and lupeol,[72] the first of which is a known hypoglycemic agent.[73] *Ficus pseudosycomorus* produces a number of coumarins that possess hypoglycemic activity.[74]

New Zealand

Very little information is available correlating plant use and treatment of diabetic disorders by the Maoris. A thorough search of the book *New Zealand Medicinal Plants*,[2] the most comprehensive

TABLE 13.1
Examples of Medicinal Plants Used by Australian Aborigines and Related Plants with Known Antidiabetic Activity

Plant Species Used for Medicinal Purposes by Australian Aboriginal People			Plant Species Known to Have Hypoglycemic Activity		
Plant Species	**Family**	**Part Used**	**Plant Species**	**Part Used**	**Ref.**
Carissa lanceolata R. Br.	Apocynaceae	Whole	*C. edulis* Vahl	Leaves	15
Cassia sp	Leguminosae	Leaves	*C. alata* L.	Leaves	15
Cleome viscose L.	Capparaceae	Seeds, leaves	*C. droserifolia* Dalile	Whole	43
Dioscorea transversa R. Br.	Dioscoreaceae	Whole	*D. dumetorum* Pax	Tuber	86
Syzygium suborbiculare T. Hartley & Perry	Myrtaceae	Bark; root; fruit	*S. jambolana* DC. (*Eugenia*)	Seeds; fruit	15; 87
Loranthus quandang auct. non Lindl.	Loranthaceae	Fruit	*L. bengwensis* L.	Leaves	15
Ocimum sanctum var. *angustifolium* Benth.	Lamiaceae	Leaves	*O. sanctum* L.	Leaves	15
Pandanus spiralis R. Br.	Pandanaceae	Wood	*P. odorus* Ridl.	Roots	78
Phyllanthus simplex Retz.; *P. virgatus* Forst. f.	Euphorbiaceae	Leaves; whole	*P. amarus* Schumm. & Thonn.	Whole	15
Polichia zeylanica (= *Trichodesma zeylandicum* R. Br.)	Boraginaceae	Whole	*P. campestris* Aiton	Whole	15
Smilax australis R. Br.; *S. glyciphylla* Sm.	Liliaceae	Whole leaves	*S. glabra* Roxb.	Rhizome	15
Tinospora smilacina Benth.	Menispermaceae	Seeds	*T. crispa* Hook. f. & Thoms; *T. cordifolia* Miers	Seeds; leaves	14; 86
Zizyphus oenoplia Mill.	Rhamnaceae	Bark; fruit	*Z. sativa* Gaert.	Leaves	15

collection on the topic, revealed only one example (*Apium graveolens*; Apiaceae). In this section, medicinal plants used by the Maoris that are closely related to those used to treat diabetes elsewhere are considered. Some plants that produce secondary metabolites known to exhibit hypoglycemic properties have also been included.

- *Apium australe* (Apiaceae) is an edible herb found throughout New Zealand. It was probably used in indigenous medicine in vapor baths. The more widely distributed *A. graveolens* (wild celery) is mentioned in several continental pharmacopoeias and has been used as a hypoglycemic agent.[2]
- *Coprosma australis*, *C. robusta*, and *C. acerosa* (Rubiaceae) are common shrubs in New Zealand and were used to treat a number of internal disorders. A decoction from the leaves of *C. robusta* was used for kidney troubles. From these species, the following metabolites have been isolated[2]: the coumarin scopoletin[75] and the flavonoids quercetin[74] and kaempferol glycoside,[15] which are known hypoglycemic agents.
- *Geranium homeanum* (*australe*) (Geraniaceae) is found in both of the main islands in New Zealand. The leaves were used to treat boils and sore backs. *G. maculatum*, a native of North America, has been considered useful for diabetes and shows hypoglycemic activity.[2]
- *Pomaderris kumeraho* (Rhamnaceae) is a common shrub in northern New Zealand. A decoction was taken for internal complaints such as bronchitis and kidney problems. In one case, it was reported to have been used to good effect against diabetes. The leaves contain quercetin,[76] kaempferol,[15] and ellagic acid[77] — all useful in the treatment of diabetes.

- *Rubus fruticosus* (Rubiaceae) has long been used in Europe to treat diabetes. An extract of the leaves showed a hypoglycemic effect on diabetic rats.[14] In New Zealand, an infusion of the leaves of *R. cissoides* was taken for internal disorders.[2] The fruits of *Syzygium jambolana* (Myrtaceae) have traditionally been used against diabetes in Asia and Europe. Extracts of the fruit and the plant induce an increase in serum levels of insulin in normoglycemic and diabetic rats.[43] The bark of *S. maire*, used in the treatment of ringworm in New Zealand, was shown to contain di- and trimethyl ethers of ellagic acid.[2]
- The water from boiled leaves of *Vitex lucens* (Verbenaceae) was used for sore throats. Of the secondary metabolites present in this plant, vitexin and *p*-hydroxybenzoic acid are of some significance because they are known hypoglycemics. Recently, *p*-hydroxybenzoic acid was shown to be the active principle of *Pandanus odorus* (Pandanaceae), a plant used as a food and in traditional medicine. This compound (5 mg/kg) increased insulin levels upon oral administration.[78]
- *Disphyma australe* (Ficoidaceae) and *Tetragonia trigyna* (Ficoidaceae) are common plants on the sea coasts of New Zealand and Australia. *T. trigyna* and the closely related *T. tetragonioides* are referred to as New Zealand spinach. *Disphyma* and *Tetragonia* spp have found limited use as medicinal plants.[2] A study of these and other coastal plants indigenous to New Zealand found that D-pinitol (11) (Figure 13.1) is the major soluble carbohydrate in the leaves of these plants.[79] Recent studies have shown that the oral and injectable forms of pinitol enhance the action of insulin, and therefore the uptake of glucose, in immature rat muscle cells and in mice with type I-like diabetes.[80] In a study involving subjects who were obese and had mild type II diabetes or impaired blood-sugar control, pinitol did not improve the actions of insulin in carbohydrate or fat metabolism.[81]

CONCLUDING REMARKS

Remarkably little is known about Australian plants with antidiabetic properties and even less is known about the traditional use of these by the Aboriginal people. To some extent, this may indicate that diabetes was not a major problem. Indeed, some evidence suggests that in pre-European times, the prevalence of diabetes among these people was low. It is now evident that the Aboriginal and Maori people have paid a high price in adapting to a Western style diet. Studies have indicated that metabolic parameters associated with NIDDM can be improved by lifestyle changes in Aborigines involving a reversion to traditional food intake and physical activity.[9,82,83] In this context, it is interesting to note an increased interest in the development of Australian native edible plants.[84]

Prevention of the initiation of insulin resistance and glucose intolerance can be achieved by suitable nutrition.[85] Alternatively, herbal dietary supplements containing fiber and phytochemicals that influence glucose metabolism can be beneficial. Natural products that stimulate insulin secretion or utilization, improve insulin binding, improve skeletal muscle capillary function, and inhibit polyunsaturated fatty acid oxidation are useful in controlling diabetes. Given the uniqueness and diversity of the Australian and New Zealand flora, it is likely that new antidiabetic compounds will be discovered from these sources. The plant foods, seeds, roots, nuts, and fruits that formed the basis of their traditional diet would seem worthwhile targets in a systematic search for antidiabetic agents.

REFERENCES

1. Fox, M.D., Present environmental influences on the Australian flora, in *Flora of Australia*, vol. 1, *Introduction*, 2nd ed. Orchard, A.E., Ed., Melbourne: ABRS/CSIRO, Australia, 205, 1999.

2. Brooker, S.G., Cambie, R.C. and Cooper, R.C., *New Zealand Medicinal Plants*, Reed Books, Auckland, 1991.
3. Stack, E., Aboriginal pharmacopoeia, the third Eric Johnston Lecture, occasional paper no. 10, Northern Territory Library Service, Darwin, 1989.
4. Fallon, S. and Enig, M.G. (1999) Australian Aborigines. http://www.price-pottenger.org/Articles/Aborigines.html (8 April 2002).
5. Cleland, J., Disease in the Australian native, *J. Trop. Med. Hyg.*, 65, 95, 1962.
6. O'Dea, K., Traditional diet and food preferences of Australian Aboriginal hunter-gatherers, *Phil. Trans. R. Soc. Lond. B*, 334, 233, 1991.
7. Latz, P., *Bushfire and Bushtucker. Aboriginal Plant Use in Central Australia*. IAD Press, Alice Springs, 1995.
8. Isaacs, J., *Bush Food. Aboriginal Food and Herbal Medicines*, Weldons, McMahon Point, New South Wales, 1987.
9. de Courten, M. et al., Review of the epidemology, etiology, oathogenesis and preventability of diabetes in Aboriginal and Torres Strait Islander populations. International Diabetes Institute. Office for Aboriginal and Torres Strait Islander Health Services, Commonwealth Department of Health and Family Services, Canberra, ACT, 1998.
10. O'Dea, K., Obesity and diabetes in the "land of milk and honey," *Diabetes/Metab. Rev.*, 8, 373, 1992.
11. Edwards, R.W. and Madden, R., The health and welfare of Australia's Aboriginal and Torres Straits Islander peoples and Australian Institute of Health and Welfare catalogue no. 4704.0, Australian Bureau of Statistics (ABS) Canberra: Commonwealth of Australia, 2001.
12. Diabetes Health Funding Authority Te Mana Putea Hauora O Aotearoa, Wellington, New Zealand, 2000. http://www.moh.govt.nz/moh.nsf/ea6005dc347e7bd44c2566a40079ae6f/4735077ed3fd9b56cc256a41000975ca/$FILE/Diabetes2000.PDF (4-April-2002).
13. Lassak, E.V. and McCarthy, T., *Australian Medicinal Plants*, Methuen, Australia, 1983.
14. Bailey, C.J. and Day, C., Traditional plant medicines as treatments for diabetes, *Diabetes Care*, 12, 553, 1989.
15. Lamba, S.S. et al., Phytochemicals as potential hypoglycemic agents, in *Studies in Natural Products Chemistry,* vol. 21, Bioactive Natural Products (Part B), Atta-ur-Rahman, Ed., Elsevier, pp 457–496, 2000.
16. Bowman, D.M.J.S., Tansley review no. 101. The impact of Aboriginal landscape burning on the Australian biota, *New Phytologist*, 140, 385, 1998.
17. Lister, P.R., *Acacia* in Australia: ethnobotany and potential food crop, in *Progress in New Crops*, Janick, J., Ed., ASHS Press, Alexandria, VA, pp. 228, 1996.
18. Wassel, G.M. et al., Phytochemical examination and biological studies of *Acacia nilotica* L. Willd and *Acacia farnesiana* L. Willd growing in Egypt, *Egypt. J. Pharm. Sci.*, 33, 327, 1992.
19. Sharma, R.D, Hypoglycemic effect of gum acacia in healthy human subjects, *Nutr. Res. (N.Y.)*, 5, 1437, 1985.
20. Singh, K.N.and Chandra, V.J., Hypoglycemic and hypocholesterolemic effects of proteins of *Acacia milanoxylon* and *Bauhinia retusa* wild leguminous seeds in young albino rats, *Indian Med. Assoc.*, 68, 201, 1977.
21. Singh, K.N., Chandra, V. and Barthwal, K.C., Hypoglycemic activity of *Acacia arabica*, *Acacia benthami* and *Acacia modesta* leguminous seed diets in normal young albino rats, *Indian J. Physiol. Pharmacol.,* 19, 167, 1975.
22. Wadood, A., Wadood, N. and Shah, S.A., Effects of *Acacia arabica* and *Caralluma edulis* on blood glucose levels of normal and alloxan diabetic rabbits, *J. Pak. Med. Assoc.*, 39, 208, 1989.
23. Thorburn, A.W. et al., Lower postprandial plasma glucose and insulin after addition of *Acacia coericea* to wheat bread, *Aust. New Zeal. J. Med.*, 17, 24, 1987.
24. Fitzgerald, J.S. and Sioumis, A.A., Alkaloids of the Australian Leguminosae V. The occurrence of methylated tryptamines in *Acacia maidenii* F. Muell., *Aust. J. Chem.*, 18, 433, 1965.
25. Liu, K.-C., Chou, C.-J. and Lin, J.-H., Studies on the constituents of the cortex radicis of *Acacia confusa*. *Hua Hsueh*, 15, 1977. *Chem. Abst.*, 92, 116323, 1980.
26. Hsu, C.-T., Fu, C.-C. and Su, N.-Y., Effect of methyltryptamine on blood sugar, *Taiwan Yixuehui Zazhi*, 59, 828, 1960. *Chem. Abst.*, 55, 88799, 1961.

27. Clark-Lewis, J.W. and Dainis, I., Teracacidin and isoteracacidin from *Acacia obtusifolia* and *Acacia maidenii* heartwoods; phenolic hydroxylation patterns of heartwood flavonoids characteristic of sections and subsections of the genus *Acacia*, *Aust. J. Chem.*, 20, 2191, 1967.
28. Saayman, H.M. and Roux, D.G., The origins of tannins and flavonoids in black-wattle barks and heartwoods, and their associated ìnontanninî components, *Biochem. J.*, 97, 79, 1965.
29. Elliot, W.R. and Jones, D.L., *Encyclopedia of Australian Plants Suitable for Cultivation*, Vol. 4. Lothian Publications, Melbourne, pp. 3, 1994.
30. Swanston–Flatt, S.K. et al., Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice, *Diabetologia*, 33, 462, 1990.
31. Gray, A.M. and Flatt, P.R., Antihyperglycemic fractions of *Eucalyptus globulus* (Eucalyptus) are associated with pancreatic and extrapancreatic effects in mice, *J. Nutr.*, 128, 2319, 1998.
32. Ghisalberti, E.L., Bioactive acylphloroglucinol derivatives from *Eucalyptus* species, *Phytochemistry*, 41, 7, 1996.
33. Singh, A.K., Khare, M. and Kumar, S., Nonvolatile constituents of eucalypts: a review on chemistry and biological activities, *J. Med. Arom. Plant Sci.,* 21, 375, 1999.
34. Murata, M. et al., Macrocarpals, antibacterial compounds from *Eucalyptus*, inhibit aldose reductase, *Biosci. Biotech. Biochem.*, 56, 2062, 1992.
35. Singh, I.P. and Etoh, H., Biological activity of phloroglucinol derivatives from *Eucalyptus* species, *Nat. Prod. Sci.*, 3, 1, 1997.
36. Ghisalberti, E.L., The ethnopharmacology and phytochemistry of *Eremophila* species, *J. Ethnopharm.*, 44, 1, 1994.
37. Kohda, H. et al., Studies on lens-aldose-reductase inhibitor in medicinal plants. II. Active constituents of *Monochasma savatierii* Franch. et Maxim., *Chem. Pharm. Bull.*, 37, 3153, 1989.
38. Ghisalberti, E.L., Biological and pharmacological activity of naturally occurring iridoids and secoiridoids. *Phytomedicine*, 5, 147, 1998.
39. Trovato, A. et al., Hypoglycemic activity of different extracts of *Olea europaea* L. in rats, *Plant. Med. Phytother.*, 26, 300, 1993.
40. Miura, T. et al., Hypoglycemic activity and structure-activity relationship of iridodial glycoside*, Biol. Pharm. Bull.*, 19, 160, 1996.
41. Torres, I.C. and Suarez, J.C., A preliminary study of hypoglycemic activity of *Lythrum salicaria, J. Nat. Prod.*, 43, 559, 1980.
42. Lamela, M., Cadavid, I. and Calleja, J.M., Effects of *Lythrum salicaria* extracts on hyperglycemic rats and mice, *J. Ethnopharm.*, 15, 153, 1986.
43. Wang, H.X. and Ng, T.B., Natural products with hypoglycemic, hypotensive, hypocholesterolemic, antiatherosclerotic and antithrombic activities, *Life Sci.*, 65, 2663, 1999.
44. Rauha, J.P. et al., Characterization of the polyphenolic composition of purple loosestrife (*Lythrum salicaria*), *Z. Natur. Section C. J. Biosci.*, 56, 13, 2001.
45. Okamoto, Y. and Yoshizawa, T., Angiotensin-converting enzyme inhibitors and aldose reductase inhibitors containing *Passiflora quadrangularis* extracts or vitexin. *Jpn. Kokai Tokkyo Koho* JP 06293657 A2 19941021 Heisei, 1994, *Chem. Abst.*, 122, 89387, 1995.
46. Andrade–Cetto, A. and Wiedenfeld, H., Hypoglycemic effect of *Cecropia obtusifolia* on streptozotocin diabetic rats, *J. Ethnopharmacol.*, 78, 145, 2001.
47. Kato, K. and Nakano, M., Pharmaceuticals containing substances having superoxide dismutase-like activities and/or antioxidant activities for diabetes treatment *Jpn. Kokai Tokkyo Koho* JP 06199695 A2 19940719 Heisei, *Chem. Abst.,* 121, 272193, 1994.
48. Rhineheart, B.L. et al., Castanospermine blocks the hyperglycemic response to carbohydrates *in vivo*: a result of intestinal disaccharide inhibition, *Life Sci.*, 41, 2325, 1987.
49. Baslas, R.K. and Agarwal, R., Isolation and characterization of different constituents of *Euphorbia hirta* Linn., *Curr. Sci.*, 49, 311, 1980.
50. Galvez, J. et al., Antidiarrheal activity of *Euphorbia hirta* extract and isolation of an active flavonoid constituent, *Planta Med.*, 59, 333, 1993.
51. Pathak, D., Pathal, K. and Singla, A.K., Flavonoids as medicinal agents — recent advances, *Fitoterapia*, 62, 371, 1991.
52. Webb, L.J., Guide to the medicinal and poisonous plants of Queensland. Council for Scientific and Industrial Research, bulletin no. 232. Government Printer, Melbourne, 1948.

53. Lahey, F.N. and Strasser, P.H.A., Triterpene acids; the occurrence of ursolic acid in *Goodenia ovata*. *Australian Chem. Inst. J. Proc.*, 14, 432, 1947.
54. Yamahara, J. et al., Biologically active principles of crude drugs. Antidiabetic principles of *Corni fructus* in experimental diabetes induced by streptozotocin, *Yakugaku Zasshi*, 101, 86, 1981.
55. Olajide, O.A. et al., Evaluation of the antidiabetic property of *Morinda lucida* leaves in streptozotocin-diabetic rats, *J. Pharm. Pharmacol.*, 51, 1321, 1999.
56. Sang, S. et al., Iridoid glycoside from the leaves of *Morinda citrifolia, J. Nat. Prod.*, 64, 799, 2001.
57. Bandaranayake, W.M., Traditional and medicinal uses of mangroves, *Mangroves Salt Marshes*, 2, 133, 1998.
58. Brahmachari, H.D. and Augusti, K.T., Isolation of orally effective hypoglycemic compounds from *Ficus bengalensis, Indian J. Physiol. Pharmacol.*, 8, 60, 1964.
59. Achrekar, S. et al., Hypoglycemic activity of *Eugenia jambolana* and *Ficus bengalensis*: mechanism of action, *In Vivo*, 5, 143, 1991.
60. Augusti, K.T., Hypoglycemic action of bengalenoside, a glucoside isolated from *Ficus bengalensis* Linn. in normal and alloxan diabetic rabbits, *Indian J. Physiol. Pharmacol.*, 19, 218, 1975.
61. Kumar, R.V. and Augusti, K.T., Antidiabetic effect of a leucocyanidin derivative isolated from the bark of *Ficus bengalensis* Linn., *Indian J. Biochem. Biophys.*, 26, 400, 1989.
62. Kumar, R.V. and Augusti, K.T., Insulin sparing action of a leucocyanidin derivative isolated from Ficus bengalensis Linn., *Indian J. Biochem. Biophys.*, 31, 73, 1994.
63. Augusti, K.T. et al., Effect of leucopelargonin derivative from *Ficus bengalensis* Linn. on diabetic dogs, *Indian J. Med. Res.*, 99, 82, 1994.
64. Cherian, S. et al., Antidiabetic effect of a glycoside of pelargonidin isolated from the bark of *Ficus bengalensis* Linn., *Indian J. Biochem. Biophys.*, 29, 380, 1992.
65. Geetha, B.S., Mathew, B.C. and Augusti, K.T., Hypoglycemic effects of leucodelphinidin derivative isolated from *Ficus bengalensis* (Linn.), *Indian J. Physiol. Pharmacol.*, 38, 220, 1994.
66. Cherian, S. and Augusti, K.T., Antidiabetic effects of a glycoside of leucopelargonidin isolated from *Ficus bengalensis* Linn., *Indian J. Exp. Biol.*, 31, 26, 1993.
67. Cherian, S. and Augusti, K.T., Insulin sparing action of leucopelargonin derivative isolated from *Ficus bengalensis* Linn., *Indian J. Exp. Biol.*, 33, 608, 1995.
68. Perez, C. et al., Hypoglycemic and hypolipidemic activity of *Ficus carica* leaf acidic extract in streptozotocin-diabetic rats, *J. Bangladesh Acad. Sci.*, 21, 145, 1997.
69. Serraclara, A. et al., Hypoglycemic action of an oral fig-leaf decoction in type-1 diabetic patients, *Diabetes Res. Clin. Prac.*, 39, 19, 1998.
70. Rahman, N.N., Khan, M. and Hasan, R., Bioactive components from *Ficus glomerata*, *Pure Appl. Chem.*, 66, 2287, 1994.
71. Mandal, S.C., Mukherjee, P.K., Saha, K., Das, J., Pal, M. and Saha, B.P., Hypoglycemic activity of *Ficus racemosa* L. (Moraceae) leaves in streptozotocin-induced diabetic rats, *Nat. Prod. Sci.*, 3, 38, 1997.
72. Baslas, R.K. and Agha, R., Isolation of a hypoglycemic principle from the bark of *Ficus glomerata* Roxb., *Himalayan Chem. Pharm. Bull.*, 2, 13, 1985.
73. Ambike, S.H., Rao, M.R., and Rajaram, R., Studies on a phytosterolin from the bark of *Ficus religiosa*, *Indian J. Pharm.*, 29, 91, 1967.
74. Abd El-Wahab et al., Coumarin constituents and biological study of *Ficus pseudosycomorus* D., *J. Pharm. Sci.*, 25, 101, 2000.
75. Mishkinsky, J.S. et al., Hypoglycemic effect of *Trigonella foenum graecum* and *Lupinus termis* (Leguminosae) seeds and their major alkaloids in alloxan-diabetic and normal rats, *Arch. Int. Pharmacodyn. Ther.*, 210, 27, 1974.
76. Nuraliev, Y.N. and Averzov, G.A., The efficacy of quercetin in alloxan diabetes, *Eksp. Klin. Farmakol.*, 55, 42, 1992. *Chem. Abst.*, 118, 139617, 1993.
77. Sakano, K., Higashihashi, N. and Hashimoto, R., Methods and substances for elevating the concentration of free insulin-like growth factor *in vivo*, and methods for screening the substances for clinical use. PCT Int. Appl. Application: WO 97-JP4881, 1998. *Chem. Abst.*, 129, 104688, 1998.
78. Peungvicha, P. et al., 4-Hydroxybenzoic acid: a hypoglycemic constituent of aqueous extract of *Pandanus odorus* root, *J. Ethnopharm.*, 62, 79, 1998.

79. Bieleski, R.L., Pinitol is a major carbohydrate in leaves of some coastal plants indigenous to New Zealand, *N.Z. J. Bot.*, 32, 73, 1994.
80. Bates, S.H, Jones, R.B. and Bailey, C.J., Insulin-like effect of pinitol, *Br. J. Pharmacol.*, 130, 1944, 2000.
81. Davis, A. et al., Effect of pinitol treatment on insulin action in subjects with insulin resistance, *Diabetes Care*, 23, 1000, 2000.
82. O'Dea, K., Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary revisions to traditional lifestyle, *Diabetes*, 33, 596, 1984.
83. O'Dea, K., White, N.G. and Sinclair, A.J., An investigation of nutrition-related risk factors in an isolated Aboriginal community in Northern Australia. Advantages of a traditionally oriented lifestyle, *Med. J. Aust.*, 148, 177, 1998.
84. Ahmed, A.K. and Johnson, K.A., Horticultural development of Australian native edible plants, *Aust. J. Bot.*, 417, 48, 2000.
85. Broadhurst, C.L., Nutrition and non-insulin-dependent *Diabetes mellitus* from an anthropological perspective, *Alt. Med. Rev.,* 2, 378, 1997.
86. Perez G. et al., Antidiabetic compounds isolated from plants, *Phytomedicine*, 5, 55, 1996.
87. Grover, J.K., Vats, V. and Rathi, S.S., Antihyperglycemic effect of *Eugenia jambolana* and *Tinospora cordifolia* in experimental diabetes and their effects on key metabolic enzymes involved in carbohydrate metabolism, *J. Ethnopharm.*, 73, 461, 2000.

14 Plant Polysaccharides in the Prevention and Treatment of Diabetes Mellitus

Patricia A. Judd and Peter R. Ellis

CONTENTS

INTRODUCTION

The role of diet in the treatment of people with diabetes mellitus (DM) has been recognized throughout history; even the earliest records of treatment of the disease focus on carbohydrate-containing foods.[1] Early records from the Egyptian New Kingdom period (1550 B.C.) suggested that the foods prescribed for people with diabetes were high in carbohydrate but low in fat and, therefore, in calories.[2] In the subsequent 450 years, the recommended diets have been through several cycles in which low-carbohydrate diets have followed high-carbohydrate diets, with varying amounts of protein and fat supplementing the energy requirements.[2] In many ways, the current nutritional guidelines for people with DM have come full circle: most authorities recommend diets high in complex carbohydrates and low in saturated fats.[3,4]

The human diet contains a wide range of carbohydrates (CHO), the vast majority of which are of plant origin. In the past 40 years, it has become recognized that carbohydrates are not just a simple energy source, but rather are important food components that moderate the way in which nutrients are released from food. It is not simply the amount of carbohydrate that is important; the structure and properties of carbohydrates in food and the way in which they are processed domestically and commercially also have important implications for the prevention and treatment of diabetes.

DEFINITION OF POLYSACCHARIDES

Dietary carbohydrates can be divided into the three main categories of free sugars (mono- and disaccharides), short-chain carbohydrates, and polysaccharides (Table 14.1), according to how they are digested or fermented in the gastrointestinal tract. The polysaccharide group covers a large range of high molecular weight compounds, which are usually classified according to their chemical structure. Thus, polysaccharides can be classified according to whether they have more than one type of monosaccharide and also whether the polysaccharide chains are linear or branched. For example, they may contain only one type of sugar (monomer) such as cellulose and the amylose polymer of starch, which are essentially linear and are polymers of glucose; amylopectin, the other polymer of starch, also consists of glucose but is highly branched.

Starch is the major source of carbohydrate in the human diet and is traditionally viewed as "available" carbohydrate, an important source of energy for the consumer. Available carbohydrate is defined in this review as carbohydrate in the diet that is digested by α-amylase in the upper gastrointestinal tract and absorbed into the hepatic portal vein (mostly as glucose); this includes starch, dextrins, and simple sugars (e.g., sucrose, lactose). For the digestion of cooked starch, most of the glycosidic linkages (e.g., α (1→4)) that link glucose residues in the polymer chains of starch are easily and rapidly hydrolyzed by α-amylase and other carbohydrases to produce glucose. Other polysaccharides, the nonstarch polysaccharides (NSPs), may consist of only one

TABLE 14.1
Carbohydrates Found in Plant Foods Classified According to Susceptibility to Digestion or Fermentation in the Gastrointestinal Tract

Component	Characteristics
Free Sugars	
Mono- and disaccharides and their alcohols Mainly free glucose + glucose from sucrose	Usually rapidly released and absorbed in the small intestine, unless encapsulated by an intact plant cell wall (e.g., fruits)
Short-Chain Carbohydrates	
Maltodextrins	Rapidly digested by α-amylase and other carbohydrases and absorbed in the small intestine
Nondigestible Short-Chain Carbohydrates	
Oligosaccharides, e.g., fructo-oligosaccharides	Fermented by bacterial enzymes in the large bowel and may stimulate growth of probiotic bacteria
Starch	
Rapidly digestible starch (RDS)	Digestion is rapid and glucose absorbed
Slowly digestible starch (SDS)	Digestion is retarded and absorption prolonged
Resistant starch (RS)	Escapes digestion in the small intestine and includes retrograded amylose and starch encapsulated in plant tissue; a variable amount of this starch will be fermented by bacterial enzymes in the large bowel
Nonstarch Polysaccharides (NSPs)	
Plant cell-wall NSP	Encapsulate and slow absorption of nutrients within the cells; marker for naturally high-fiber diets; fermented by bacterial enzymes in the large bowel to different extents
Other NSPs	Food additives; minor components of the human diet; fermented by bacterial enzymes in the large bowel to different extents

type of monosaccharide (e.g., cellulose) but usually contain two or more different types. For example, there might be a backbone of one type of sugar such as mannose, with side chains of another (e.g., galactose); such a compound would be termed a galactomannan, as found in guar and locust bean gums.

Many different types of NSPs exist, depending on the plant source and the function within the plant. These NSPs were traditionally regarded as "unavailable," mainly because the β(1→4) linkages between the monosaccharides cannot be easily hydrolyzed by enzymes produced in the stomach and small intestine and therefore do not provide an available energy source. However, glycosidic linkages of NSP are more easily degraded by bacterial enzymes in the large intestine, thus producing a range of products including short chain fatty acids such as butyrate.[5]

It is now recognized that this concept of availability was too simplistic and that the structure and properties of starches and NSPs influence the way in which simple and complex carbohydrates are digested and absorbed; this may have important effects on metabolism. For example, most of the NSPs present in a typical British diet are in the form of plant cell walls (dietary fiber), which are supramolecular structures composed of an extremely complex, heterogeneous network of cellulose, hemicelluloses, and pectic substances.

The amounts and relative proportions of these components vary depending on factors such as the type and maturity of the plant tissue.[6–8] The hemicelloses in particular consist of a broad range of polymeric components; thus, xyloglucans are commonly found in the plant cell walls of fruits and vegetables, and arabinoxylans and mixed linkage (1→3), (1→4)-β-D-glucan (or simply β-glucan) predominate in wheat- and oat-based food products, respectively. Noncarbohydrate components (lignin, protein, cutin, etc.) are also present as minor components quantitatively; however, some are known to form covalent cross links with polysaccharides of cell walls[6,7] and can modify their properties and biological activity significantly.[6]

At a molecular level, the physical properties of individual polysaccharides will be influenced by their molecular shape or conformation. Important factors here include the types of glycosidic linkages between sugar residues in the polysaccharides chains, the presence of charged groups, and the extent of branching in the polymer.[9] The shape of polysaccharides in three dimensions can be stable or in a continuous state of fluctuation, depending on the particular polysaccharide and the prevailing environmental conditions. The conformation that predominates will determine how atoms and groups in the polymer are orientated to the outside and thus interact with other molecules, solvents, and biological surfaces.

Molecular shape will determine, for example, the relative solubility of polysaccharides in an aqueous medium — a property of paramount importance in biological systems, including, of course, the process of digestion and absorption of nutrients in the mammalian gut.[10] Cellulose, for instance, is made up of an assembly of polymer chains, each of which is composed of glucopyranose units connected by β(1→4) linkages, with chains stabilized by intra- and intermolecular hydrogen bonding. This highly ordered structure is mechanically strong and resistant to solubilization in water, which also explains why cellulose tends to be resistant to chemical and enzyme degradation. The inclusion of different types of glycosidic bonds, such as mixed linkage (1→3), (1→4)-β-D-glucan, or side chains, such as xylose on the cellulosic backbone (i.e., a xyloglucan), will promote solubility in water.

The following sections will consider the effects of the differential digestion of available carbohydrates and the way in which NSPs may moderate this, as well as specific beneficial effects of NSPs on glucose absorption and insulin secretion and action.

THE ROLE OF STARCH

Starch is the major carbohydrate component in the human diet. It is the main storage polysaccharide of plants and is found in considerable amounts in dietary staples such as cereal grains, potatoes, and other root crops such as yam. Starches contain varying amounts of two types of glucose

polymers: amylose and amylopectin. Amylose is an essentially linear chain of glucose units with $\alpha(1 \rightarrow 4)$ linkages, with $\alpha(1 \rightarrow 6)$ branch points of one per 300 to 1000 glucan residues, a molecular weight of 5×10^5 to 1×10^6 and degree of polymerization (DP) of 10^3 to 10^4. Amylopectin is much larger, with a molecular weight of several millions and DP of 5×10^4 to 5×10^5, and is also highly branched with 15 to 30 $\alpha(1 \rightarrow 4)$ linked anhydroglucose units in each branch; the branches are joined by $\alpha(1 \rightarrow 6)$ linkages. The majority of starches contain between ~15 and 35% amylose, but the relative amounts of amylose and amylopectin can vary even more widely among different plant sources — from 2% amylose in waxy maize starch to 80% amylose in high-amylose maize starch.[11]

Starch is stored within the plant cells in the form of water-insoluble granules, which have sizes and shapes characteristic of the botanical species of origin. Average starch granule sizes vary between 2 and 100 μm. In the unprocessed or native form, the starch granules are birefringent in that they exhibit a characteristic Maltese cross pattern when examined by microscopy under polarized light, indicating an organized crystalline arrangement. Thus, granules are described as semicrystalline, with alternating layers of crystalline (ordered) parts and amorphous (disordered) parts that display an ordered arrangement with central symmetry.[11,12]

Although the detailed structural architecture of the granules is very complex and beyond the scope of this review, it is important to note that such native structures are considerably less susceptible to the amylase action than hydrothermally (cooked) treated starch granules.[13] When starch granules are heated in the presence of water, the crystalline structure is disrupted and the polysaccharide chains take up a more disordered conformation as a result of swelling and gelatinization of the granules. The starch is then much more accessible to amylase action. Upon cooling, a process of recrystallization of the gelatinized starch known as retrogradation begins. This occurs very rapidly for amylose, but the retrogradation of amylopectin, known to be responsible for the staling of bread, takes place over several days. The retrogradation of amylose is of particular interest to nutritionists because the product is completely resistant to amylase action.

Because of the nature of the linkages between the glucose units, all dietary starch is potentially degradable by the action of α-amylase. However, certain factors can reduce the rate at which starch is hydrolyzed and absorbed *in vivo*; this delays the appearance of glucose in blood after a meal and leads to description of starches according to their rate of digestion (Table 14.1) and to the concept of resistant starch.[14,15] It is now acknowledged that a significant amount of the starch in foods remains undigested in the small intestine and passes into the colon, where it is fermented by colonic bacteria and may influence the type and amount of gastric flora.[5]

These ideas have superceded the traditional view of starch digestion, which, until fairly recently, was that starch of any source is digested at more or less the same rate and to the same extent. However, it is now well known that different starchy foods containing identical amounts of starch produce widely different postprandial blood glucose and insulin responses in humans.[16,17] Made by many different research groups in many different countries, these observations have led to the method of classifying starchy foods according to their postprandial glycemic responses, the so-called "glycemic index" (GI).[17] The GI is measured by measuring blood glucose levels at baseline and 15- to 30-minute intervals for 2 hours after consumption of a portion of food containing 50 g available carbohydrate; this is compared with the area under the curve produced by consuming 50 g of glucose (in water) or 50 g of available carbohydrate as white bread,[18] i.e.:

$$\text{GI} = (\text{incremental area under blood glucose curve [AUC] for a test food containing 50 g CHO} \times 100)/\text{incremental AUC after equicarbohydrate load from glucose or white bread}$$

Many starch-rich foods, such as potatoes, wheat bread, and certain breakfast cereals, are classified as high-GI foods; foods such as pasta, rye bread, biscuits, and legumes have lower GIs.

The GI of hundreds of carbohydrate-containing foods has now been determined using standardized methods and tables reporting the GI of carbohydrate-containing foods, including those

containing mainly simpler sugars, such as fruits, milk, and table sugar, as well as starchy foods, are now available.[19] Some researchers have suggested that the concept of GI may also be applied to mixed meals.[20,21] More recently, the concept of the glycemic load, which includes the weight of carbohydrate ingested in the meal, has been described. The glycemic load of a meal is the product of the amount of carbohydrate in the food multiplied by the GI of that food; tables predicting the GI and glycemic load of commonly consumed foods are now available.[22] The glycemic load of whole diets has been calculated as the sum of the glycemic load from all the carbohydrate-containing foods in the diet.[23,24]

FACTORS AFFECTING GLYCEMIC RESPONSE TO FOODS

Many food-related factors affect the digestion kinetics of starchy foods and, ultimately, the glycemic index.[18,25] These include the structural architecture of the plant tissue — e.g., whether intact plant cell walls containing indigestible NSPs act as a physical barrier to the action of amylase on intracellular starch, the particle size of the food, and the way in which the food is processed. The characteristics of the starch per se, such as granule size and structure; the ratio of amylase to amylopectin; and the degree to which swelling and gelatinization occur on processing will also be important. The presence of water-soluble NSPs (i.e., the viscous-producing galactomannans and xyloglucans) and phytochemicals such as polyphenolic compounds is also likely to play a role.[26–30] Moreover, the presence of large amounts of fat or protein in the food has also been suggested to reduce the GI,[10,30] possibly by slowing gastric emptying [31,32] and increasing insulin secretion.[32]

The Glycemic Index and Diabetes

The GI is of considerable importance in understanding the etiology of diabetes, as well as cardiovascular disease (CVD) and the metabolic syndrome in which insulin resistance is a central feature.[18,33–35] Recent epidemiological studies have indicated that low-GI diets have a protective effect in the development of type 2 diabetes.[23–25] For example, Salmeron and colleagues found that when comparing the highest to lowest quintiles of GI in a population of 42,000 men over 6 years, men in the highest quintile had a 37% greater risk of developing diabetes.[23] Similar results were found in a cohort of 65,173 in the Nurses Study, in which the glycemic load was also shown to be an important predictor for type 2 diabetes.[24] More recently, analysis of data from the second Nurses Health Study demonstrated that consumption of a diet with a high GI and a low intake of cereal fiber were associated with increased risk of type 2 diabetes in a younger female population.[35]

High-GI foods lead to rapid rise in blood glucose levels, high glucose peaks, and increased insulin demand, and it is suggested that this is the link between high-GI diets and type 2 diabetes. High circulating insulin levels cause down-regulation of insulin receptors, lowering insulin efficiency and resulting in insulin resistance[36]; thus, a vicious circle is set up by increasing blood glucose levels and insulin secretion. Insulin resistance is known to be a risk factor for type 2 diabetes.[37,38] Low-GI foods delay absorption of glucose, resulting in lower peak levels of blood glucose and insulin concentrations, which are therefore less likely to lead to insulin resistance.[38,39]

Low-GI diets are also considered to have therapeutic advantages in the treatment of diabetes compared to high-GI diets.[18,22,39–41,43–46] Numerous clinical studies have indicated that diets characterized as producing low blood glucose responses postprandially (i.e., low-GI diets) improve long-term glycemic control in people with type 2 diabetes.[43,44,47–50] Augustin and coauthors recently reviewed the role of the GI in chronic disease. They reported that, in 10 out of 14 studies, reductions in blood concentrations of glycated hemoglobin and/or fructosamine (both indices of improvements in glycemic control) were achieved in type 1 and type 2 diabetic subjects.[51] Indeed, recent meta-analyses of randomized controlled trials showed that low-GI diets vs. high-GI diets had beneficial effects on indices of carbohydrate and lipid metabolism (i.e., reductions in glycated hemoglobin and total cholesterol, respectively) in healthy and type 2 diabetic subjects.[52]

Currently, the number of low-GI foods (e.g., legumes) consumed in the U.K. is very limited, and many are not popular components of a typical Western diet. This makes it very difficult in practice to manipulate the diet in order to lower the GI to any significant extent.[45,53,54] However, the GI of starch-rich foods can be reduced in several ways — e.g., by manipulating processing conditions or by adding specific dietary ingredients such as organic acids,[55] amylase-resistant starches,[18,40,41] and water-soluble NSPs ("soluble fiber").[18,31–34,45–50]

The Role of Water-Soluble NSP

For many years, the potential for so-called "soluble fiber" in plants to moderate postprandial levels of blood glucose, with potential benefits in glycemic control, has been of interest. The distinction made between water-soluble and -insoluble NSP is based only on *in vitro* studies and chemical analyses of cell wall material. It is not known, therefore, to what degree the soluble fractions of plant cell walls (e.g., pectins from vegetable sources) solubilize in the stomach and small intestine, although this is more likely to occur if the food has been mechanically and/or heat processed.[6,56] Assuming that some degree of solubilization takes place in the GI tract, the magnitude of effect of the soluble fraction on the rheological properties of digesta will depend critically on the molecular size and concentration of the polymer in the aqueous phase. The term *soluble fiber* can therefore be misleading for several reasons — perhaps most importantly because of a lack of information about the way that soluble NSPs behave in the gut lumen, as distinct from in the laboratory, but also because, in normal diets, the soluble NSP will be consumed as part of a complex food system.[10]

Most studies examining the potentially beneficial effects of water-soluble NSPs have been carried out by adding specific, purified materials extracted from plants and added to test meals. The earliest studies were performed by Jenkins and co-workers, who fed breakfasts of bread supplemented with guar gum (a galactomannan) and jam fortified with pectin (mainly composed of galacturonic acid).[57] They reported that, compared to a control meal of ordinary bread and jam containing the same amount of available carbohydrate, a test meal of guar and pectin reduced the blood concentrations of glucose and insulin at intervals from 30 minutes to 2 hours postprandially. In the past three decades, similar effects have been seen in single-meal studies using a variety of plant sources rich in water-soluble NSP. These sources include guar gum,[58,59] psyllium seed,[60–62] pectins,[57,58] konjac (a glucomannan derived from the tubers of *Amorphophallus konjac* C. Koch),[63,64] and cereals, including β-glucan extracts from oats[65–67] as well as arabinoxylan extracts derived from wheat.[68]

As the concept of functional food science has developed, more products containing soluble NSP have been developed. Studies examining the longer term effects of addition of these products to the diets of patients with diabetes have demonstrated improved glycemic control[69–75] and beneficial effects on blood lipid levels[69,71,75] in type 1 and type 2 diabetes. Improvements in glycemic control and lipid metabolism were mainly seen as reductions in glycated hemoglobin and fasting blood concentrations and in total and LDL cholesterol, respectively.

Mechanisms of Action of Viscous Polysaccharides

Guar gum has been the most commonly used polysaccharide in studies examining the effects of these materials in diabetes; its ease of isolation and purification explains why it is frequently used as a "model" polymer in physiological and clinical studies. Also, because it is well characterized with respect to other sources of dietary nonstarch polysaccharide, it is an ideal candidate for clinical use. It is extracted from the seed endosperm of a leguminous plant (*Cyamopsis tetragonoloba* (L.) Taub; see Figure 14.1) indigenous to the Indian subcontinent.

To recover guar gum from the seed, the endosperm halves (splits) must be separated from the hull and the cotyledon. The splits are ground to a fine flour and may then be purified by repeated

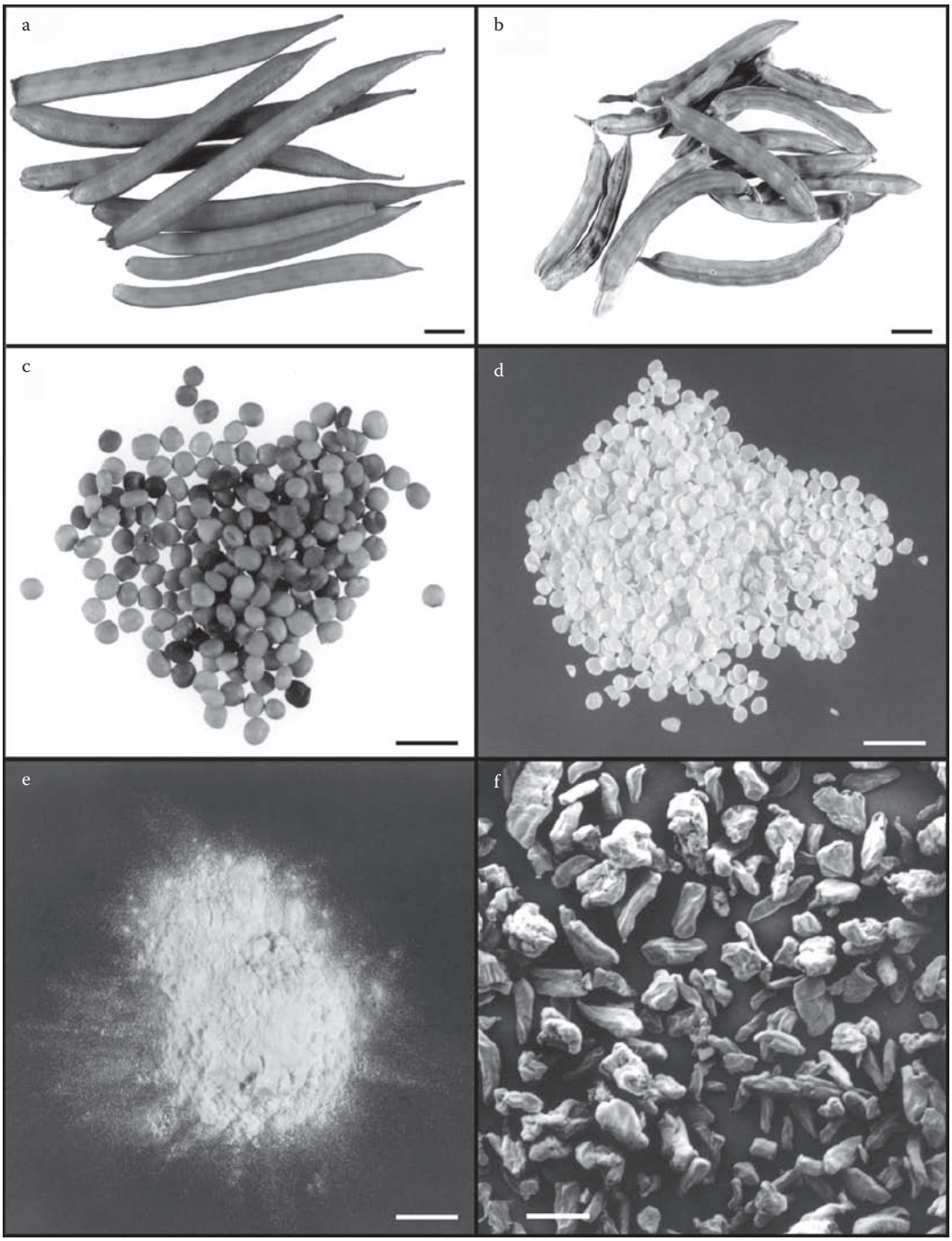


FIGURE 14.1 Pictures of pods, seeds, and endosperm extract of the guar plant (*Cyamopsis tetragonoloba* (L.) Taub.), a member of the Leguminosae family. (a) Green pods, scale bar = 1.3 cm. (b) Dried pods, scale bar = 1.6 cm. (c) Seeds, scale bar = 1 cm. (d) Endosperm halves (splits), scale bar = 1 cm. (e) Guar gum flour, scale bar = 1 cm. (f) Scanning electron micrograph of guar gum flour, scale bar = 100 μm. (From Ellis, P.R., et al., *Handbook of Dietary Fiber*, Marcel Dekker, New York, 2001. With permission.)

alcohol washings. In this way, guar gum is commercially produced as a flour and is frequently used as an additive (E412) in the food industry for its thickening and stabilizing properties.[76]

The ability of the galactomannan component of guar gum to hydrate and increase the viscosity, or thickness, of the intestinal contents is an important determinant of its physiological effects. The majority of polysaccharides used in nutritional studies exist in solution as "random coils" and the number and molecular size of the polymer chains are critical determinants of viscosity and thus physiological activity.[9]

One reasonable explanation of the effects of guar on postprandial blood glucose and insulin is that it reduces the rate (and perhaps the extent) of digestion and absorption of available carbohydrate in the gastrointestinal tract.[77,78] Obtaining quantitative estimates of glucose absorption in humans is extremely difficult; for example, measuring direct glucose delivery to the liver is not possible because access to the hepatic portal vein is very difficult. However, studies in pigs — a useful animal model for studies on dietary polysaccharides — have provided direct evidence that guar gum decreases the rate of glucose absorption. In these experiments, it was possible to measure glucose concentrations simultaneously in the hepatic portal vein and peripheral blood (via the mesenteric artery) as well as the flow rate of the portal blood. Significant reductions in glucose absorption over 4 hours were observed in the experimental animals given guar gum doses equivalent to those consumed by humans in clinical studies.[79,80]

In the same studies, insulin secretion was significantly decreased over the same period in response to the guar diet. This suggests that the attenuation in the plasma insulin levels seen in humans is attributed to a reduction in insulin secretion from the pancreatic islet β-cells in response to a lowered rate of glucose absorption. Also, a number of human studies have shown that guar gum decreases the postprandial rise in the insulinotropic hormones, plasma gastric inhibitory polypeptide, and glucagon-like peptide-1; this may partly explain the insulin-lowering action of guar gum.[81,82] Another interpretation of data showing decreases in the peripheral blood insulin concentrations is that hepatic extraction of insulin, a normal process by which insulin is removed from the blood circulation, has increased. Studies carried out to substantiate this have been largely contradictory, however.

In relation to long-term studies of insulin action in experimental animals and humans, it has been reported that guar gum increases (improves) insulin sensitivity.[83] A reduction in sensitivity to insulin (i.e., insulin resistance) is seen as a decrease in the response of tissues to insulin stimulation and is considered to be an important risk factor for coronary heart disease and type 2 diabetes.[84]

There is little doubt that the consumption of guar gum, whether mixed in a drink or solid food, can significantly modify digesta properties at all sites of the gastrointestinal tract. One important feature is the capacity of guar gum at relatively low concentrations to form a highly viscous network in solution. In complex systems such as those in the stomach and gut lumen, it is unlikely that one mechanism can fully explain the effects of guar gum. A number of physicochemical mechanisms may be involved that are largely dependent on the type and form of the guar gum ingested (this has been discussed in detail by Ellis et al.[10]). Much of the literature indicates that guar gum decreases the rate of glucose absorption into the hepatic portal vein by inhibiting the processes associated with digestion and absorption of available carbohydrates. These processes include gastric function, intestinal transit and mixing, α-amylase–starch interactions, and the movement of products of starch hydrolysis to the gut mucosa.

Also important, particularly when the NSP is part of a complex food matrix such as bread, may be the inhibition of the rate of digestion by the formation of an enzyme-resistant "barrier" around the starch granules.[85] To investigate this possibility, the topological relationship between the galactomannan and starch in wheat bread was examined, using a range of microscopical techniques; the effect of galactomannan on the rate of hydrolysis of wheat starch by pancreatic α-amylase was also determined. Microstructural studies of digesta taken from pigs 4 hours after they had been fed guar wheat bread revealed that the galactomannan component of guar gum still adhered to the surface of individual starch granules in the bread.[86] This suggests that, in addition to its

rheological effects, the galactomannan polymer may also act as a physical barrier to enzyme–substrate interactions and the release of nutrients from the food matrix.

A more recent study has also shown that guar galactomannan inhibits the action of pancreatic amylase by binding noncompetitively with the enzyme.[87] These binding mechanisms may partly explain why guar galactomannan partially depolymerized to reduce molecular weight still retains its capacity to reduce postprandial hyperglycemia and plasma insulin concentrations in diabetic and nondiabetic human subjects.[59,85]

NEW SOURCES OF PLANT POLYSACCHARIDES

Although only a small range of NSPs extracted from plant sources have been studied in any depth with respect to their potential biological effects, it is likely that there are other polysaccharides present in plant foods that are used by particular communities as food thickeners or commodities, which may have similar effects. For example, in West Africa, various plant materials have traditionally been used to give a viscous (thickened) texture to soups and stews. Several such materials were obtained and preliminary studies examined the effect of including flours from three of the most commonly used materials — *Afzelia africana* Se Pers, *Detarium senegalense* Gmelin (both leguminous seeds), and *Cissus rotundifolia* (the stem of a shrub) — on plasma cholesterol levels of rats.

All three materials resulted in lower cholesterol values after feeding for 14 days compared to the control semisynthetic diet; however, the rats fed *A. africana* showed some ill-effects.[87,88] The other two materials, *D. senegalense* and *C. rotundifolia*, were therefore used for further studies in healthy adults and in people with diabetes mellitus. The effects of these two plant materials illustrate the complex ways in which polysaccharides in foods may modify blood glucose and insulin levels.

The materials used in the studies were flours made from the detarium seeds (see Figure 14.2) and cissus stem prepared as closely as possible to the way in which they are used in Nigeria and they were initially tested in normal adults. The materials were studied in two breakfast meal formats: first, they were fed as a stew (with boiled rice providing the carbohydrate load) in the way in which

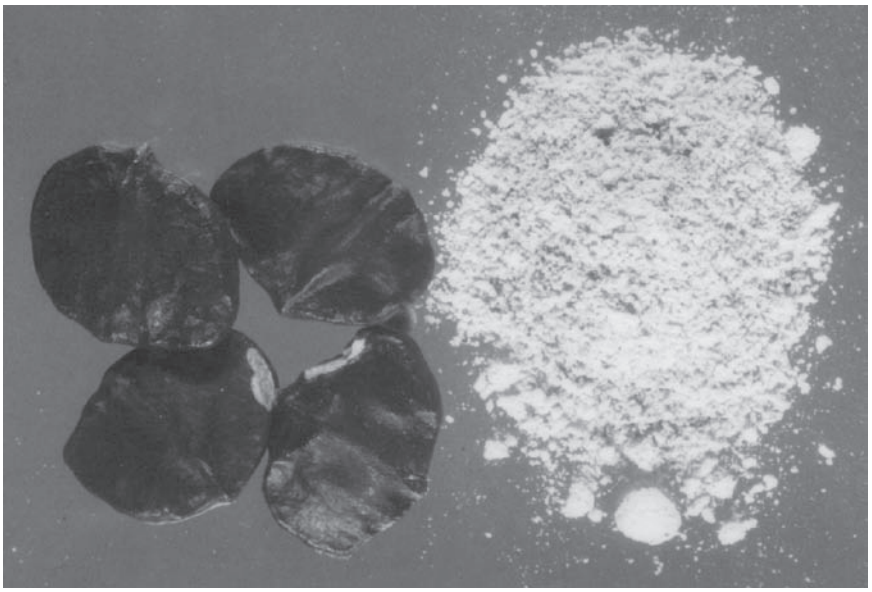


FIGURE 14.2 Seeds and flour of *Detarium senegalense* Gmelin.

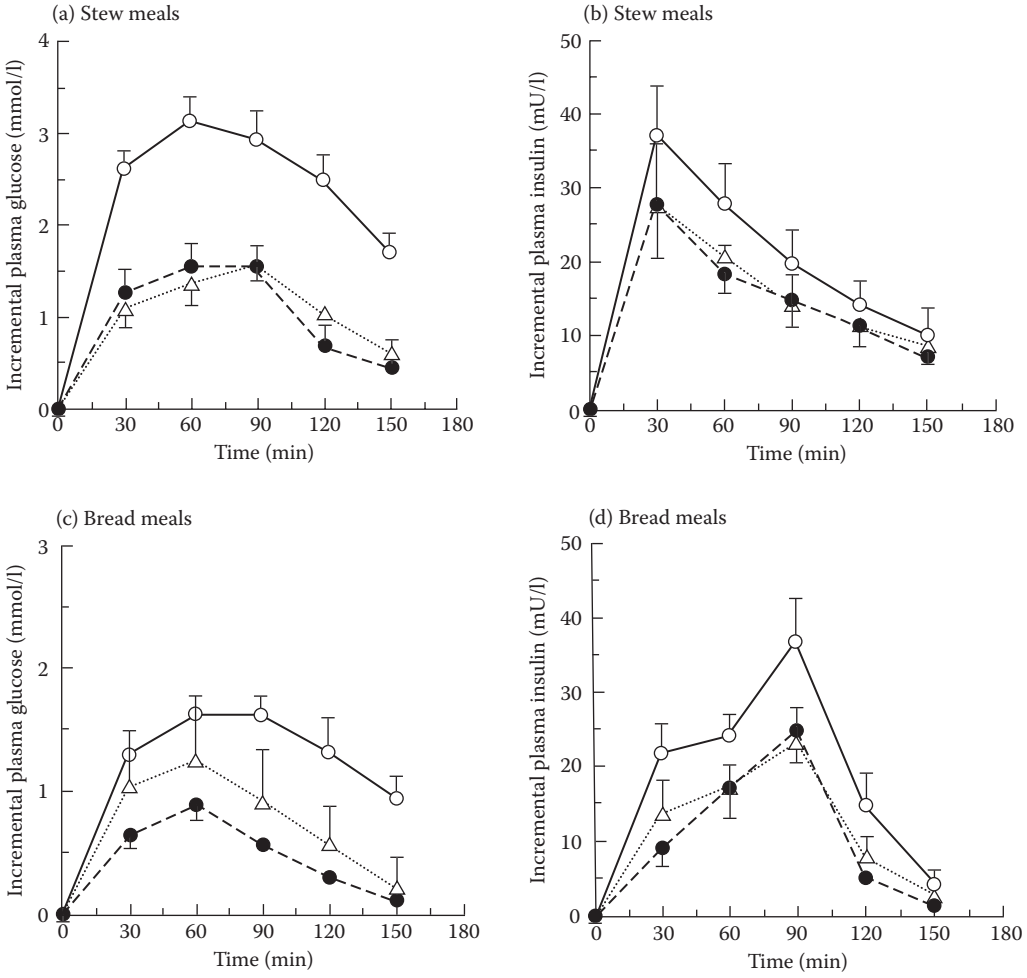


FIGURE 14.3 Incremental plasma glucose concentrations of healthy human subjects at five time points after meals of stew and rice or bread and jam (c,d) containing detarium flour (------), cissus flour (···Δ···), or without plant flour supplement (_ _ _). (From Onyechi, U.A., Judd, P.A., and Ellis, P.R., *Br. J. Nutr.*, 80, 419–428, 1998. With permission.)

they would be traditionally eaten in Nigeria; second, they were fed after incorporation into wheat bread.[54] In each case, the effect of the NSP-containing meals was compared with a similar meal without the added fiber. Compared to the control meals, the detarium and cissus meals elicited significant reductions in plasma glucose levels at most time points (measured at 30-minute intervals for 2.5 hours) and in the overall area under the blood glucose curve (AUC reductions 38 to 62%). Significant reductions were also seen in plasma insulin concentrations at various postprandial time points and for the area under the curve for the detarium and cissus breads, but not for the stew meals (see Figure 14.3).

The results of this study illustrate several of the points made in the earlier part of this review. Analysis of the detarium flour shows that it contains about 600 g/kg of a water-soluble non-starch polysaccharide composed mainly of xyloglucan with an intrinsic viscosity of 8 to 9 dl/g — i.e., it is a high molecular weight polymer.[89,90] It is also clear from characterization studies (e.g., rheology) of the extracted xyloglucan that this component is responsible for the increase in viscosity when the detarium flour is added to water.[89,90] It is likely, therefore, that the viscosity-producing effect

of the xyloglucan in detarium has an important, if not major, role in slowing the rate of digestion of available carbohydrate in the detarium meals.

When detarium was fed in the form of bread in which the polysaccharide was intimately mixed with the wheat flour and baked, a greater reduction in blood glucose levels was found (despite the actual concentration of the polysaccharide being slightly less). This suggests that the presence of detarium xyloglucan acts as a "barrier" to amylase–starch reaction in the small intestine, as shown previously with guar gum.[86] This illustrates the concept that the physicochemical properties of NSPs and the form in which the NSPs are fed are important factors when assessing biological activity.

Preliminary analysis of the cissus flour indicates that it contains a water-soluble, nonstarch polysaccharide with an intrinsic viscosity of 5.5 dl/g — i.e., significantly lower than that of detarium flour. The cissus stew meal contained about 40% less water-soluble non-starch polysaccharide than the detarium meal and yet had similar blood glucose-lowering effects. This may be explained by the differences in the types of starch between the meals containing detarium and cissus. The meals had similar amounts of starch, but about 50% of the starch in the cissus meal was accounted for by the uncooked cissus flour, which was added to the stew towards the end of cooking. It is therefore possible that the starch in the flour was less swollen and gelatinized than that in the rice and bread. This could account for the better than predicted effect of the cissus in the stew. The starch may also have been more resistant to amylase action in the upper gastrointestinal tract[92]; some indication of this was seen in the preliminary testing of the African foods in a rat model.[87,88] In the bread study, when similar amounts of water-soluble, nonstarch polysaccharide were fed, the cissus bread appeared less effective at lowering blood glucose and insulin than the detarium bread was. Compared with the stew meal, the starch in the cissus may have been rendered more digestible by the cooking process, thus increasing the glycemic response.

Because the effects of the detarium were more marked than those for cissus when given as a bread meal, it was decided to test the effect on blood glucose and insulin of breakfasts containing detarium-supplemented bread in 12 patients with type 2 diabetes. The results demonstrated significant depressions in the glycemic and insulinemic responses. In this study, the detarium bread had a GI of 65 compared to standard white wheat bread with a GI of 100.[93]

Foods such as detarium, cissus, and a range of others are part of the traditional diet in West Africa, but are consumed less as populations become more urbanized. It is interesting to speculate whether the move away from their use may be contributing to the increase in incidence of diabetes in developing populations.[94]

CONCLUSIONS

Dietary polysaccharides are high molecular weight compounds with complex structures and properties. Some, such as starches, will act as an energy source in the body; however, the digestion of the starches and the availability of hydrolyzed products released (e.g., maltose) will depend upon many factors including, most importantly, the structure and properties of the starch, which will vary in different foods. As part of an intact plant cell wall, NSPs will affect the way in which the available carbohydrate is released from plant cells and plant polysaccharide extracts that form viscous solutions in water have specific effects in reducing postprandial blood glucose. When added to foods, these soluble NSPs will reduce the GI of carbohydrate containing foods.

Plant foods naturally high in NSP and starch, such as many legume species, usually have a low GI; this may be due not only to the presence of the NSP, but also to the physical state of intracellular starch and perhaps to the presence of α-amylase inhibitors. These properties have been thoroughly researched over the last three to four decades and are all important in the diet of people with DM. This view would probably not have surprised the ancient Indian physicians who wrote, at least as early as the first century A.D. (in the Caraka–Samita), of the use of legumes in the treatment of glycosuria — even before Aretaeus had applied the term *diabetes*.[1]

REFERENCES

1. Leeds, A.R., The dietary management of diabetes in adults, *Proc Nutr Soc*, 38, 365–71, 1979.
2. Wheeler, M.L., Cycles: diabetes nutrition recommendations — past, present, and future, *Diabetes Spectrum*, 13(3), 116–123, 2000.
3. Franz, M.J., Hozmeister, L.A., Bantle, J.P. et al., Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related conditions, *Diabetes Care*, 25, 148–198, 2002.
4. Nutrition Sub-Committee of the Diabetes Care Advisory Committee of Diabetes U.K., The dietitians challenge: the implementation of nutritional advice for people with diabetes. *J Hum Nutr Dietetics*, 16, 421–424, 2003.
5. Cummings, J.H, Macfarlane, G.T., The control and consequences of bacterial fermentation in the human colon, *J Appl Bacteriol*, 70, 443–459, 1991.
6. Selvendran, R.R., Stevens, B.J.H., Du Pont, M.S. Dietary fibre: chemistry, analysis and properties. In *Advances in Food Research*, Vol. 31, 118–213 (Chichester, C.O., Mrak, E.M, and Schweigert, B.S., Eds.) London: Academic Press, 1987.
7. Carpita, N.C. The chemical structure of the cell walls of higher plants, in *Dietary Fibre, Chemistry, Physiology and Health Effects*, 15–30 (D. Kritchevsky, C. Bonfield and J.W. Anderson, Eds.) London: Plenum Press, 1990.
8. Waldron, K.W., Parker, M.L., Smith, A.C., Plant cell walls and food quality, *Compr Rev Food Sci Food Saf,* 2, 101–119, 2003.
9. Morris, E.R., Physicochemical properties of food polysaccharides, in *Dietary Fibre — a Component of Food, Nutritional Function in Health and Disease*, 41–56 (Schweizrer, T.A. and Edwards, C.A., Eds.) London: Springer–Verlag, 1992.
10. Ellis, P.R., Rayment, P., Wang, Q., A physicochemical perspective of plant polysaccharides in relation to glucose absorption, insulin secretion and the entero–insular axis, *Proc Nutr Soc*, 55, 881–898, 1996.
11. O.R. Fennema, *Food Chemistry,* 3rd ed., New York: Marcel Dekker Inc., 192–193, 1996.
12. French, D. Organization of starch granules, in *Starch Chemistry and Technology* (Whistler, R.L., BeMiller, J.N., Paschall, E.F., Eds.) Orlando, FL: Academic Press Inc., 1984.
13. Slaughter, S.L., Ellis, P.R., Jackson, E.C. et al., An investigation of the action of porcine pancreatic alpha-amylase on native and gelatinised starches, *Biochim Biophys Acta*, 1525(1–2), 29–36, 2001.
14. Englyst, H.N, Cummings, J.H., Nonstarch polysaccharides (dietary fiber) and resistant starch, in *New Developments in Dietary Fiber. Physiological, Physicochemical, and Analytical Aspects* (Furda, I. and Brine, C.J., Eds.) New York: Plenum Press, 205–225, 1990.
15. Englyst, H.N., Cummings, J.H., Dietary fibre and starch: definition, classification and measurement, in *Dietary Fibre Perspectives*: *Reviews and Bibliography* (Leeds, A.R., Ed.) London: John Libbey, 3–26, 1990.
16. Crapo, P.A., Reaven, G., Olefsky, J., Postprandial plasma-glucose and -insulin responses to different complex carbohydrates, *Diabetes*, 26, 1178–83, 1977.
17. Resistant starch. Proceedings for the 2nd plenary meeting of EURESTA: European FLAIR Concerted Action No. 11 on physiological implications of the consumption of resistant starch in man. Crete, 29 May–2 June 1991, *Eur J Clin Nutr*, Oct; 46 Suppl 2:S1–148, 1992.
18. Wolever, T.M., The glycemic index Wld., *Rev Nutr Dietet*, 61, 120–185, 1990.
19. Foster–Powell, K., Brand–Miller, J.C., International tables of glycemic index. *Am J Clin Nutr*, 62, 871S–893S, 1995.
20. Wolever, T.M.S., Nuttell, F.Q., Lee, R. et al., Prediction of the relative blood glucose response of mixed meals using the white bread glycemic index, *Diabetes Care*, 8, 418–428, 1985.
21. Le Floch, J.P., Baudin, E., Escuyer, P. et al., Reproducibility of glucose and insulin responses to mixed meal in type II diabetic patients, *Diabetes Care*, 14, 138–140, 1991.
22. Foster–Powell, K., Holt, S.H.A., Brand–Miller, J.C., International table of glycemic index and glycemic load, *Am J Clin Nutr*, 76, 5–56, 2002.
23. Salmeron, J., Ascherio, A., Rimm, E.B. et al., Dietary fiber, glycemic load, and risk of NIDDM in men, *Diabetes Care*, 20, 545–50, 1997.
24. Salmeron, J., Manson, J.E., Stampfer, M.J. et al., Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women, *JAMA*, 277, 472–477, 1997.

25. Hu, F.B., Manson, J.E, Stampfer, M.J. et al., Diet, lifestyle and the risk of type 2 diabetes in women, *NEJM*, 34, 5790–5797, 2001.
26. Thompson, L.U., Yoon, J.H., Jenkins, D.J.A. et al., Relationship between polyphenol intake and blood glucose response of normal and diabetic individuals, *Am J Clin Nutr,* 39, 745–751, 1984.
27. Yoon, J.H., Thompson, L.U., Jenkins, D.J.A., The effect of phytic acid on *in vitro* rate of starch digestibility and blood glucose response, *Am J Clin Nutr,* 38, 835–842, 1983.
28. Bryans, J., Judd, P.A., Ellis, P.R. An investigation of the effects of black tea (*Camellia sinensis* (L)) on postprandial glycemia in healthy humans, *Proc Nutr Soc*, 62, 63A, 2003.
29. Johnston, K.L., Clifford, M.N., Morgan, L.M., Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine, *Am J Clin Nutr*, 78(4), 728–733, 2003.
30. Nuttall, F.Q., Mooradian, A.D., Gannon, M.C. et al., Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load, *Diabetes Care*, 7, 465–470, 1984.
31. Bornet, F.R.J., Costagliola, D., Rizkalla, S.W. et al., Insulinemic and glycemic indexes of six starch-rich foods taken alone and in a mixed meal by type 2 diabetics, *Am J Clin Nutr*, 45, 588–595, 1987.
32. Welch, I.M., Bruce, C., Hill, S.E. et al., Duodenal and ileal lipid suppresses postprandial blood glucose and insulin responses in man: possible implications for the dietary management of diabetes mellitus, *Clin Sci (Lond),* 72, 209–216, 1987.
33. Gannon, M.C., Nuttall, F.Q., Neil, B.J., Westphal, S.A., The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects, *Metabolism,* 37, 1081–1088, 1988.
34. Wolever, T.M.S., Katzman–Relle, L., Jenkins, A.L. et al., Glycemic index of 102 complex carbohydrate foods in patients with diabetes, *Nutr Res,* 14, 651–669, 1994.
35. Schilze, M.B., Liu, S., Rimm, E.B. et al., Glycemic index, glycemic load, and dietary fibre intake and incidence of type two diabetes in younger and middle-aged women, *Am J Clin Nutr,* 80, 384–356, 2004.
36. Reaven, G.M., Role of insulin resistance in human disease (syndrome X): an expanded definition, *Annu Rev Med*, 44, 121–131, 1993.
37. Nipels, G., Determinants for the progression from impaired glucose tolerance to non-insulin dependent diabetes mellitus, *Eur J Clin Invest*, 28(suppl 2), 8–13, 1998.
38. Burke, B.J., Hartog, M., Heaton, K.W., Hooper, S., Assessment of the metabolic effects of dietary carbohydrate and fibre by measuring urinary excretion of C-peptide, *Hum Nutr Clin Nutr*, 36(5), 373–380, 1982.
39. Jenkins, D.J.A., Wolever, T.M.S., Taylor, R.H. et al., Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr,* 34, 362–366, 1981.
40. FAO/WHO Expert Consultation Committee Carbohydrates in human nutrition (FAO Food and Nutrition paper 66) Rome, FAO of United Nations, 1998.
41. Saris, W.H., Asp, N.G., Bjorck, I. et al., Functional food science and substrate metabolism, *Br J Nutr*, 80, Suppl. 1, S47–S75, 1998.
42. Frost, G., Dornhorst, A., The relevance of the glycemic index to our understanding of dietary carbohydrates, *Diabetes Med,* 17, 336–345, 2000.
43. Brand, J.C., Colagiuri, S., Crossman, S., Low-glycemic index foods improve long-term glycemic control in NIDDM, *Diabetes Care,* 14, 95–101, 1991.
44. Jarvi, A.E., Karlstrom, B.E., Granfeldt, Y.E. et al., Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients, *Diabetes Care, 22*, 10–18, 1999.
45. Rendell, M., Dietary treatment of diabetes mellitus. *N Engl J Med*, 342, 1440–1441, 2000.
46. Ellis, P.R., *The Right Fibre for the Right Disease*, 33–42, London: The Royal Society of Medicine Press Ltd, 1999.
47. Simpson, H.C., Simpson, R.W., Lousley, S. et al., A high carbohydrate leguminous fiber diet improves all aspects of diabetic control, *Lancet*, 1, 1–5, 1981.
48. Fuessl, H.S., Williams, G., Adrian, T.E. et al., Guar sprinkled on food: effect on glycemic control, plasma lipids and gut hormones in non-insulin dependent diabetic patients, *Diabetes Med,* 4, 463–468, 1987.
49. Peterson, D.B., Ellis, P.R., Baylis, J.M. et al., Low dose guar in a novel food product: improved metabolic control in non-insulin-dependent diabetes, *Diabetes Med*, 4, 111–115, 1987.

50. Chandalia, M., Garg, A., Lutjohann, D., Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus, *N Engl J Med,* 342, 1392–98, 2000.
51. Augustin, L.S., Franchesci, S., Jenkins, D.J.A, Glycemic index in chronic disease: a review, *Eur J Clin Nutr,* 56, 1049–1071, 2000.
52. Anderson, J.W., Randles, K.M., Kendall, C.W.C., Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence*, J Am Coll Nutr*, 23(1), 5–17, 2004.
53. Feskens, E.J.M, Bowles, C.H, Kromhout, D., Carbohydrate intake and body mass index in relation to the risk of glucose intolerance in an elderly population, *Am J Clin Nutr,* 54, 136–140, 1991.
54. Onyechi, U.A., Judd, P.A., Ellis, P.R., African plant foods rich in non-starch polysaccharides reduce postprandial blood glucose and insulin concentrations in healthy human subjects, *Br J Nutr*, 80, 419–428, 1998.
55. Liljeberg, H.G.M., Björck, I.M.E., Delayed gastric emptying rate as a potential mechanism for lowered glycemia after eating sourdough bread: studies in humans and rats using test products with added organic acids or an organic salt, *Am J Clin Nutr*, 64, 886–893, 1996.
56. Thibault, J.F., Lahaye, M., Guillon, F., Physicochemical properties of food plant cell walls, in *Dietary Fibre — a Component of Food. Nutritional Function in Health and Disease,* 21–39 (Schweizer, T.F. and Edwards, C.A., Eds.) London: Springer–Verlag, 1992.
57. Jenkins, D.J.A, Goff, D.V, Leeds, A.R. et al., Unabsorbable carbohydrates and diabetes: decreased postprandial hyperglycemia, *Lancet*, 2, 172–174, 1976.
58. Ellis, P.R., Polysaccharide gums, their modulation of carbohydrate and lipid metabolism and role in the treatment of diabetes mellitus, in *Gums and Stabilisers for the Food Industry* (Phillips, G.O., Wellock, D.J., Williams, P.A., Eds.) Oxford: Pergammon, 207–216, 1994.
59. Gatenby, S.J, Ellis, P.R., Morgan, L.M., Judd, P.A., Effect of partially depolymerized guar gum on acute metabolic variables in patients with non-insulin dependent diabetes, *Diabetic Medicine*, 13, 378–381, 1996.
60. Florholmen, J., Arvidsson–Lenner, R., Jorde, R. et al., The effect of Metamucil on postprandial blood glucose and plasma gastric inhibitory peptide in insulin-dependent diabetics, *Acta Med Scand,* 212, 237–239, 1982.
61. Frati–Munari, A.C., Fernandez–Harp, J.A., Becerril, M. et al., Decrease in serum lipids, glycemia and body weight by *Plantago psyllium* in obese and diabetic patients, *Arch Invest Med*, 14, 259–268, 1983.
62. Pastors, J.G., Blaisdell, P.W., Balm, T.K., Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-dependent diabetes, *Am J Clin Nutr*, 53, 1431–1435, 1991.
63. Doi, K., Matsura, M., Kawra, A. et al., Treatmant of diabetes with glucomannan, *Lancet*, 1, 987–988, 1979.
64. Shima, K., Tabta, M., Tanakia, A., Effect of dietary fiber (guar gum and Konjac powder) on diabetic control, *Nutr Rep Int*, 26, 297–302, 1982.
65. Braaten, J.D., Scott, F.W., Wood, P.J. et al., High β-glucan oat bran and oat gum reduce postprandial blood glucose and insulin in subjects with and without type 2 diabetes, *Diabetes Med*, 11, 312–318, 1994.
66. Jenkins, A.L., Jenkins, D.J.A., Zdravkovic, U. et al., Depression of the glycemic index by high levels of β-glucan fiber in two functional foods tested in type 2 diabetes, *Eur J Clin Nutr*, 56: 622–688, 2002.
67. Tappy, L., Gugolz, E., Wursch, P., Effects of breakfast cereals containing various amounts of beta-glucan fibers on plasma glucose and insulin responses in NIDDM subjects, *Diabetes Care*, 19, 831–834, 1996.
68. Zhong, X.X., Lu, X., Walker, K.Z. et al., Arabinoxylan fiber, a byproduct of wheat flour processing, reduces the postprandial glucose response in normoglycemic subjects, *Am J Clin Nutr*, 71(5), 1123–1128, 2000.
69. Groop, P.H., Aro, A., Stenman, S. et al., Long-term effects of guar gum in subjects with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr*, 58, 513–518, 1993.
70. Aro, A., Uusitopa, M., Voutlainen, E. et al., Improved diabetic control and hypocholesterolemic effect induced by long-term dietary supplementation with guar gum in type 2 diabetes, *Diabetalogia*, 21, 29–33, 1981.

71. Fuessl, H.S., Williams, G., Adrian, T.E. et al., Guar sprinkled on food: effect on glycemic control, plasma lipids and gut hormones in non-insulin dependent diabetic patients, *Diabetes Med*, 4, 463–468, 1987.
72. Petersen, D.B., Ellis, P.R., Baylis, J.M. et al., Low-dose guar in a novel food product: improved metabolic controls, *Diabetes Med*, 4, 111–115, 1987.
73. Pick, M.E., Hawrish, Z.J., Gee, M.I. et al., Oat-bran concentrate bread products improve long-term control of diabetes: a pilot study, *J Am Diet Assoc*, 96, 1254–1261, 1996.
74. Wursch, P., Pi-Sunyer, X., The role of viscous soluble fiber in the metabolic control of blood glucose. A review with special emphasis on cereals rich in β-glucan, *Diabetes Care,* 20, 1774–1780, 1997.
75. Ebling, P., Hannele, Y-J., Aro, A. et al., Glucose and lipid metabolism and insulin sensitivity in type 1 diabetes: the effect of guar gum, *Am J Clin Nutr*, 48, 98–103, 1988.
76. Ellis, P.R., Wang, Q., Rayment, P. et al., Guar gum: agricultural and botanical aspects, physicochemical and nutritional properties, and its use in the development of functional foods, in *Handbook of Dietary Fiber* (Cho, S.S. and Dreher, M., Eds.) New York: Marcel Dekker, 2001.
77. Edwards, C.A., Read, N.W., Fibre and small intestinal function, in *Dietary Fibre Perspectives 2*, 52–75 (Leeds, A.R. and Burley, V.J., Eds.) London: John Libbey, 1990.
78. Wilmhurst, P., Crawley, J.C.W., The measurement of gastric transit time in obese subjects using ^{24}Na and the effects of energy content and guar gum on gastric emptying and satiety, *Br J Nutr*, 44, 1–6, 1980.
79. Ellis, P.R., Roberts, F.G., Low, A.G. et al., The effect of high-molecular-weight guar gum on net apparent glucose absorption and net apparent insulin and gastric inhibitory polypeptide production in the growing pig: relationship to rheological changes in jejunal digesta, *Br J Nutr*, 74, 539–556, 1995.
80. Blake, D.E., Roberts, F.G., Canibe, N. et al. Quantitative determination of the effect of guar gum on gut hormone secretion in the pig and use of a transit time ultra-sound flow probe, *Proc XV Int Congr Nutr*, Adelaide, Australia. P880, 1993.
81. Morgan, L.M., Goulder, T.J., Tsiolakis, D. et al., The effect of unabsorbable carbohydrate on gut hormones: modification of postprandial GIP secretion by guar, *Diabetologia*, 17, 85–89, 1979.
82. Morgan, L.M., Tredger, J.A., Wright, J. et al., The effect of soluble and insoluble fibre supplemetation on postprandial glucose tolerance, insulin and gastric inhibitory polypeptide secretion in healthy subjects, *Br J Nutr,* 64, 103–110, 1990.
83. Landin, K., Holm, G., Tengborn, L. et al., Guar gum improves insulin sensitivity, blood lipids, blood pressure, and fibrinolysis in healthy men, *Am J Clin Nutr*, 56, 1061–1065, 1992.
84. DeFronzo, R.A., Ferrannini, E., Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease, *Diabetes Care*, 14, 173–194, 1991.
85. Ellis, P.R., Dawoud, F.M., Morris, E.R., Blood glucose, plasma insulin and sensory responses to guar-containing wheat breads: effect of molecular weight and particle size of guar gum, *Br J Nutr*, 66, 363–379, 1991.
86. Brennan, C.S., Blake, D.E., Ellis, P.R. et al., Effect of guar galactomannan on wheat bread microstructure and on the *in vitro* and *in vivo* digestibility of starch in bread, *J Cereal Sci,* 24, 151–160, 1996.
87. Onyechi, U., Potential role of indigenous Nigerian foods in the treatment of non-insulin dependent diabetes mellitus, Ph.D. thesis. London University, 1995.
88. Bell, S., Judd, P.A., Ellis, P.R. et al., An investigation of the effects of two indigenous African foods, *Detarium sengalense* and *Cissus rotundifolia*, on rat plasma cholesterol levels, *Proc Nutr Soc*, 52, 372A, 1993.
89. Wang, Q., Ellis, P.R., Ross–Murphy, S.B. et al., A new polysaccharide from a traditional Nigerian plant food: *Detarium senegalense* Gmelin*, Carbohydr Res,* 284(2), 229–239, 1996.
90. Wang, Q., Ellis, P.R., Ross–Murphy, S.B. et al., Solution characteristics of the xyloglucan extracted from *Detarium senegalense* Gmelin*, Carbohydr Polym*, 31, 115–124, 1997.
91. Colonna, P., Lelou, V., Buléon, A., Limiting factors of starch hydrolysis, *Eur J Clin Nutr*, 46, Supple 2, S17–32, 1992.
92. Slaughter, S.L., Ellis, P.R., Jackson, E.C., Butterworth, P.J., The effect of guar galactomannan and water availability during hydrothermal processing on the hydrolysis of starch catalyzed by pancreatic α-amylase, *Biochim Biophys Acta,* 1571, 55–63, 2002.

93. Ellis, P.R., Oneyechi, U.A., Judd, P.A. et al., Wheat bread containing xyloglucan-rich flour reduces postprandial plasma glucose and insulin concentrations in subjects with type 2 (non-insulin-dependent) diabetes mellitus, *Proceeding of the International Symposium on the Metabolic Syndrome*, August 1999, Ystad, Sweden.
94. Amos, A.F., McCarty, D.J., Zimmet, P., The rising global burden of diabetes and its complications: estimates and projections to the year 2010, *Diabetes Med,* 14, Suppl 5, S1–85, 1997.

15 Saponins

Masayuki Yoshikawa and Hisashi Matsuda

CONTENTS

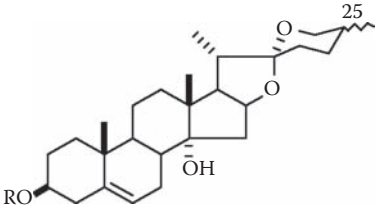
Saponins have been known to be natural detergents, which are structurally constructed of aglycone (triterpenes or steroids) and sugar moieties and are widely distributed throughout the plant kingdom; several types have been found in animals. Saponins have been shown to have many biological and pharmacological functions such as hemolysis, piscicidal, cardiotonic, hypoglycemic, hypocholesterolemic, immunomodulatory, hepatoprotective, anti-inflammatory, antioxidant, and anticarcinogenic activities.[1] The hypoglycemic and/or antihyperglycemic effects of various saponins have been reported using experimental animals, but very few studies on humans have been conducted using purified or partially purified saponins.

Recent studies of saponins from several Chinese medicinal herbs revealed that saponins are metabolized by intestinal microflora; the metabolites are then absorbed via the gastrointestinal tract and act systemically.[2–4] However, in most studies of the hypoglycemic effects of saponins, they were intraperitoneally administered to diabetic mice and rats without this consideration. On the other hand, our recent studies about triterpene saponins with antihyperglycemic effects in sugar-loaded rats suggested that various saponins act in the gastrointestinal tract to inhibit the rate of gastric emptying and the glucose uptake at intestinal brush border membranes as their mechanism of action. This chapter reviews saponin research of the last decade focusing on the hypoglycemic effects in experimentally diabetic animals and accelerating effects on glucose uptake *in vitro*, followed by our recent studies of the antihyperglycemic effects of triterpene saponins.

STEROIDAL SAPONINS WITH HYPOGLYCEMIC EFFECTS IN DIABETIC ANIMALS

Two steroidal saponins, PO-1 (1) and PO-2 (2) (Figure 15.1) were isolated as hypoglycemic constituents from the rhizomes of *Polygonatum falcutum* (Liliaceae). Compound 2 showed marked hypoglycemic activity after intraperitoneal (i.p.) injection into normal mice. In addition, compounds 1 and 2 showed significant hypoglycemic effects in streptozotocin (STZ)-induced diabetic mice. However, a sapogenol, diosgenin (3), did not affect the blood glucose level in normal or STZ-induced diabetic mice (Table 15.1).[5]

Pseudoprototimosaponin AIII (4), prototimosaponin AIII (5), and timosaponin AIII (6) (Figure 15.2) isolated from the rhizomes of *Anemarrhena asphodeloides* (Liliaceae) showed hypoglycemic activity at a dose of 50 mg/kg, i.p., in alloxan-induced diabetic mice. In STZ-induced diabetic mice, compounds 4 and 5 also lowered the blood glucose levels in a dose-dependent manner, and



PO-1 (**1**): R=-Gal—(4)—Glc [25 (*R*) +25 (*S*)]
PO-2 (**2**): R=-Gal—(4)—Glc(2,3)—Glc [25 (*R*) +25 (*S*)]
diosgenin (**3**): R=H [25 (*R*)]
Gal: β-D-galactopyranosyl, Glc: β-D-glucopyranosyl

FIGURE 15.1 Structures of PO-1 (1) and PO-2 (2) from *Polygonatum falcutum*.

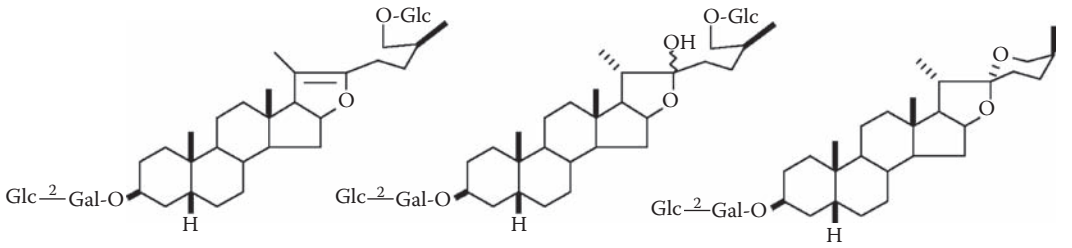
TABLE 15.1
Effects of PO-1 (1) and PO-2 (2) and Diosgenin (3) on Blood Glucose Levels in STZ-Induced Diabetic Mice

		Blood Glucose (mg/100 ml)	
	Dose (mg/kg, i.p.)	0 h	4 h
Control	—	587 ± 28	545 ± 30
PO-1 (1)	10	577 ± 18	501 ± 18[a]
	50	535 ± 24	342 ± 34[b]
PO-2 (2)	10	538 ± 8	453 ± 28[a]
	50	557 ± 17	383 ± 36[b]
Diosgenin (3)	10	570 ± 28	640 ± 28
	50	568 ± 48	531 ± 29

Note: Values are means ± S.E. (n = 4–7).

[a] $p < 0.05$.
[b] $p < 0.01$.

Source: A. Kato et al., *Biol. Pharm. Bull.* 18, 1995, 167–168.



pseudoprototimosaponin AIII (**4**) prototimosaponin AIII (**5**) timosaponin AIII (**6**)

FIGURE 15.2 Structures of pseudoprototimosaponin AIII (4), prototimosaponin AIII (5) and timosaponin AIII (6) from the rhizomes of *Anemarrhena asphodeloides*.

the 50% inhibitory dose values were 4.33 and 6.62 mg/kg, respectively. They did not affect glucose uptake in isolated diaphragms or insulin-releasing activity in mouse pancreas, suggesting that the hypoglycemic mechanism may be due to inhibition of hepatic gluconeogenesis and/or glycogenolysis.[6]

TRITERPENE SAPONINS WITH HYPOGLYCEMIC EFFECTS IN DIABETIC ANIMALS

The 1-butanol extract and a principal dammarane-type triterpene saponin constituent, christinin-A (7) (Figure 15.3) isolated from an Egyptian folk medicine consisting of the leaves of *Zizyphus spina-christi* (Rhamnaceae) significantly reduced the serum glucose level and liver phosphorylase and glucose-6-phosphatase activities, and it significantly increased the serum pyruvate level and liver glycogen content after 4 weeks treatment in STZ-induced diabetic rats. Glucose utilization in normal and diabetic rats was markedly improved, and serum insulin and pancreatic cAMP levels showed significant increases in diabetic rats.[7]

Kim et al. reported hypoglycemic effects of oleanane-type triterpene saponins, kalopanaxsaponins, using STZ-induced diabetic rats. The hypoglycemic effects of hederagenin 3,28-bisdesmosides, kalopanaxsaponins B (10) and H (11), from *Kalopanax pictus* (Araliaceae) and hederagenin (8) and kalopanaxsaponin A (9) (Figure 15.4) obtained as the metabolite of compound 10 by human intestinal microflora were examined in the diabetic rats. Compounds 10 and 11 (25 or 50 mg/kg, i.p.) did not show hypoglycemic effects in the diabetic rats. However, metabolite (9) showed a marked hypoglycemic effect in the diabetic rats at a dose of 25 mg/kg, i.p. In addition, compound 9 effectively reduced the level of serum total and serum VLDL- and LDL-cholesterol, total

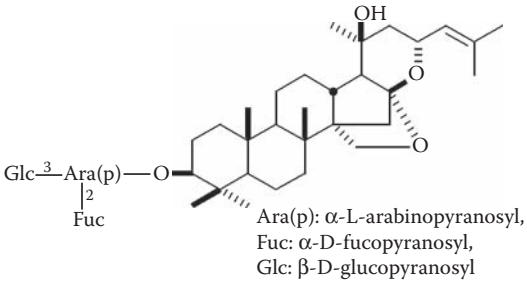


FIGURE 15.3 Structure of christinin-A (7) from *Zizphus spina-christi*.

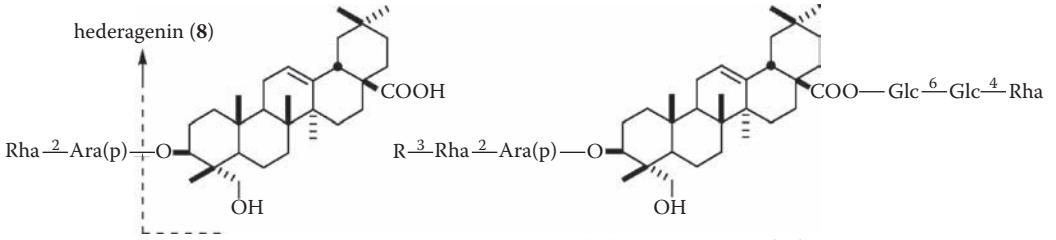


FIGURE 15.4 Structure of kalopanxsaponins A (9), B (10), and H (11) from *Kalopanax pictus*.

TABLE 15.2
Effects of Hederagenin (8) and Kalopanaxsaponins A (9), B (10), and H (11) on Serum Glucose, TG, and Cholesterol (Total and VLDL + LDL) Levels in STZ-Induced Diabetic Rats

				Cholesterol (mg/100 ml)	
	Dose (mg/kg, i.p.)	Glucose (mg/100 ml)	TG (mg/100 ml)	Total	VLDL + LDL
Normal	—	88.5 ± 10.6[a]	74.7 ± 12.9[a]	86.9 ± 8.2[a]	58.9 ± 6.7[a]
Control (STZ)	—	323.3 ± 52.5	132.2 ± 20.3	127.5 ± 7.7	105.2 ± 12.1
Hederagenin (8)	50	203.3 ± 45.7[a]	107.1 ± 10.8[a]	107.2 ± 9.4[a]	88.5 ± 10.9[a]
Kalopanaxsaponin A (9)	25	105.8 ± 12.2[a]	99.0 ± 10.0[a]	104.1 ± 6.7[a]	69.4 ± 15.3[a]
Kalopanaxsaponin B (10)	50	315.0 ± 49.5	128.1 ± 17.4	117.4 ± 17.5	110.7 ± 14.0
Kalopanaxsaponin H (11)	25	320.8 ± 54.2	119.8 ± 13.3	116.9 ± 15.3	108.0 ± 17.1

Note: Values are means ± S.D. ($n = 8$).

[a] $p < 0.05$.

Source: D.H. Kim et al., *Biol. Pharm. Bull.* 21, 1998, 360–365.

lipid, and triglyceride (TG) levels in the diabetic rats. The sapogenol, hederagenin (8), showed weak activity (Table 15.2).[8]

An oleanane-type triterpene saponin, kaikasaponin III (12) (Figure 15.5), from the flowers of *Pueraria thunbergiana* (Leguminosae) showed potent hypoglycemic and hypolipidemic effects in STZ-induced diabetic rats. Treatment with this saponin (5 and 10 mg/kg, i.p.) for 7 days reduced the blood glucose, total cholesterol, LDL- and VLDL-cholesterol, and TG levels. Kaikasaponin III (12) protected the Vero cell line (normal monkey kidney) from injury by hydrogen peroxide. This antioxidant action was suggested to alleviate the STZ-induced toxicity and contribute to the hypoglycemic and hypolipidemic effects of this saponin.[9]

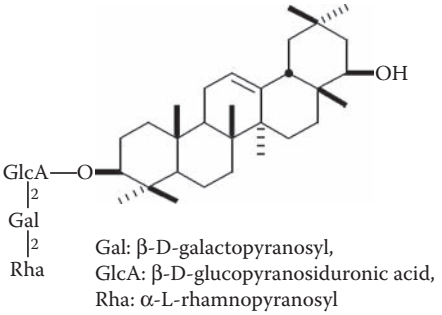


FIGURE 15.5 Structure of kaikasaponin III (12) from *Pueraria thumbergiana*.

TRITERPENE SAPONINS WITH ACCELERATING EFFECTS ON GLUCOSE TRANSPORT *IN VITRO*

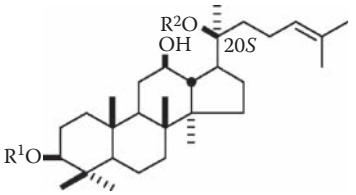
Glucose transporters (GLUTs) are considered to play important roles in providing glucose to various types of cells, regulation of blood glucose levels, absorption of glucose in the intestine and kidney, and regulation of insulin secretion in the pancreas. The root of *Panax ginseng* (Araliaceae) is one of the most important ingredients in traditional medicines in China, Japan, Korea, and other Asian countries for the treatment of various diseases, including psychiatric and neurological diseases and diabetes mellitus. Using sheep erythrocytes, Hasegawa et al. examined the effects of the saponin constituents (ginsenosides) form *P. ginseng* and related dammarane-type triterpene saponins on the initial rates of glucose transport by measurements of 2-deoxy-D-glucose (2-DG) uptake.

The extract (100 μg/ml) of *P. ginseng* stimulates glucose transport in sheep erythrocytes. The saponin constituents, ginsenosides — Rb_1 (14), Rb_2 (15), Rc (16), Re (21), Rf (22), Rg_1 (23), Rg_2 (24), Rh_1 (25), and F1 (20) — and their sapogenols — 20(*R*)-protopanaxadiol (18), 20(*S*)-protopanaxatriol (19) (Figure 15.6), and oleanolic acid (26) — had significant stimulatory effects on 2-DG uptake with an increase of 15 to 30% at concentrations of 0.01 to 10 μ*M*. The maximum stimulatory effect was observed at 0.1 μ*M* of 20(*S*)-protopanaxatriol (19) and represented an increase of 29% over the basal level. In contrast, chikusetsusaponin Ia (17) had significant inhibitory effects (14% under the basal level at 10 μ*M*). It appears likely that their stimulatory effects on glucose uptake via GLUT1 play an important role in various metabolic reactions of tissues, which contribute to the tonic action on the human body.[10]

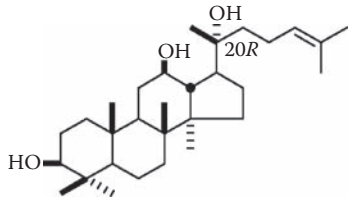
TRITERPENE SAPONINS WITH ANTIHYPERGLYCEMIC EFFECTS IN SUGAR-LOADED ANIMALS

Medicines that reduce postprandial hyperglycemia by suppressing the absorption of carbohydrates have been shown to be effective for prevention and treatment of non-insulin-dependent diabetes mellitus. Many foodstuffs are known to have not only nutritive and taste values but also medicinal effects. Recently, the methanolic extracts of several medicinal foodstuffs were found to show potent inhibitory activity on the increase of serum glucose levels in oral sucrose or glucose-loaded rats.

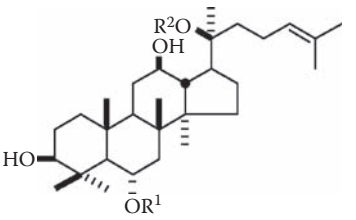
Through a bioassay-guided separation, many triterpene saponins were isolated as the active principles and their chemical structures were determined. By examination of the structure requirements for the hypoglycemic activity, the active saponins could be classified into three types[11–13] (Figure 15.7):



	R^1	R^2
20(*S*)-protopanaxadiol (**13**):	-H	-H
ginsenoside-Rb_1 (**14**):	-Glc^{2}—Glc	-Glc^{6}—Glc
ginsenoside-Rb_2 (**15**):	-Glc^{2}—Glc	-Glc^{6}—Ara(p)
ginsenoside-Rc (**16**):	-Glc^{2}—Glc	-Glc^{6}—Ara(f)
chikusetsusaponin Ia (**17**):	-Glc^{6}—Xyl	-H



20(*R*)-protopanaxadiol (**18**)



	R^1	R^2
20(*S*)-protopanaxatriol (**19**):	-H	-H
ginsenoside-F1 (**20**):	-H	-Glc
ginsenoside-Re (**21**):	-Glc^{2}—Rha	-Glc
ginsenoside-Rf (**22**):	-Glc^{2}—Glc	-H
ginsenoside-Rg_1 (**23**):	-Glc	-Glc
ginsenoside-Rg_2 (**24**):	-Glc^{2}—Rha	-H
ginsenoside-Rh_1 (**25**):	-Glc	-H

Ara(f): α-L-arabinofuranosyl, Ara(p): α-L-arabinopyranosyl
Glc: β-D-glucopyranosyl, Rha: α-L-rhamnopyranosyl,
Xyl: β-D-xylopyranosyl

FIGURE 15.6 Structure of ginsenosides (14–17, 20–25) and related compounds from *Panax ginseng*.

Olean-12-en-28-oic acid 3-monodesmoside
Acylated polyhydroxyolean-12-ene 3-monodesmoside
Olean-12-ene 3,28-acylated bisdesmoside

These types of saponins were found to exhibit antihyperglycemic effects on oral glucose-loaded rats, mainly by decreasing the rate of gastric emptying and partly by inhibiting the glucose transport system at the small intestinal brush border.

Olean-12-en-28-oic Acid 3-Monodesmosides

The bark and root cortex of *Aralia elata* (Araliaceae) have been used in Japanese and Chinese traditional medicines as a tonic and as antidiabetic and antiarthritic agents. The young shoot of this medicinal plant, which is commonly called "taranome" in Japanese, has been known as a food garnish in Japanese-style dishes. It was found that the methanol extracts of the bark, root cortex, and young shoots of this plant have an inhibitory effect on the increase in serum glucose levels in sucrose- or glucose-loaded rats.

The methanol extracts were subjected to bioassay-guided separation procedures to afford 11 new oleanane-type triterpene saponins named elatosides A through K, together with many known oligoglycosides. Among the compounds tested, oleanolic acid 3-monodesmosides (elatosides A, E, and I) and caulophyllogenin (olean-3β,16α,23-trihydroxy-12-en-28-oic acid) 3-monodesmosides (elatosides G), and ectinocystic acid (olean-3β,16α-dihydroxy-12-en-28-oic acid) 3-monodesmoside (elatoside H) showed antihyperglycemic effects in sucrose-loaded rats at a dose of 100 mg/kg, p.o. On the other hand, the 3,28-bisdesmosides of their aglycone (elatosides C, F, and K) exhibited weak inhibitory effects and oleanolic acid (26), an aglycone of these saponins, lacked the activity completely.[14–16]

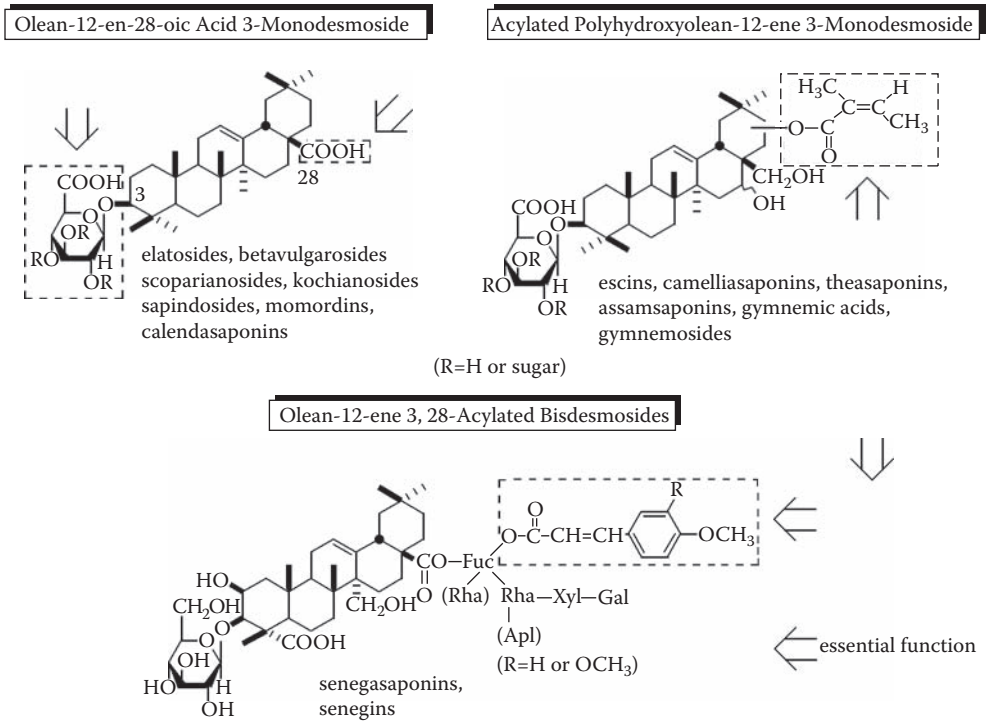


FIGURE 15.7 Three types of triterpene saponin with antihyperglycemic effect.

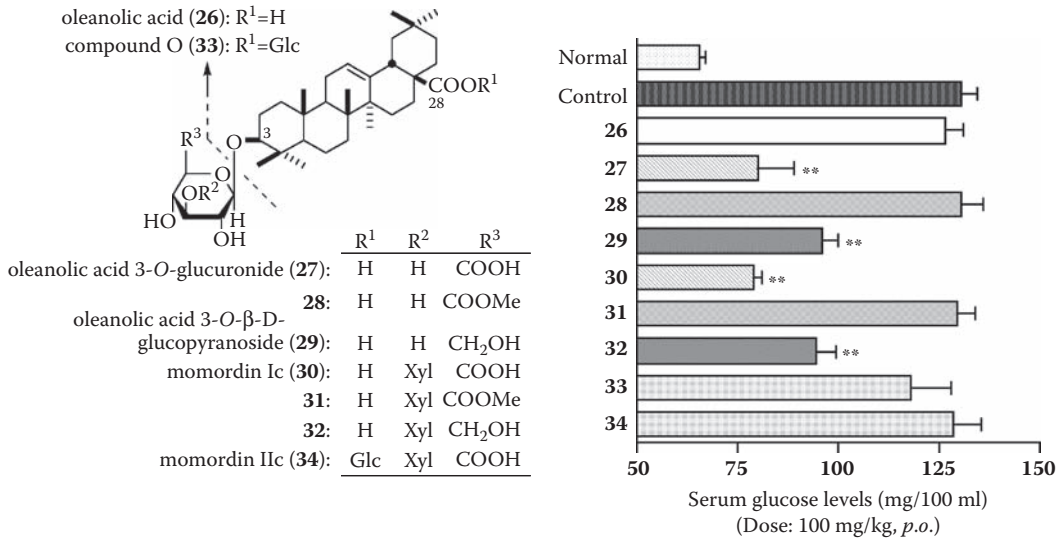
Furthermore, many oleanolic acid glycosides have been obtained from various natural medicines, such as:

Betavulgarosides from *Beta vulgaris* (leaves and roots, Chenopodiaceae)[17–20]
Momordins and kochianosides from *Kochia scoparia* (fruit, Chenopodiaceae) and *Momordica cochinchinensis* (seeds and roots, Cucurbitaceae)[21,22]
Basellasaponins from *Basella rubra* (aerial parts, Basellaceae) and *Spinacia oleacea* (aerial parts, Chenopodiaceae)[23,24]
Calendasaponins from *Calendula officinalis* (flowers, Compositae)[25]
Chikusetsusaponins from *Panax japonicus* (rhizomes, Araliaceae)

The effects of these glycosides on the increase in serum glucose levels in glucose-loaded rats have been examined to clarify structure–activity relationships for the antihyperglycemic activity. An example of the results is shown in Figure 15.8. Oleanolic acid 3-*O*-glucuronide (27) and momordin Ic (30) strongly inhibited the increase in serum glucose levels. The 3-*O*-β-D-glucopyranosyl derivatives (29, 32) also produced significant inhibition but were weaker than the corresponding 3-*O*-glucuronides (27, 30), respectively.

On the other hand, the 6′-methyl esters (28, 31) lacked significant activity. Momordin IIc (34) and compound O (33), which have a 28-ester glucoside moiety, also lacked activity. These results suggest the following structure requirements of oleanolic acid glycosides[26]:

- The 3-*O*-glycoside moiety is essential for activity.
- The 28-ester glucoside moiety reduces activity.



	R^1	R^2	R^3
oleanolic acid 3-*O*-glucuronide (**27**):	H	H	COOH
28:	H	H	COOMe
oleanolic acid 3-*O*-β-D-glucopyranoside (**29**):	H	H	CH_2OH
momordin Ic (**30**):	H	Xyl	COOH
31:	H	Xyl	COOMe
32:	H	Xyl	CH_2OH
momordin IIc (**34**):	Glc	Xyl	COOH

FIGURE 15.8 Chemical Structures of oleanolic acid (26) and its glycosides (27–34) and their effects on serum glucose levels in oral glucose-loaded rats.[26] Each column represents the mean with S.E. of serum glucose levels at 30 min after administration of D-glucose (0.5 g/kg, *p.o.*). Values are means ± S.E. (n = 5, 6), $^{**}p<0.01$. (From Matsuda, H. et al., *Biol. Pharm. Bull.*, 1998. With permission.)

- The 3-*O*-glucuronic acid glycosides are more potent than the 3-*O*-glucopyranosyl analogs.
- The 6′-methyl ester of glucuronic acid moiety markedly reduces the activity.

Acylated Polyhydroxyolean-12-ene 3-Monodesmoside

Escins

Escin, one of the most important saponin constituents, is known as a mixture of saponins occurring in the seeds of *Aesculus hippocastanum* (horse-chestnut tree, Hippocastanaceae). Due to its anti-inflammatory, antiedematous, and capillaroprotective properties, escin is widely employed in therapy of peripheral vascular disorders and also in the cosmetic field for prevention and treatment of cellulitis.

The methanol extract and saponin fraction from the seeds of *Aesculus hippocastanum* L. were found to show an inhibitory effect on increases in serum glucose levels in glucose-loaded rats. Through the bioassay-guided separation, various acylated saponins named escins Ia (35), Ib (36), IIa (40), IIb (41), IIIa, IIIb, IV, V, and VI and isoescins Ia (37), Ib (38), and V (Figure 15.9) were isolated and their chemical structures determined on the basis of chemical and physicochemical evidence.

Escins (35, 36, 40, 41), desacylescins (36, 40), and isoescins (37, 38, 42) were examined for inhibitory activity on the increase in serum glucose levels in oral glucose-loaded rats. As shown in Table 15.3 a single oral administration of the saponin fraction (200 mg/kg) from horse-chestnut seeds showed antihyperglycemic activity. The principal saponin constituents, escins (35, 36, 40, 41), in the saponin fraction were found to exhibit antihyperglycemic activity at a dose of 100 mg/kg, and escin IIa (40) showed the most potent activity among them. In addition, escins IIa (40) and IIb (41) with the 2′-*O*-xylopyranosyl moiety in their oligosaccharide part were found to show much more potent activity than escins Ia (35) and Ib (36) that had the 2′-*O*-glucopyranosyl moiety. On the other hand, isoescins Ia (37), Ib (38), and IIa (42) showed less activity than compounds 35,

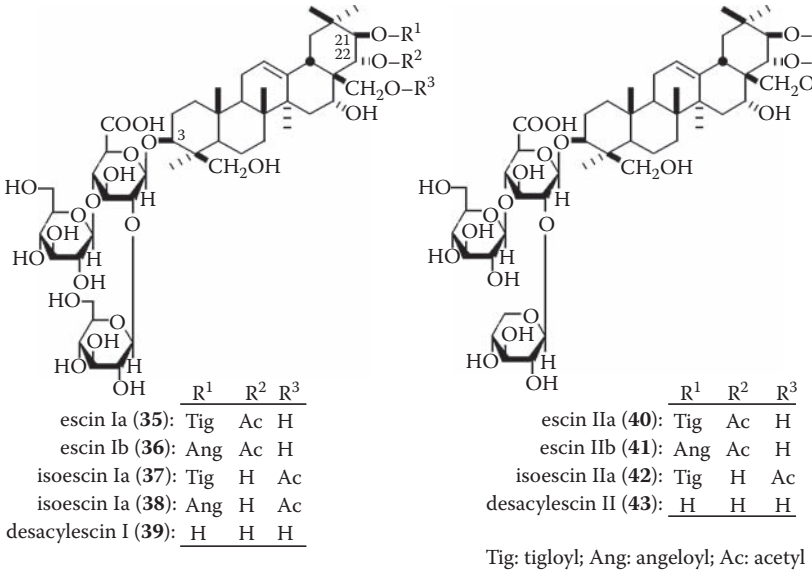


FIGURE 15.9 Chemical Structures of escins (35, 36, 40, 41) and isoescins (37, 38, 42) from the seeds of *Aesculus hippocastanum*.

36, and 40, respectively; desacylescins I (39) and II (43) lacked the activity. This evidence suggests that the 21,22-acyl groups in escins are essential for the antihyperglycemic activity.[27–29]

Gymnema Saponins

The leaves of *Gymnema sylvestre*, known as "gur-mar" in Indian folklore, have been used as a stomachic, a diuretic, and a remedy for cough and eye pain. Recently, the crude saponin fraction of this plant named "gymnemic acid" was shown not only to suppress sweet test sensation but also to inhibit glucose absorption in the small intestine of rats in sucrose-loaded rats. Several purified saponins of *G. sylvestre* (e.g., gymnemoside b, 45, and gymnemic acids II, 47; IV, 49; and V, 50) inhibit glucose absorption *in vitro* and/or in *in vivo* experiments, but not so strongly.[30–32]

Shimizu et al. also reported that the related saponins GiA-2, GiA-5, and GiA-7 from *G. inodorum* inhibited glucose absorption *in vitro*, and concluded that the 23-hydroxyl group was important for the activity.[33] In STZ-induced diabetic mice, saponin fraction (60 mg/kg, i.p.) and gymnemic acid IV (49) (3.4 to 13.4 mg/kg, i.p.), but not gymnemic acids I through III (46, 47, and 48) (Figure 15.10) reduced the blood glucose levels by 13.5 to 60% 6 h after the administration. This was comparable with the potency of glibenclamide and did not change the blood glucose levels of normal mice.[34]

Tea Saponins

Theasaponins E_1 (52) and E_2 (53) (Figure 15.11), assamsaponins A through I, and camelliasaponin B were isolated from the seeds and leaves of *Camellia sinensis* and/or *C. sinensis* var. *assamica*. The saponin fraction (100) (200 mg/kg, p.o.) and a principal saponin, theasaponin E_1 (52) (25 and 50 mg/kg, p.o.), strongly inhibited the rate of gastric emptying, which influences sugar absorption from the intestinal tract in mice. However, another principal saponin, theasaponin E_2 (53), lacking the 22-acetyl moiety did not bring about such an effect.[35,36]

TABLE 15.3
Inhibitory Effects of the Saponin Fraction, Escins (35, 36, 40, 41), Isoescins (35, 38, 42), and Desacylescins (39, 43) on Increase in Serum Glucose Level in Glucose-Loaded Rats

	Dose (mg/kg, *p.o.*)	n	Serum Glucose Levels (mg/100 ml) 0.5 h	1 h	2 h
	—	4	91.1 ± 3.4[b]	—	—
Control (glucose loading)	—	5	168.1 ± 5.5	—	—
Saponin fraction	200	5	139.1 ± 6.0[b]	—	—
Control (normal)	—	15	80.3 ± 2.7[b]	100.2 ± 3.3[b]	90.1 ± 3.1[b]
Control (glucose loading)	—	16	147.6 ± 3.0	138.1 ± 2.8	107.6 ± 3.4
Escin Ia (35)	50	5	132.5 ± 8.8	140.5 ± 5.7	118.6 ± 3.5
	100	5	117.3 ± 3.6[b]	130.9 ± 5.7	100.5 ± 6.1
Escin Ia (36)	50	5	140.3 ± 11.4	148.6 ± 3.4	111.2 ± 3.5
	100	5	127.1 ± 4.9[b]	143.7 ± 4.2	107.7 ± 8.0
Escin IIa (40)	50	5	130.3 ± 14.5	145.0 ± 5.9	123.0 ± 4.1[a]
	100	5	98.4 ± 7.2[b]	105.9 ± 7.8[b]	92.9 ± 7.4
Escin IIb (41)	50	5	119.8 ± 7.9[b]	132.5 ± 6.3	109.4 ± 4.6
	100	7	107.7 ± 5.5[b]	124.9 ± 4.9[a]	106.4 ± 6.4
Desacylescin I (39)	100	5	140.6 ± 5.7	136.6 ± 3.6	114.7 ± 1.8
Desacylescin II (43)	100	5	146.2 ± 4.5	140.4 ± 7.5	118.9 ± 3.8
Isoescin Ia (37)	100	4	124.7 ± 4.9[a]	148.8 ± 14.4	130.5 ± 16.6
Isoescin Ib (38)	100	4	131.4 ± 8.1	138.4 ± 11.2	111.4 ± 4.3
Isoescin IIa (42)	100	4	126.0 ± 4.5[a]	150.9 ± 4.2	118.1 ± 11.6

Notes: Glucose solution (10% w/v) was given orally (5 ml/kg) to fasted rats. Blood samples were collected 0.5, 1, and 2 h after glucose loading. Test samples were given orally 30 min before administration of glucose. Values are means ± S.E.

[a] $p < 0.05$.
[b] $p < 0.01$.

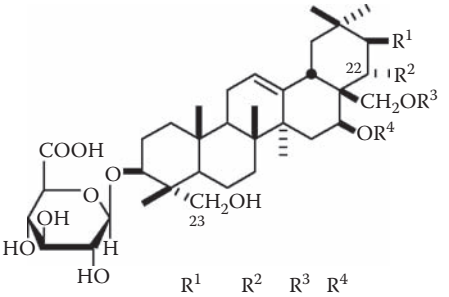
Source: M. Yoshikawa et al., *Chem. Pharm. Bull.* 44, 1996, 1454–1464.

Olean-12-ene 3,28-Acylated Bisdesmoside

Senega Saponins

Senegae Radix, the root of *Polygala senega* and *P. senega* var. *latifolia* (Polygalaceae), has been used clinically as an expectorant. The methanol extract of Japanese Senegae Radix, the root of *P. senega* var. *latifolia*, was found to exhibit an inhibitory effect on increases in serum glucose levels in glucose-loaded rats. By the bioassay-guided separation, new types of inhibitors named *E*-senegasaponins a (54), b (57), and c (60), *Z*-senegasaponins a (55), b (58), and c (61), and *Z*-senegins II (64), III (67), and IV (70) were isolated from Japanese Senegae Radix together with senegins II (63), III (66), and IV (69) (Figure 15.12).

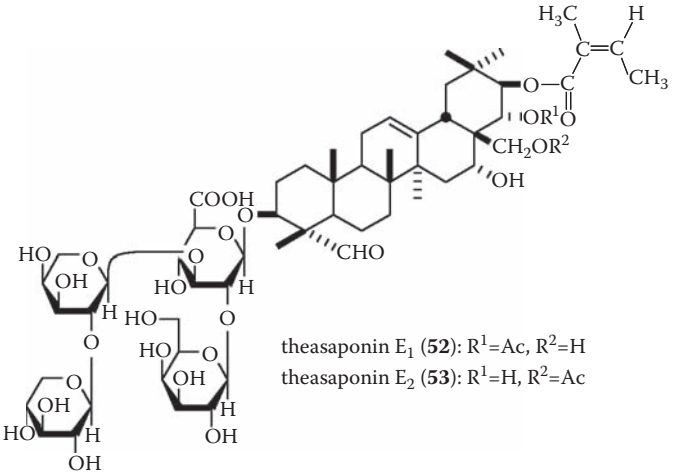
On the basis of chemical and physicochemical evidence, the chemical structures of *E*-senegasaponins a (54), b (57), and c (60) having the *E*-4-methoxycinnamoyl group were determined. *Z*-senegasaponins a (55), b (58), and c (61) and *Z*-senegins II (64), III (67), and IV (70) were found to be the *Z*-isomers of the 4-methoxycinnamoyl group in *E*-senegasaponins a (54), b (57), and c (60) and senegins II (63), III (66), and IV (69). In addition, the geometrical isomeric structure



	R^1	R^2	R^3	R^4
gymnemoside a (**44**):	OTig	OAc	H	H
gymnemoside b (**45**):	OTig	OH	H	Ac
gymnemic acid I (**46**):	OTig	OH	Ac	H
gymnemic acid II (**47**):	OMB	OH	Ac	H
gymnemic acid III (**48**):	OMB	OH	H	H
gymnemic acid IV (**49**):	OTig	OH	H	H
gymnemic acid V (**50**):	OTig	OTig	H	H
gymnemic acid VII (**51**):	OH	H	H	H

Tig: tigloyl, MB: (2*S*)-methylbuthyroyl, Ac: acetyl

FIGURE 15.10 Structures of gymnemosides (44, 45) and gymnemic acids (46–51) from *Gymnemia sylvestre*.

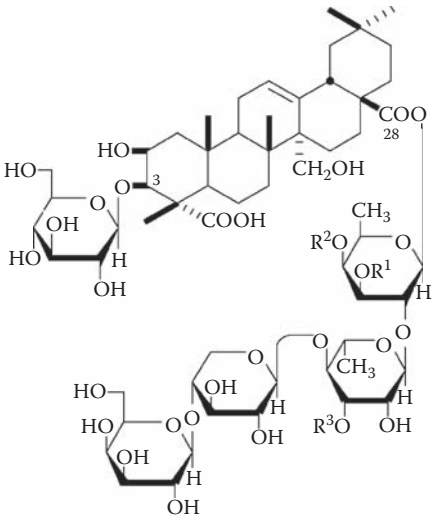


theasaponin E_1 (**52**): R^1=Ac, R^2=H
theasaponin E_2 (**53**): R^1=H, R^2=Ac

FIGURE 15.11 Structures of theasaponins E_1 (52) and E_2 (53) from *Camellia sinensis*.

of the 4-methoxycinnamoyl group in each saponin was also found to show tautomer-like behavior under irradiation with a fluorescence lamp.

The inhibitory effect of senegasaponins a (54 + 55), b (57 + 58), and c (60 + 61) and senegins II (63 + 64), III (66 + 67), IV (69 + 70) (the mixture of *E* and *Z* isomers), and their desacyl derivatives (56, 59, 62, 68, 71) are summarized in Table 15.4. *E,Z*-senegasaponins a (54 + 55) and b (57 + 58) and *E,Z*-senegins II (63 + 64) showed the antihyperglycemic effects in glucose-loaded rats. On the other hand, their derivatives showed weaker activities than those of senegasaponins and senegins. Thus, the methoxycinnamoyl group of senegasaponins and senegins is required for potent activity.[37–39]



	R^1	R^2	R^3
E-senegasaponin a (**54**):	H	*E*-MC	Api
Z-senegasaponin a (**55**):	H	*Z*-MC	Api
desacylsenegasaponin a (**56**):	H	H	Api
E-senegasaponin b (**57**):	H	*E*-MC	H
Z-senegasaponin b (**58**):	H	*Z*-MC	H
desacylsenegasaponin b (**59**):	H	H	H
E-senegasaponin c (**60**):	6-acetyl-Glc	*E*-MC	Api
Z-senegasaponin c (**61**):	6-acetyl-Glc	*Z*-MC	Api
desacylsenegasaponin c (**62**):	Glc	H	Api
senegin II (**63**):	H	*E*-DMC	H
Z-senegin II (**64**):	H	*Z*-DMC	H
desacylsenegin II (**65**):	H	H	H
senegin III (**66**):	Rha	*E*-MC	H
Z-senegin III (**67**):	Rha	*Z*-MC	H
desacylsenegin III (**68**):	Rha	H	H
senegin IV (**69**):	Rha	*E*-MC	Api
Z-senegin IV (**70**):	Rha	*Z*-MC	Api
desacylsenegin IV (**71**):	Rha	H	Api

MC: 4-methoxycinnamoyl, DMC: 3, 4-dimethoxycinnamoyl,
Api: β-D-apiofuranosyl, Glc: β-D-glucopyranosyl,
Rha: α-L-rhamnopyranosyl

FIGURE 15.12 Structures of senegasaponins and senegins from *Polygala senega* var. *latifolia*.

Kako et al. also reported that the hypoglycemic effect of the 1-butanol extract (the saponin fraction; 5 mg/kg) reduced the blood glucose of normal mice from 191 ± 3 to 120 ± 3 mg/100 ml 4 h after i.p. administration and also showed a significant decrease in the glucose level of KK-A^y mice from 469 ± 38 to 244 ± 14 mg/100 ml. However, the extract did not show a significant effect in STZ-induced diabetic mice, suggesting that it needs the presence of insulin to act. In addition, senegin II (63) was identified as an active constituent of this natural medicine.[40]

MODE OF ACTION OF TRITERPENE SAPONINS ON THE ANTIHYPERGLYCEMIC EFFECT IN GLUCOSE-LOADED RATS

The mode of action for the triterpene saponins was studied using oleanolic acid 3-*O*-glucuronide (27), momordin Ic (30), escins Ia (35) and IIa (40), and *E,Z*-senegin II (63 + 64). These saponins (25 to 100 mg/kg, p.o.) inhibited the increase in the serum glucose level dose dependently 30 min after oral loading with glucose, but did not lower serum glucose levels in normal and intraperitoneal glucose-loaded rats. They also lacked hypoglycemic effects in alloxan-induced diabetic mice. The results suggest that these saponins have neither insulin-like activity nor insulin-releasing activity and that they affect glucose absorption in the gastrointestinal tract.

Next, the effects of these saponins on the mobility of glucose from the stomach to the small intestine were examined. Oleanolic acid 3-*O*-glucuronide (27) (25 and 50 mg/kg, p.o.), momordin Ic (30) (25 and 50 mg/kg, p.o.), escins Ia (35) (100 mg/kg, p.o.) and IIa (40) (25 to 100 mg/kg, p.o.), and *E,Z*-senegin II (63 + 64) (100 mg/kg, p.o.) significantly suppressed the rate of gastric emptying (GE) in rats. In particular, compound 30 strongly suppressed GE. These suppressing effects of the saponins on GE can be important for the inhibition of increases in the serum glucose level after oral administration of glucose.

To evaluate the inhibitory effects of the saponins on glucose absorption in the small intestine, the effects of the saponins on glucose uptake in the jejunum were examined *in vitro*. Small fragments (0.1 to 0.15 g) of rat jejunum were incubated with D-[^{14}C]-glucose (2 m*M*) or L-[^{3}H]-glucose

TABLE 15.4
Inhibitory Effect of *E,Z*-Senegasaponins and *E,Z*-Senegins and Their Desacyl Derivatives on Increases in Serum Glucose Levels in Glucose-Loaded Rats

	Dose (mg/kg, *p.o.*)	n	Serum Glucose Levels (mg/100 ml) 0.5 h	1.0 h	2.0 h
Control (normal)	—	10	75.5 ± 4.1[b]	101.8 ± 4.1[b]	96.8 ± 4.2
Control (glucose tolerance)	—	10	138.6 ± 3.8	142.5 ± 2.6	107.1 ± 3.2
Saponin fraction	200	4	117.6 ± 7.7	132.9 ± 6.3	120.4 ± 6.6
	500	5	99.5 ± 3.3[b]	120.7 ± 4.6[a]	110.5 ± 3.9
Control (normal)	—	6	85.3 ± 2.3[b]	93.7 ± 5.2[b]	86.0 ± 6.2
Control (glucose tolerance)	—	7	150.4 ± 3.4	132.7 ± 3.7	108.1 ± 3.5
E,Z-senegasaponin a (54 + 55)	100	5	107.5 ± 7.0[b]	117.1 ± 5.7[a]	104.4 ± 6.2
Desacylsenegasaponin a (56)	100	5	132.3 ± 8.7[a]	133.6 ± 4.3	95.6 ± 6.0
E,Z-Senegasaponin b (57 + 58)	100	5	122.9 ± 4.1[b]	132.6 ± 5.3	113.7 ± 4.4
Desacylsenegasaponin b (59)	100	5	141.3 ± 8.4	159.5 ± 10.7	142.0 ± 1.5
Control (normal)	—	5	70.6 ± 3.7[b]	90.6 ± 6.1[b]	73.9 ± 4.7[b]
Control (glucose tolerance)	—	5	137.5 ± 2.3	125.0 ± 4.8	97.9 ± 2.3
E,Z-Senegasaponin c (60 + 61)	100	5	128.0 ± 3.9	128.6 ± 3.6	103.9 ± 7.4
Desacylsenegasaponin c (62)	100	4	135.0 ± 4.3	126.6 ± 8.1	97.8 ± 5.9
Control (normal)	—	12	88.6 ± 4.2[b]	103.6 ± 3.3[b]	100.8 ± 4.8
Control (glucose tolerance)	—	16	145.6 ± 2.3	139.5 ± 2.3	113.1 ± 2.5
E,Z-Senegin II (63 + 64)	100	12	120.9 ± 4.8[b]	135.3 ± 3.4	128.0 ± 4.0[b]
E,Z-Senegin III (66 + 67)	100	13	127.3 ± 3.8[b]	139.3 ± 3.6	119.5 ± 3.0
E,Z-Senegin IV (69 + 70)	100	7	133.1 ± 5.6	150.4 ± 4.8	127.1 ± 6.9
Control (normal)	—	6	76.6 ± 6.0[b]	94.3 ± 4.6[b]	86.6 ± 6.1[a]
Control (glucose tolerance)	—	9	153.1 ± 4.4	136.9 ± 3.7	103.7 ± 2.9
Desacylsenegin III (68)	100	5	157.7 ± 5.9	152.8 ± 4.2	121.7 ± 5.7
Desacylsenegin IV (71)	100	6	160.5 ± 2.5	147.0 ± 5.0	115.0 ± 7.5

Notes: Glucose solution (10% w/v) was administered orally (5 ml/kg) to fasted rats. Blood samples were collected 0.5, 1, and 2 h after glucose loading. Test samples were administered orally 30 min before administration of glucose. Values are means ± S.E.

[a] $p < 0.05$.
[b] $p < 0.01$.

Sources: M. Yoshikawa et al., *Chem. Pharm. Bull.* 43, 1995, 2115–2122, and M. Yoshikawa et al., *Chem. Pharm. Bull.* 44, 1996, 1305–1313.

(2 m*M*). The saponins (5 to 500 μ*M*) significantly inhibited D-glucose uptake, but not L-glucose uptake, in rat small intestinal fragments *in vitro*. This was similar to phlorizin, a compound well known to inhibit the Na^+/D-glucose cotransport system (SGLUT) at the intestinal brush border membrane.

On the basis of the preceding evidence, it can be assumed that these active saponins delay glucose absorption mainly by suppressing the transfer of glucose from the stomach to the small intestine, which is an important site for the absorption of glucose. This is accomplished partly by inhibiting the glucose transport system at the intestinal brush border membrane.[26,41]

INHIBITORY EFFECTS OF OLEANOLIC ACID GLYCOSIDES ON GE IN MICE

An examination was conducted of the effects of oleanolic acid (26) and its glycosides (27–34) and escins (35, 36, 40, 41) on GE at 30 min after the loading of the test meals consisting of 1.5% CMC-Na, 40% glucose, and milk in normal mice. As shown in Table 15.5, oleanolic acid 3-*O*-monodesmosides (oleanolic acid 3-*O*-glucuronide (27) (12.5–50 mg/kg), momordin Ic (30) (25 and 50 mg/kg), and momordin I (12.5 to 50 mg/kg) strongly inhibited the GE in 1.5% CMC-Na test meal-loaded mice. Momordin I (12.5 and 25 mg/kg) especially showed stronger inhibition than atropine sulfate monohydrate, a reference drug. Momordins I and Ic (30) also inhibited gastric emptying in mice given the three different test meals. Compound 27 inhibited GE in mice given milk, but lacked significant inhibition in the 40% glucose test meal-loaded mice.

Oleanolic acid 3,28-bisdesmosides (momordin IIc (34), chikusetsusaponins IV and V) and an oleanolic acid 28-monodesmoside (compound O, 33), and their common sapogenol (oleanolic acid, 26) did not show any effect. In addition, oleanolic acid 3-monodesmoside with the 2′-*O*-β-D-glucopyranosyl moiety (e.g., 28-deglucosyl-chikusetsusaponin V) showed weak activity. These results parallel the structural requirements of oleanolic acid glycosides needed for the inhibition of increased blood glucose levels in glucose-loaded rats[25,42]:

- The 3-*O*-glycoside moiety is essential for the activity.
- The 28-ester glucoside moiety markedly reduces the activity.
- The 2′-*O*-β-D-glucopyranosyl group of the sugar moiety reduced the activity.

Escins (35, 36, 40, 41) also inhibited GE of 1.5% CMC-Na by 11.1 to 54.2% at 12.5 to 200 mg/kg, GE of a 40% glucose test meal by 21.1 to 23.5% at 50 mg/kg, except for (35), and GE of a milk test meal by 18.4 to 33.1% at 50 mg/kg.[43]

Finally, the mechanism of GE inhibition by the saponins was studied using momordin Ic (30) and escins (35, 36, 40, 41) in mice. In addition to norepinephrine and epinephrine, dopamine (DA) potentially inhibits gastric motor activity, whereas serotonin (5-HT) generally accelerates GE.

Pretreatment with a depletor of catecholamines and DA synthesis inhibitor (reserpine and 6-hydroxydopamine) and DA_2 receptor antagonists (metoclopramide, haloperidol, and domperidone), but not with a DA_1 receptor antagonist (SCH 23390) and a 5-HT_2 receptor antagonist (cyproheptadine), attenuated momordin Ic (30)- and escin Ib (40)-induced GE inhibition.

These findings suggest that catecholamines, possibly DA, and DA_2 receptors are involved in the GE inhibition by these saponins. In addition, the effects of these saponins on GE were markedly attenuated in the mice systematically pretreated with an ablator of capsaicin-sensitive sensory nerves (capsaicin) and an inhibitor of prostaglandin (PG) synthesis (indomethacin); this suggests the involvement of capsaicin-sensitive sensory nerves and endogenous PGs. Therefore, it is postulated that oleanolic acid 3-monodesmosides and escins, at least in part, stimulate the synthesis and/or release of DA mediated by the capsaicin-sensitive sensory nerves, which in turn causes the release of PGs, and finally inhibit GE.[44–46]

Medicines that decrease postprandial hyperglycemia by suppressing the absorption of carbohydrates have been known to be effective for prevention and treatment of non-insulin-dependent diabetes mellitus. Therefore, triterpene saponins that delay glucose absorption may also be used for the prevention and treatment of mild type II diabetes. In addition, we found that oleanolic acid glycosides and escins showed other various medicinal effects such as antiallergic, anti-inflammatory, antinociceptive, antipruritive, and gastroprotective effects and acceleration of small intestinal transit.[25,47–57] Because oleanane-type triterpene saponins are widely distributed in various foodstuffs, pharmacological activities of the saponins must be further studied for a better understanding of the medicinal role of foodstuffs in better health.

TABLE 15.5
Effects of Oleanolic Acid (26) and Its Glycosides on Gastric Emptying (GE) in Mice

Treatment	Dose (mg/kg, *p.o.*)	GE (%)					
		n	CMC-Na Test Meal	n	40% Glucose Test Meal	n	Milk Test Meal
Control	—	10	89.9 ± 1.0	10	62.1 ± 2.0	10	71.1 ± 1.9
Oleanolic acid 3-*O*-	5	8	87.2 ± 1.3		—		—
glucuronide (27)	12.5	8	78.2 ± 2.8[a]		—	8	61.1 ± 1.4[a]
	25	8	54.4 ± 4.3[b]	8	59.3 ± 1.4	8	58.7 ± 3.3[b]
	50	8	38.3 ± 2.8[b]	8	55.6 ± 2.2	8	30.2 ± 2.4[b]
Momordin Ic (30)	5	8	91.8 ± 0.9		—		—
	12.5	8	82.1 ± 1.2	8	64.7 ± 1.6	8	62.1 ± 3.3[a]
	25	8	68.9 ± 2.3[b]	8	53.3 ± 2.1	8	55.3 ± 2.2[a]
	50	8	33.1 ± .6[b]	8	40.9 ± 3.7[b]	8	42.7 ± 2.7[b]
Momordin I	5	8	88.6 ± 1.1		—		—
	12.5	8	65.0 ± 1.3[b]	8	58.3 ± 2.2	8	68.2 ± 2.8
	25	8	44.2 ± 2.6[b]	8	43.6 ± 3.1[b]	8	47.4 ± 2.4[b]
	50	8	11.7 ± 3.8[b]	8	33.7 ± 2.7[b]	8	40.2 ± 2.7[b]
Control	—	10	91.6 ± 1.0	10	64.0 ± 1.6	10	67.4 ± 1.9
28-Deglucosyl-chikusetsusaponin IV	5	8	89.0 ± 1.4		—		—
	12.5	8	76.9 ± 2.5[b]	8	62.3 ± 1.3	8	55.9 ± 3.0[b]
	25	8	70.3 ± 3.6[b]	8	48.6 ± 2.6[b]	8	46.0 ± 1.5[b]
	50	8	31.8 ± 3.6[b]	8	47.2 ± 3.4[b]	8	40.1 ± 1.9[b]
28-Deglucosyl-chikusetsusaponin V	25	8	83.7 ± 1.2		—	8	68.2 ± 2.0
	50	8	73.3 ± 2.8[b]	8	57.2 ± 1.5	8	59.0 ± 2.1[a]
Control	—	10	91.3 ± 1.2	10	64.0 ± 1.6	10	71.2 ± 1.8
Oleanolic acid (26)	50	8	90.2 ± 0.8	8	64.7 ± 1.9	8	69.0 ± 2.4
Compound O (33)	50	8	89.3 ± 0.8	8	57.2 ± 1.8	8	66.7 ± 0.9
Momordin IIc (34)	50	8	87.3 ± 1.4	8	57.0 ± 1.7	8	68.2 ± 1.0
Chikusetsusaponin IV	50	8	88.9 ± 1.6	8	58.2 ± 1.6	8	70.1 ± 0.9
Chikusetsusaponin V	50	8	90.4 ± 1.3	8	59.5 ± 1.9	8	71.5 ± 1.4
Control	—	10	89.4 ± 1.2		—		—
Atropine sulfate	5	8	78.7 ± 1.0[b]		—		—
	12.5	8	73.1 ± 3.0[b]		—		—
	25	8	67.7 ± 1.2[b]		—		—

Notes: A solution of 1.5% CMC-Na, 40% glucose, or milk (milk powder:water (w/w) = 1:3) test meal containing 0.05% phenol red as a marker was given orally (0.5 ml/mouse) to mice. Gastric emptying was determined 30 min after administration of the test meals. The test sample was given orally 30 min before administration of the test meals. Values are means ± S.E.

[a] $p < 0.05$.
[b] $p < 0.01$.

Source: H. Matsuda et al., *Bioorg. Med. Chem.* 7, 1999, 323–327.

REFERENCES

1. G.R. Waller and K. Yamasaki (Eds.), *Advances in Experimental Medicine and Biology Volume 404: Saponins Used in Traditional and Modern Medicine*, New York: Plenum Press, 1996.
2. H. Hasegawa, K.S. Lee, T. Nagaoka, Y. Tezuka, M. Uchiyama, S. Kadota and I. Saiki, Pharmacokinetics of ginsenoside deglycosylated by intestinal bacteria and its transformation to biologically active fatty acid esters, *Biol. Pharm. Bull.* 23, 2000, 298–304.
3. T. Akao, H. Kida, M. Kanaoka, M. Hattori and K. Kobashi, Intestinal bacterial hydrolysis is required for the appearance of compound K in rat plasma after oral administration of ginsenoside Rb1 from *Panax ginseng, J. Pharm. Pharmacol.* 50, 1998, 1155–1160.
4. H. Kida, T. Akao, M.R. Meselhy and M. Hattori, Metabolism and pharmacokinetics of orally administered saikosaponin b1 in conventional, germ-free and *Eubacterium* sp. A-44-infected gnotobiote rats, *Biol. Pharm. Bull.* 21, 1998, 588–593.
5. A. Kato, T. Miura and T. Fukunaga, Effects of steroidal glycosides on blood glucose in normal and diabetic mice, *Biol. Pharm. Bull.* 18, 1995, 167–168.
6. N. Nakashima, I. Kimura and M. Kimura, Isolation of pseudoprototimosaponin AIII from rhizomes of *Anemarrhena asphodeloides* and its hypoglycemic activity in streptozotocin-induced diabetic mice, *J. Nat. Prod.* 56, 1993, 345–350.
7. K.-W. Glombitza, G.H. Mahran, Y.W. Mirhom, K.G. Michel and T.K. Motawi, Hypoglycemic and antihyperglycemic effects of *Zizyphus spina-christi* in rats, *Planta Med.* 60, 1994, 244–247.
8. D.H. Kim, K.W. Yu, E.A. Bae, H.J. Park and J.W. Choi, Metabolism of kalopanaxsaponin B and H by human intestinal bacteria and antidiabetic activity of their metabolites, *Biol. Pharm. Bull.* 21, 1998, 360–365.
9. K.T. Lee, I.C. Sohn, D.H. Kim, J.W. Choi, S.H. Kwon, H.J. Park, Hypoglycemic and hypolipidemic effects of tectorigenin and kaikasaponin III in the streptozotocin-induced diabetic rat and their antioxidant activity *in vitro*, *Arch. Pharm. Res.* 23, 2000, 461–466.
10. H. Hasgawa, S. Matsumiya, C. Murakami, T. Kurokawa, R. Kasai, S. Ishibashi and K. Yamasaki, Interactions of ginseng extract, ginseng separated fractions, and some triterpenoid saponins with glucose transporters in sheep erythrocytes, *Planta Med.* 60, 1994, 153–157.
11. M. Yoshikawa, T. Murakami and H. Matsuda, Triterpene glycosides with antidiabetogenic activity from sugar beet — absolute stereostructures, structure–activity relationships, and action mechanism in: *Towards Natural Medicine Research in the 21st Century*, H. Ageta, N. Aimi, Y. Ebizuka, T. Fujita and G. Honda (Eds.), Elsevier, Amsterdam–Tokyo, 1998, pp. 137–149.
12. M. Yoshikawa and H. Matsuda, Chemical and pharmacological studies on triterpene saponins, escins, from horse chestnut seeds in: *Saponins in Food, Feedstuffs and Medicinal Plants*, W. Oleszek and A. Marston (Eds.), Kluwer Academic Publishers, Dordrecht–London, 2000, pp. 189–203.
13. M. Yoshikawa and H. Matsuda, Antidiabetigenic activity of oleanolic acid glycosides from medicinal foodstuffs, *BioFactors* 13, 2000, 231–237.
14. M. Yoshikawa, H. Matsuda, E. Harada, T. Murakami, N. Wariishi, J. Yamahara, N. Murakami and Elatoside E, a new hypoglycemic principle from the root cortex of *Aralia elata* SEEM.: structure-related hypoglycemic activity of oleanolic acid glycosides, *Chem. Pharm. Bull.* 42, 1994, 1354–1356.
15. M. Yoshikawa, S. Yoshizumi, T. Ueno, H. Matsuda, T. Murakami, J. Yamahara and N. Murakami, Medicinal foodstuffs. I. Hypoglycemic constituents from a garnish foodstuff "taranome," the young shoot of *Aralia elata* SEEM.: Elatosides G, H, I, J, and K, *Chem. Pharm. Bull.* 43, 1995, 1878–1882.
16. M. Yoshikawa, T. Murakami, E. Harada, N. Murakami, J. Yamahara and H. Matsuda, Bioactive saponins and glycosides. VII. On the hypoglycemic principles from the root cortex of *Aralia elata* SEEM.: structure-related hypoglycemic activity of oleanolic acid oligoglycoside, *Chem. Pharm. Bull.* 44, 1996, 1923–1927.
17. M. Yoshikawa, T. Murakami, M. Kadoya, H. Matsuda, O. Muraoka, J. Yamahara and N. Murakami, Medicinal foodstuffs. III. Sugar beet. (1): Hypoglycemic oleanolic acid oligoglycosides, betavulgarosides I, II, III, and IV from the root of *Beta vulgaris* L. (Chenopodiaceae), *Chem. Pharm. Bull.* 44, 1996, 1212–1217.
18. M. Yoshikawa, T. Murakami, M. Inaduki, K. Hirano, J. Yamahara and H. Matsuda, Absolute stereostructures of betavulgarosides III and IV, inhibitors of glucose absorption, from the roots of *Beta vulgaris* L. (sugar beet), *Chem. Pharm. Bull.* 45, 1997, 561–563.

19. M. Yoshikawa, T. Murakami, M. Kadoya, J. Yamahara and H. Matsuda, Medicinal foodstuffs. XV. Sugar beet. (2): Structures of betavulgarosides V, VI, VII, VIII, IX, and X from the roots and leaves of sugar beet (*Beta vulgaris* L., Chenopodiaceae), *Chem. Pharm. Bull.* 46, 1998, 1758–1763.
20. T. Murakami, H. Matsuda, M. Inadzuki, K. Hirano and M. Yoshikawa, Medicinal foodstuffs. XVI. Sugar beet. (3): Absolute stereostructures of betavulgarosides II and IV, hypoglycemic saponins having a unique substituent, from the roots of *Beta vulgaris* L., *Chem. Pharm. Bull.* 47, 1999, 1717–1724.
21. M. Yoshikawa, Y. Dai, H. Shimada, T. Morikawa, N. Matsumura, S. Yoshizumi, H. Matsuda, H. Matsuda and M. Kubo, Studies on Kochiae Fructus. II. On the saponin constituents from the fruit of Chinese *Kochia scoparia* (Chenopodiaceae): chemical structures of kochianosides I, II, III, and IV, *Chem. Pharm. Bull.* 45, 1997, 1052–1055.
22. M. Yoshikawa, H. Shimada, T. Morikawa, S. Yoshizumi, N. Matsumura, T. Murakami, H. Matsuda, K. Hori and J. Yamahara, Medicinal foodstuffs. VII. On the saponin constituents with glucose and alcohol absorption-inhibitory activity from a food garnish "tonburi," the fruit of Japanese *Kochia scoparia* (L.) SCHRAD.: structures of scoparianosides A, B, and C, *Chem. Pharm. Bull.* 45, 1997, 1300–1305.
23. T. Murakami, K. Hirano and M. Yoshikawa, Medicinal foodstuffs. XXIII. Structures of new oleanane-type triterpene oligoglycosides, basellasaponins A, B, C, and D, from the fresh aerial parts of *Basella rubra* L., *Chem. Pharm. Bull.* 49, 2001, 776–779.
24. M. Yoshikawa, T. Murakami, K. Hirano, H. Matsuda, J. Yamahara, K. Ohtani, R. Kasai and K. Yamasaki, Absolute stereostructures of spinacosides C and D with a novel acetal type substituent from *Spinacia oleracea* (spinach) and *Basella rubra* (Indian spinach), *Heterocycles* 49, 1998, 93–96.
25. M. Yoshikawa, T. Murakami, A. Kishi, T. Kageura and H. Matsuda, Medicinal flowers. III. Marigold. (1): Hypoglycemic, gastric emptying inhibitory, and gastroprotective principles and new oleanane-type triterpene oligoglycosides, calendasaponins A, B, C, and D from Egyptian *Calendula officinalis*, *Chem. Pharm. Bull.* 49, 2001, 863–870.
26. H. Matsuda, Y. Li, T. Murakami, N. Matsumura, J. Yamahara and M. Yoshikawa, Antidiabetic principles of natural medicines. III. Structure-related inhibitory activity and action mode of oleanolic acid glycosides on hypoglycemic activity, *Chem. Pharm. Bull.* 46, 1998, 1399–1403.
27. M. Yoshikawa, E. Harada, T. Murakami, H. Matsuda, N. Wariishi, J. Yamahara, N. Murakami and I. Kitagawa, Escins-Ia, Ib, IIa, IIb, and IIIa, bioactive triterpene oligoglycosides from the seeds of *Aesculus hippocastanum* L.: their inhibitory effects on ethanol absorption and hypoglycemic activity on glucose tolerance test, *Chem. Pharm. Bull.* 42, 1994, 1357–1359.
28. M. Yoshikawa, T. Murakami, H. Matsuda, J. Yamahara, N. Murakami and I. Kitagawa, Bioactive saponins and glycosides. III. Horse chestnut. (1): The structures, inhibitory effects on ethanol absorption, and hypoglycemic activity of escins Ia, Ib, IIa, IIb, and IIIa from the seeds of *Aesculus hippocastanum* L., *Chem. Pharm. Bull.* 44, 1996, 1454–1464.
29. M. Yoshikawa, T. Murakami, J. Yamahara and H. Matsuda, Bioactive saponins and glycosides. XII. Horse chestnut. (2): Structures of escins IIIb, IV, V, and VI and Isoescins Ia, Ib, and V, acylated polyhydroxyoleanene triterpene oligoglycosides, from the seeds of horse chestnut tree (*Aesculus hippocastanum* L., Hippocastanaceae), *Chem. Pharm. Bull.* 46, 1998, 1764–1769.
30. N. Murakami, T. Murakami, M. Kadoya, H. Matsuda, J. Yamahara and M. Yoshikawa, New hypoglycemic constituents in "gymnemic acid" from *Gymnema sylvestre*, *Chem. Pharm. Bull.* 44, 1996, 469–471.
31. M. Yoshikawa, T. Murakami, M. Kadoya, Y. Li, N. Murakami, J. Yamahara and H. Matsuda, Medicinal foodstuffs. IX. The inhibitors of glucose absorption from the leaves of *Gymnema sylvestre* R. BR. (Asclepiadaceae): structures of gymnemosides a and b, *Chem. Pharm. Bull.* 45, 1997, 1671–1676.
32. M. Yoshikawa, T. Murakami and H. Matsuda, Medicinal foodstuffs. X. Structures of new triterpene glycosides, gymnemosides-c, -d, -e, and -f from the leaves of *Gymnema sylvestre* R. BR.: influence of gymnema glycosides on glucose uptake in rat small intestinal fragments, *Chem. Pharm. Bull.* 45, 1997, 2034–2038.
33. K. Shimizu, M. Ozeki, A. Iino, S. Nakajyo, N. Urakawa and M. Atsuchi, Structure–activity relationships of triterpenoid derivatives extracted from *Gymnema inodorum* leaves on glucose absorption, *Jpn. J. Pharmacol.* 86, 2001, 223–229.

34. Y. Sugihara, H. Nojima, H. Matsuda, T. Murakami, M. Yoshikawa and I. Kimura, Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice, *J. Asian Nat. Prod. Res.* 2, 2000, 321–327.
35. I. Kitagawa, K. Hori, T. Motozawa, T. Murakami and M. Yoshikawa, Structures of new acylated oleanene-type triterpene oligoglycosides, theasaponins E_1 and E_2, from the seeds of tea plant, *Camellia sinensis* (L.) O. Kuntze, *Chem. Pharm. Bull.* 46, 1998, 1901–1906.
36. T. Murakami, J. Nakamura, T. Kageura, H. Matsuda and M. Yoshikawa, Bioactive saponins and glycosides. XVII. Inhibitory effect on gastric emptying and accelerating effect on gastrointestinal transit of tea saponins: structures of assamsaponins F, G, H, I, and J from the seeds and leaves of the tea plant, *Chem. Pharm. Bull.* 48, 2000, 1720–1725.
37. M. Yoshikawa, T. Murakami, T. Ueno, M. Kadoya, H. Matsuda, J. Yamahara and N. Murakami, *E*-Senegasaponins a and b, *Z*-senegasaponins a and b, *Z*-senegins II and III, new type inhibitors of ethanol absorption in rats from Senegae Radix, the roots of *Polygala senega* L. var *latiofolia* Torrey et Gray., *Chem. Pharm. Bull.* 43, 1995, 350–352.
38. M. Yoshikawa, T. Murakami, T. Ueno, M. Kadoya, H. Matsuda, J. Yamahara and N. Murakami, Bioactive saponins and glycosides. I. Senegae Radix. (1): *E*-Senegasaponins a and b and *Z*-senegasaponins a and b, their inhibitory effect on alcohol absorption and hypoglycemic activity, *Chem. Pharm. Bull.* 43, 1995, 2115–2122.
39. M. Yoshikawa, T. Murakami, H. Matsuda, T. Ueno, M. Kadoya, J. Yamahara and N. Murakami, Bioactive saponins and glycosides. II. Senegae Radix. (2): Chemical structures, hypoglycemic activity, and ethanol absorption-inhibitory effect of *E*-senegasaponin c, *Z*-senegasaponin c, and *Z*-senegins II, III, and IV, *Chem. Pharm. Bull.* 44, 1996, 1305–1313.
40. M. Kako, T. Miura, Y. Nishiyama, M. Ichimaru, M. Moriyasu and A. Kato, Hypoglycemic effect of the rhizomes of *Polygala senega* in normal and diabetic mice and its main component, the triterpenoid glycoside senegin-II, *Planta Med.* 62, 1996, 440–443.
41. H. Matsuda, T. Murakami, Y. Li, J. Yamahara and M. Yoshikawa, Mode of action of escins Ia and IIa and *E*,*Z*-senegin II on glucose absorption in gastrointestinal tract, *Bioorg. Med. Chem.* 6, 1998, 1019–1023.
42. H. Matsuda, Y. Li, T. Murakami, J. Yamahara and M. Yoshikawa, Structure-related inhibitory activity of oleanolic acid glycosides on gastric emptying in mice, *Bioorg. Med. Chem.* 7, 1999, 323–327.
43. H. Matsuda, Y. Li, T. Murakami, J. Yamahara and M. Yoshikawa, Effects of escins Ia, Ib, IIa, and IIb from horse chestnuts on gastric emptying in mice, *Eur. J. Pharmacol.* 368, 1999, 237–243.
44. H. Matsuda, Y. Li, J. Yamahara and M. Yoshikawa, Inhibition of gastric emptying by triterpene saponin, momordin Ic, in mice: roles of blood glucose, capsaicin-sensitive sensory nerves, and central nervous system, *J. Pharmacol. Exp. Ther.* 289, 1999, 729–734.
45. H. Matsuda, Y. Li and M. Yoshikawa, Roles of endogenous prostaglandins and nitric oxide in inhibitions of gastric emptying and accelerations of gastrointestinal transit by escins Ia, Ib, IIa, and IIb in mice, *Life Sci.* 66, 2000, PL 41–46.
46. H. Matsuda, Y. Li and M. Yoshikawa, Possible involvement of dopamine and dopamine$_2$ receptors in the inhibitions of gastric emptying by escin Ib in mice, *Life Sci.* 67, 2000, 2921–2927.
47. H. Matsuda, Y. Dai, Y. Ido, S. Ko, M. Yoshikawa and M. Kubo, Studies on Kochiae Fructus III. Antinociceptive and antiinflammatory effects of 70% ethanol extract and its component, momordin Ic from dried fruits of *Kochia scoparia* L., *Biol. Pharm. Bull.* 20, 1997, 1086–1091.
48. H. Matsuda, Y. Li, T. Murakami, K. Ninomiya and M. Yoshikawa, Effects of escins Ia, Ib, IIa, and IIb, from horse chestnut, the seeds of *Aesculus hippocastanum* L., on acute antiinflammation in animals, *Biol. Pharm. Bull.* 20, 1997, 1092–1095.
49. H. Matsuda, Y. Dai, Y. Ido, M. Yoshikawa and M. Kubo, Studies on Kochiae Fructus IV. Anti-allergic effects of 70% ethanol extract and its component, momordin Ic from dried fruits of *Kochia scoparia* L., *Biol. Pharm. Bull.* 20, 1997, 1165–1170.
50. H. Matsuda, Y. Dai, Y. Ido, T. Murakami, H. Matsuda, M. Yoshikawa and M. Kubo, Studies on Kochiae Fructus. V. Antipruritic effects of oleanolic acid glycosides and the structure-requirement, *Biol. Pharm. Bull.* 21, 1998, 1231–1233.
51. H. Matsuda, Y. Li, T. Murakami, J. Yamahara and M. Yoshikawa, Protective effects of oleanolic acid oligoglycosides on ethanol- or indomethacin-induced gastric mucosal lesions in rats, *Life Sci.* 63, 1998, PL 245–250.

52. H. Matsuda, Y. Li and M. Yoshikawa, Roles of capsaicin-sensitive sensory nerves, endogenous nitric oxide sulfhydryls, and prostaglandins in gastroprotection by momordin Ic, an oleanolic acid oligoglycoside, on ethanol-induced gastric mucosal lesions in rats, *Life Sci*. 65, 1999, PL 27–32.
53. H. Matsuda, Y. Li and M. Yoshikawa, Gastroprotections of escins Ia, Ib, IIa, and IIb on ethanol-induced gastric mucosal lesions in rats, *Eur. J. Pharmacol*. 373, 1999, 63–70.
54. Y. Li, H. Matsuda and M. Yoshikawa, Effects of oleanolic acid glycosides on gastrointestinal transit and ileus in mice, *Bioorg. Med. Chem*. 7, 1999, 1201–1205.
55. Y. Li, H. Matsuda, J. Yamahara and M. Yoshikawa, Acceleration of gastrointestinal transit by momordin Ic in mice: possible involvement of 5-hydroxytryptamine, 5-HT_2 receptors and prostaglandins, *Eur. J. Pharmacol*. 392, 2000, 71–77.
56. H. Matsuda, Y. Li and M. Yoshikawa, Effects of escins Ia, Ib, IIa, and IIb from horse chestnuts on gastrointestinal transit and ileus in mice, *Bioorg. Med. Chem*. 7, 1999, 1737–1741.
57. H. Matsuda, Y. Li and M. Yoshikawa, Possible involvement of 5-HT and 5-HT_2 receptors in acceleration of gastrointestinal transit by escin Ib in mice, *Life Sci*. 66, 2000, 2233–2238.

16 Flavonoids, Xanthones, and Other Antioxidant Polyphenols

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CONTENTS

Environmental factors play an essential role in the etiology and management of diabetes, and antioxidants in food and medicinal plants are potential modulators of diabetes onset, progression, and complications. Among naturally occurring compounds, the polyphenolic flavonoids, xanthones, and α-tocopherol have received the most attention. These and other compounds may generally improve oxidative status, protect and enhance endogenous defenses, and directly mediate various mechanisms of pathology.

After providing an overview of the role of oxidative stress in diabetes and its complications, this chapter reviews current data linking antioxidant polyphenols and diabetes. Their implications for understanding traditional uses of plants and their potential application in addressing contemporary diabetes problems are discussed.

DIABETES AND OXIDATIVE STRESS

Oxidative stress as a consequence of hyperglycemia and changes in energy metabolism and inflammatory mediators plays an important role in the pathophysiology of diabetes in association with

depleted cellular antioxidant defense systems and enhanced production of reactive oxygen species (ROS).[1] Subnormal levels of plasma α-tocopherol,[2] ascorbate,[3] total glutathione, and serum malonaldehyde[4] — along with increased levels of oxidative stress markers such as thiobarbituric acid reactive substances (TBARS)[5] and oxidized low-density lipoproteins (LDL)[6] — occur in diabetics.

In type 1 diabetes, a redox imbalance may result in apoptosis of pancreatic islet cells.[7] Islet cells are particularly susceptible to free radical damage due to their low levels of superoxide dismutase (SOD), glutathione peroxidase (GSH), and catalase.[8] In type 2 diabetes, hyperglycemia and hyperinsulinemia may induce a rise in plasma free radical production, and insulin resistance is associated with increased intracellular concentrations of free radicals and depleted antioxidant defenses.[9]

ROLE IN DIABETIC COMPLICATIONS

Oxidative stress associated with hyperglycemia impairs cellular function and alters vascular and neural function. Moreover, it leads to endothelial dysfunction, a key step in atherosclerosis etiology. High glucose concentrations promote free radical production via the following three biochemical pathways:

- *Advanced glycation endproducts* (*AGEs*). Glucose can react nonenzymatically with proteins, forming advanced glycation endproducts (AGEs). Structural components of the connective tissue matrix or basement membrane, such as collagen, are prime targets of AGEs leading to cross-link formations, resulting in stiffness of the protein matrix,[10] sclerosis of renal glomeruli, thickening of the capillary basement membrane, and atherosclerosis.[11] The binding of AGE to receptors (RAGE) in smooth muscle cells, monocytes, macrophages, and endothelial cells[12] produces free radicals and activation of NF-κB, a transcription factor involved in vascular function, inflammation, and pathology.[13]
- *Protein kinase C activation*. Hyperglycemia and AGEs enhance activation of protein kinase C (PKC) in endothelial cells,[14] leading to increased synthesis of vasoconstrictor prostaglandins and generation of ROS.[1]
- *Aldose reductase pathway.* Aldose reductase (AR) catalyzes the reduction of glucose at abnormally high intracellular concentrations to sorbitol, which is in turn oxidized to fructose by sorbitol dehydrogenase (SDH). Increased flux through this polyol pathway depletes intracellular NADPH, rendering it unavailable for regeneration of reduced glutathione and thereby reducing the antioxidative capacity of cells and contributing to intracellular oxidative stress.[15]

Tumor Necrosis Factor-α

Tumor necrosis factor-α (TNF) increases reactive oxygen species,[16] forms a possible connection between obesity and diabetes,[17] and has been linked to insulin resistance[18] and diabetic complications.[19] Three medicinal species high in antioxidant activity and used for symptoms of diabetes inhibit TNF production in cell culture.[20]

Endothelial Dysfunction: Diabetic Macro- and Microvascular Complications

Free radicals are major contributors to endothelial dysfunction.[21] Hyperglycemia leads to nonenzymatic glycation of LDL, increased susceptibility of LDL to oxidation,[22] and subsequent promotion of atherosclerosis.[23] Microvascular complications, such as neuropathy, retinopathy, and nephropathy, arise in part from high intracellular sorbitol and fructose levels.[24,25] In nervous tissue,

endoneural hypoxia is improved with antioxidant administration.[26] In retinopathy, increased vascular permeability and microaneurysms result[27]; glycation and oxidation of lens crystalline and AGE-induced changes are likely the major mechanisms for cataract formation.[11]

ANTIOXIDANTS AND DIABETES

General Antioxidants

A wide range of phenolic and other phytochemicals have antioxidant activity.[28] These compounds typically contain at least one aromatic ring with hydroxyl groups and include[28]:

Tannins
Coumarins
Flavonoids (isoflavonoids, anthocyanins, catechins, chalcones, flavones, and flavonols)
Xanthones
Cinamic acid derivatives (caffeic acid, ferulic acid, and chlorogenic acid)
Coumarins
Tocopherols
Polyfunctional organic acids
Lignins

Structures of a selection of antioxidant polyphenols mentioned in this chapter are shown in Figures 16.1 through 16.6. Antioxidants can have many targets within the body because they can be hydrophilic (e.g., ascorbic acid, uric acid, and thiols) or hydrophobic (e.g., α-tocopherol (Figure 16.1) [vitamin E]). Flavonoids have intermediate and variable solubility depending on hydroxylation and glycoside character.

α-Tocopherol

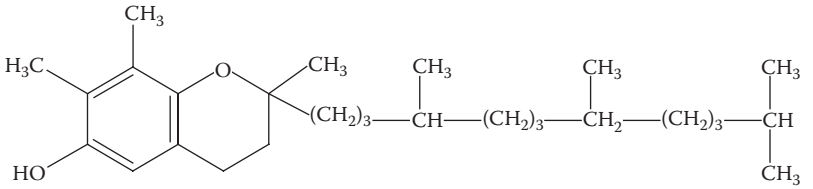

FIGURE 16.1 Structure of a α-tocopherol.

Curcumin

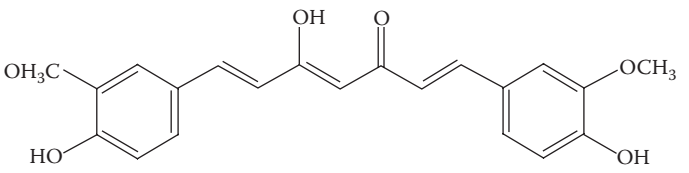

FIGURE 16.2 Structure of curcumin.

Flavonoids

Quercetin

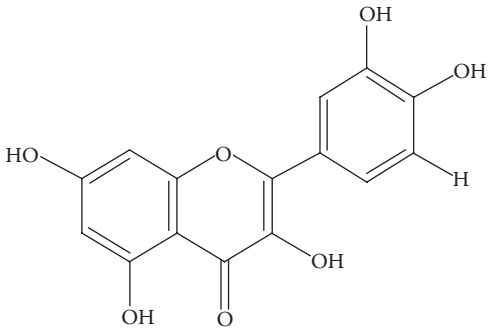

FIGURE 16.3 Structure of quercetin.

Isoliquiritigenin

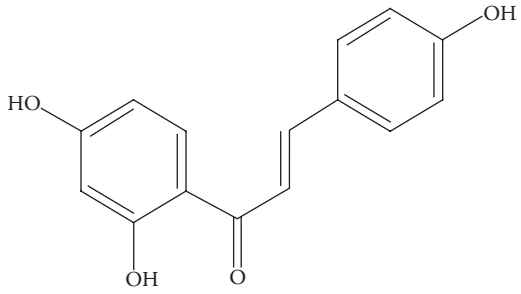

FIGURE 16.4 Structure of isoliquiritigenin.

Silybin

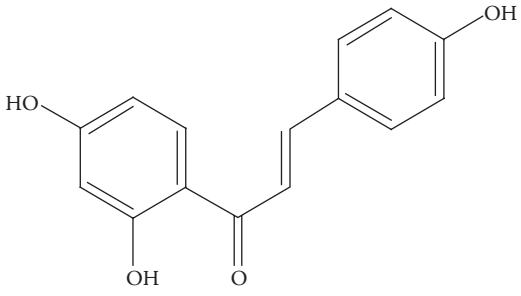

FIGURE 16.5 Structure of silybin.

Diabetes-related antioxidant activity as demonstrated for a range of flavonoids (including flavanones, flavones, chalcones, and their glycosides) and xanthones appears to depend on ortho dihydroxy substitution in an aromatic ring and/or hydroxyl groups forming hydrogen bonds with the keto group.[29]

Antioxidants can be free radical scavengers, singlet oxygen quenchers, and/or chelators of pro-oxidant metals. Low blood levels of α-tocopherol[2] and ascorbate[3] strongly predict type 2 diabetes in human prospective studies, as do β- and α-carotene and non-nutrient carotenoids such as lycopene.[30] Lemon flavonoids reduced oxidative stress in diabetic rats.[31] Oxidative damage to

Xanthones

Mangiferin

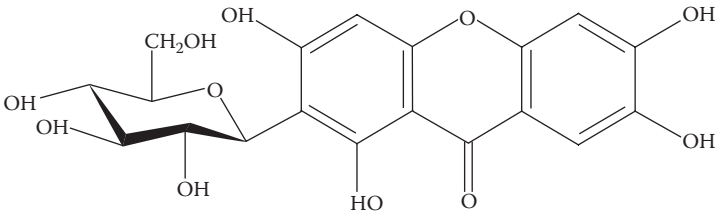

FIGURE 16.6 Structure of the xanthone, mangiferin.

lymphocyte DNA was significantly reduced in type 2 diabetes patients fed a diet supplemented with 76 to 110 mg of flavonols (mostly quercetin [Figure 16.3]) per day.[32]

Antioxidants in Models of Diabetes

Antioxidants prevent alloxan and streptozotocin (STZ)-induced damage to pancreatic β-cells in animal models of type 1 diabetes. Polyphenols reported with these positive effects include pycnogenol (mixture of flavonoids),[33] green tea polyphenols,[34] procyanidin polymers from cinnamon,[35] and the xanthone mangiferin (Figure 16.6).[36,37] In each of these cases, the studied materials also produced glucose-lowering effects.

Glucose-Lowering Effects of Flavonoids and Xanthones

Antioxidant activities of polyphenols may occur synergistically with glucose-lowering activity, although most studies using rodent models of diabetes examine the latter activity without inclusion of assays for oxidative status. Neither are mechanisms of glucose-lowering clear in most cases. Additional examples of flavonoids that reduce chemically induced hyperglycemia include silymarin (a mixture of flavanolignans, principally silybin [Figure 16.5]) from *Silybum marianum,*[38] prunin,[39] red wine polyphenols,[40] myricetin[41] (a flavone from the chloroform extract of the leaves of *Brikkellia veronicaefolia*),[42] chrysin derivatives[43] (a flavanone derivative from *Matteccia orientalis*),[44] and hesperidin (flavanone glycoside) with a mixture of phytosterols from *Schizonepata tenuifolia*.[45] Ellagitannins from the leaves of *Melaleuca quinquenervia* reduced blood glucose levels in STZ-induced diabetic mice.[46] In addition to mangiferin, the xanthones bellidifolin[47] and swerchirin[48] from *Swertia chirayita* reduce glucose in diabetic animals.

Protectors and Enhancers of Endogenous Defense

Endogenous antioxidant enzymes and nonenzymatic defenses (e.g., ascorbic acid, α-tocopherol, and glutathione) are low in blood of diabetics.[49] Alpha-tocopherol, ascorbate, and α-lipoic acid are of particular clinical interest in diabetes.

Alpha-tocopherol improved or reversed insulin resistance in cell cultures, murine diabetic models,[50] and type 2 diabetes patients.[51] Alpha-tocopherol prevented LDL oxidation, reduced risk of atherosclerosis and myocardial infarction,[22] and improved retinal blood flow and renal function.[52] In addition, the deficit in maximum endothelium-dependent vasorelaxation in diabetics can be reduced[53] and sciatic motor conduction and sciatic nutritive endoneurial blood flow reduced.[54]

Ascorbate supplementation alone did not reduce oxidative stress in diabetic rats; however, in combination with an iron chelator, it led to improvement in malondialdehyde, conjugated dienes, and antioxidant vitamins.[55] Flavonoids may act by sparing and enhancing the function of these endogenous antioxidants.[56]

Inhibition of Advanced Glycation Endproducts (AGEs)

Alpha-lipoic acid is particularly beneficial against diabetic polyneuropathy, reducing symptoms and improving autonomic and peripheral functions in diabetic patients.[57] It thus provides a molecule for understanding the potential of other antioxidants including polyphenols. In vascular tissues, α-lipoic acid improved endothelial and renal function, in part by inactivating the oxidative stress-sensitive NFκB, and improved insulin-mediated glucose uptake.[58]

Among an array of common flavonoids, the isoflavonoid genistein and the flavone apigenin were particularly strong inhibitors of protein glycation.[59] Diosmin (flavone glycoside) and hesperidin decreased protein glycation in association with an increase in activities on thiol-containing proteins such as glutatione peroxidase.[60,61] Similarly, the phenolic curcumin (Figure 16.2) (diferuloylmethane) prevented AGE-induced complications in rats.[62] Other compounds in studies with measured outcomes such as LDL-peroxidation may act through similar mechanisms. Flavonoids may play a role in the low glycosylation of hemoglobin associated with high intake of fruit and vegetables among healthy subjects.[63]

Aldose Reductase Inhibitors

Various antioxidant phytochemicals, of which flavonoids are the most effective, strongly inhibit lens aldose reductase,[64] with the common quercetin III as a prototype. In recent investigations, the flavone–glycoside isoquercetin,[65] an array of flavonoid glycosides from *Myrica multiflora*[66] and *Buddleja officinalis*,[67] the flavone capillarisin from *Artemisia capillaries*,[68] and the chalcone isoliquiritigenin (Figure 16.4) from roots of *Glycyrrhiza uralensis*[69] illustrate this widespread activity related to retinopathy and other complications of diabetes.

Inhibition of LDL Peroxidation and Hypolipidemic Effects

A variety of activities attributable to flavonoids and other compounds similar to those discussed previously in this chapter have possible antioxidant contributions. Hypoglycemia and hypoinsulinemia are discussed elsewhere in this volume. Reduction in serum triglycerides in diabetic animals by the xanthones bellidifolin from *Swertia japonica*[47] and mangiferin VI[37] and flavones from *Oeanthe javanica*[70] may be secondary to LDL peroxidation.

Polyphenols are known to inhibit LDL peroxidation.[71] Specific diabetes-related inhibition has been shown for genistein[72] and soya extracts,[73] silymarin,[38,74] diosmin,[61] xanthones from *Cudrania cochinchinensis*,[75] and mangostin (xanthone).[76] In a clinical study, supplementation of women with type 2 diabetes with citrus flavonoids failed to alter lipoprotein susceptibility to oxidation.[77] However, consumption of red wine, a source of flavonoids, during meals by type 2 patients reduced LDL oxidation.[78]

IMPLICATIONS FOR THERAPIES AND DIETS

Methodological Considerations

Combinations of phenolics and other compounds often show higher antioxidant activity than single entities.[79] Conversely, polyphenols can be pro-oxidants under certain conditions and produce potentially adverse effects.[80] Isolation and study of pure compounds from medicinal plants should therefore be conducted and interpreted with caution.

The data on application of antioxidants from plants as antidiabetics overwhelmingly come from *in vitro* or animal models. Although flavonoids show consistent promise, the few clinical studies with diet-based flavonoids are equivocal.[32,77,78] Human studies need to be extended to molecules with apparent pharmacological potential. Meanwhile, recommendations for polyphenol consumption other than as part of a mixed diet should be made cautiously.

Patterns of Traditional and Contemporary Plant Use

Traditional medical practitioners may employ antioxidant plants more to treat symptoms and sequelae of diabetes than the disease itself. Oxidative stress is important in so many of the complications of diabetes[81] that medicinal plants used for various symptoms and for the disease specifically can be expected to have antioxidant activity. Indeed, in a study of 35 medicinal species used for a combination of diabetic symptoms, it was observed that the greater the number of symptoms a plant species is used for, the greater its antioxidant activity is.[82] That parts of medicinal species selected for diabetic symptoms have significantly greater activity than parts from the same plants chosen at random further reflects the rationality of traditional practices.[83]

Although traditional medicine may identify specific treatments for diabetes, antioxidant activity from various ethnopharmacological studies[82–86] illustrates the general potential of plants to mediate diabetes and its complications within the context of the traditional lifestyle. These lifestyles may improve oxidative status more generally by combining medicines with diet. Ingested plants do not easily conform to distinct categories and, as such, a "medicinal" may also contribute significant amount of antioxidants to the diet as a tonic, beverage, and/or food. For example, tea, chocolate, wine, or beer[87,88] as well as fruits and vegetables contribute dietary antioxidants. High dietary intake of fruits and vegetables appears protective against diabetes.[89]

Practices that enhance antioxidant ingestion in traditional lifestyles were hypothetically a factor in keeping the incidence of type 2 diabetes low. Antioxidants in medicinal plants and traditional diets may help control diabetic complications arising in prediabetics[90] and possibly reduce the onset of diabetes.[2] Diabetes rates rise in populations moving from a traditional lifestyle and are reaching epidemic proportions in Latin America and parts of Asia.[91] In conjunction with alterations in energy consumption and expenditure, decrease in use of traditional plants may reduce ingestion of antioxidants that could prevent complications of diabetes.[92]

CONCLUSIONS

Traditional medicines, beverages, and foods with antioxidant activity can assist human populations to adapt in a contemporary context. As the source of therapeutics and the basis for a healthy lifestyle, they offer various health and economic benefits. Sufficient data on the benefits of flavonoids and xanthones in antidiabetic models suggest that further clinical research on their therapeutic benefits is warranted. Epidemiological and population-based studies are required to quantify polyphenol consumption from total ingestive practices in traditional societies and in those in transition. As support to these activities, pharmacological screening that characterizes current research on plant antioxidants should be extended to a greater number of medicines and traditional foods.

REFERENCES

1. Tesfamariam, B., Free radicals in diabetic endothelial cell dysfunction, *Free Rad. Biol. Med.,* 16, 383, 1994.
2. Salonen, J.T. et al., Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: a 4-year follow up study in men, *Br. Med. J.,* 311, 1124, 1995.
3. Vijayalingham, S. et al., Abnormal antioxidant status in impaired glucose tolerance and non-insulin-dependent diabetes mellitus, *Diabetes Med.,* 13, 715, 1996.
4. Sharma, A. et al., Evaluation of oxidative stress before and after control of glycemia and after vitamin E supplementation in diabetic patients. *Metab.: Clin. Exp.,* 49, 160, 2000.
5. Griesbacher, A., Kinderhauser, M., and Andert, S., Enhanced serum levels of TBARS in diabetes mellitus, *Am. J. Med.,* 98, 469, 1995.
6. Sundaram, R.K. et al., Antioxidant status and lipid peroxidation in type II diabetes with and without complications, *Clin. Sci.,* 90, 255, 1996.

7. Hamaoka, R. et al., Overexpression of the aldose reductase gene induces apoptosis in pancreatic beta-cells causing a redox imbalance, *J. Biochem.,* 126, 41, 1999.
8. Lenzen, S., Drinkgern, J., and Tiedge, M., Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues, *Free Rad. Biol. Med.,* 20, 463, 1996.
9. Rudich, A. et al., Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes, *Diabetes*, 47, 1562, 1998.
10. Paul, R.G. and Bailey, A.J., The effect of advanced glycated end-product formation upon cell-matrix interaction, *Int. J. Biochem. Cell Biol.,* 31, 653, 1999.
11. Chappey, O. et al., Advanced glycation end products, oxidant stress and vascular lesions, *Eur. J. Clin. Invest.,* 27, 97, 1997.
12. Thornalley, P.J., Cell activation by glycated proteins, AGE receptors, receptor recognition factors and functional classification of AGE, *Cell. Molecular Biol.,* 44, 1013, 1998.
13. Bierhaus, A. et al., AGE and their interaction with AGE-receptors in vascular disease and diabetes. I. The AGE concept, *Cardiovasc. Res.,* 37, 586, 1998.
14. King, G.L., Ishii, H., and Koya, D., Diabetic vascular dysfunctions: a model of excessive activation of protein kinase C, *Kidney Int.,* 52, S77, 1997.
15. Williamson, J.R. et al., Hyperglycemic pseudohypoxia and diabetic complications, *Diabetes,* 42, 801, 1993.
16. Goossens, B. et al., Direct evidence for tumor necrosis factor-induced mitochondrial reactive oxygen intermediates and their involvement in cytotoxicity, *PNAS USA*, 92, 8115, 1995.
17. Boden, G., Role of fatty acids in the pathogenesis of insulin resistance and NIDDM, *Diabetes,* 45, 3, 1997.
18. Kahn, C.R., Causes of insulin resistance, *Nature,* 371, 384, 1995.
19. Nakamura, K., Fushimi, K., and Kouchi, H., Inhibitory effects of antioxidants on neonatal rat cardiac myocyte hypertrophy induced by tumor necrosis factor-alpha and angiotensin II, *Circulation,* 98, 794, 1998.
20. McCune, L.M., Antioxidants in Canadian boreal forest indigenous medicinal plant treatments in relation to non-insulin dependent diabetes mellitus, Ph.D. thesis, McGill University, Montreal, 1999.
21. Laight, D.W., Carrier, M.J., Änggård E.E., Antioxidants, diabetes and endothelial dysfunction, *Cardiovasc. Res.,* 47, 457, 2000.
22. Esterbauer, H. et al., The role of lipid peroxidation and antioxidants in oxidative modification of LDL, *Free Rad. Biol. Med.,* 13, 341, 1992.
23. Bowie, A. et al., Glycosylated low density lipoprotein is more sensitive to oxidation: implications for the diabetic patient, *Arteriosclerosis,* 102, 63, 1993.
24. Cooper, M.E., Interaction of metabolic and hemodynamic factors in mediating experimental diabetic nephropathy, *Diabetologia,* 44, 1957, 2001.
25. Giugliano, D., Ceriello, A., and Paolisso, G., Oxidative stress and diabetic vascular complications, *Diabetes Care,* 19, 257, 1996.
26. Cameron, N.E. et al., Effects of α-lipoic acid on neurovascular function in diabetic rats: interaction with essential fatty acids, *Diabetologia,* 41, 390, 1998.
27. Aiello, L.P. et al., Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders, *New Engl. J. Med.,* 331, 1480, 1994.
28. Pratt, D.E., Natural antioxidants from plant material, in *Phenolic Compounds in Food and Their Effects on Health II: Antioxidants and Cancer Prevention,* Huang, M.-T., Ho, C.-T., and Lee, C.Y, Eds., American Chemical Society, ACS Symposium Series 507, Washington, D.C., 1992, 54.
29. Cao, G., Sofic, E., and Prior R.L., Antioxidant and pro-oxidant behavior of flavonoids: structure–activity relationships, *Free Rad. Biol. Med.*, 22, 749, 1997.
30. Ford, E.S. et al., Diabetes mellitus and serum carotenoids: findings from the Third National Health and Nutrition Examination Survey, *Am. J. Epidemiol.,* 149, 168, 1999.
31. Miyake, Y., Protective effects of lemon flavonoids on oxidative stress in diabetic rats. *Lipids,* 33, 689, 1998.
32. Lean, M.E.J., Dietary flavonols, protect diabetic human lymphocytes against oxidative damage to DNA, *Diabetes (New York),* 48, 176, 1999.
33. Maritim, A. et al., Effects of pycnogenol treatment on oxidative stress in streptozotocin-induced diabetic rats, *J. Biochem. Molecular Toxicol.*, 17, 193, 2003.

34. Sabu, M.C., Smitha, K., and Kuttan, R., Antidiabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes, *J. Ethnopharmacol*., 83, 109, 2002.
35. Anderson, R.A., Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity, *J. Agric. Food Chem.,* 52, 65, 2004.
36. Muruganandan, S. et al. Mangiferin protects the streptozotocin-induced oxidative damage to cardiac and renal tissues in rats, *Toxicology,* 176, 165, 2002.
37. Miura, T. et al., The suppressive effect of mangiferin with exercise on blood lipids in type 2 diabetes, *Biol. Pharmaceut. Bull.,* 24, 1091, 2001.
38. Soto, C.P. et al., Prevention of alloxan-induced diabetes mellitus in the rat by silymarin, *Pharmacol., Toxicol. Endocrinol.,* 119, 125, 1998.
39. Choi, J.S., Yokozawa, T., and Oura, H., Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of *Prunus davidiana* stems and its main component, pruning, *Planta Med*., 57, 208, 1991.
40. Al-Awwadi, N., Antidiabetic activity of red wine polyphenolic extract, ethanol, or both in streptozotocin-treated rats*, J. Agric. Food Chem*., 52, 1008, 2004.
41. Ong, K.C., and Khoo, H.E., Effects of myricetin on glycemia and glycogen metabolism in diabetic rats, *Life Sci*., 67, 1695, 2000.
42. Perez, R.M. et al. Isolation and hypoglycemic activity of 5, 7,3′-trihydroxy-3,6,4′-trimethoxyflavone from *Brickellia veronicaefolia*, *Phytomedicine,* 7, 25, 2000.
43. Shin, J.S. et al., Synthesis and hypoglycemic effect of chrysin derivatives, *Bioorganic Med. Chem. Lett*., 9, 869, 1999.
44. Basnet, P. et al., 2′-Hydroxymatteucinol, a new C-methyl flavanone derivative from *Matteccia orientalis*; potent hypoglycemic activity in streptozotocin (STZ)-induced diabetic rat, *Chem. Pharmaceut. Bull*., 41, 1790, 1993.
45. Kim, C.J., Lim, J.S., and Cho, S.K., Antidiabetic agents from medicinal plants inhibitory activity of *Schizonepeta tenuifolia* spikes on the diabetogenesis by streptozotocin in mice, *Archiv. Pharmacol. Res*., 19, 441, 1996.
46. Moharram, F.A. et al., Polyphenols of *Melaleuca quinquenervia* leaves — pharmacological studies of grandinin, *Phytother. Res*., 17, 767, 2003.
47. Basnet, P. et al., Bellidifolin stimulates glucose uptake in rat 1 fibroblasts and ameliorates hyperglycemia in streptozotocin (STZ)-induced diabetic rats, *Planta Med.,* 61, 402, 1995.
48. Saxena, A.M., Bajpai, M.B., and Mukherjee, S.K., Swerchirin induced blood sugar lowering of streptozotocin treated hyperglycemic rats, *Ind. J. Exp. Biol.,* 29, 674, 1991.
49. Giugliano, D., Ceriello, A., and Paolisso, G., Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress? *Metabol.: Clin. Exp.,* 44, 363, 1995.
50. Jacob, S. et al., Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial, *Free Rad. Biol. Med.,* 27, 309, 1999.
51. Jacob, S. et al., The antioxidant alpha-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle, *Diabetes,* 45, 1024, 1996.
52. Rösen. P. et al., Endothelial relaxation is disturbed by oxidative stress in the diabetic heart: the influence of tocopherol as antioxidant, *Diabetologia*, 38, 1157, 1995.
53. Keegan, A. et al., Chronic vitamin E treatment prevents defective endothelium-dependent relaxation in diabetic rat aorta, *Diabetologia,* 38, 1475, 1995.
54. Cotter, M.A. et al., Effects of natural free radical scavengers on peripheral nerve and neurovascular function in diabetic rats, *Diabetologia*, 38, 1285, 1995.
55. Young, I.S. et al., The effects of desferrioxamine and ascorbate on oxidative stress in the streptozotocin diabetic rat, *Free Rad. Biol. Med*., 18, 833, 1995.
56. Bors, W., Michel, C., Schikora, S., Interaction of flavonoids with ascorbate and determination of their univalent redox potentials: a pulse radiolysis study, *Free Rad. Biol. Med.,* 19, 45, 1995.
57. Ziegler, D. et al., Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III), *Diabetes Care,* 22, 1296, 1999.
58. Bierhaus, A. et al., Advanced glycation end product-induced activation of NF-κB is suppressed by alpha-lipoic acid in cultured endothelial cells, *Diabetes*, 46, 1481, 1997.
59. Asgary, S. et al., The inhibitory effects of pure flavonoids on *in vitro* protein glycosylation, *J. Herbal Pharmacother.*, 2, 47, 2002.

60. Keenoy, B.M., Vertommen, J., and de Leeuw, I., The effect of flavonoid treatment on the glycation and antioxidant status in type 1 diabetic patients, *Diabetes, Nutr. Metab. — Clin. Exp.*, 12, 256, 1999.
61. Vertommen, J. et al., Flavonoid [diosmin] treatment reduces glycation [of proteins] and lipid peroxidation in experimental diabetic rats, *Phytother. Res.,* 8, 430, 1994.
62. Sajithlal, G.B., Pandarinathan, C., and Gowri, C., Effect of curcumin on the advanced glycation and cross-linking of collagen in diabetic rats, *Biochem. Pharmacol.,* 56, 1607, 1998.
63. Sargeant, L.A. et al., Fruit and vegetable intake and population glycosylated hemoglobin levels: the EPIC-Norfolk Study, *Eur. J. Clin. Nutr.,* 55, 342, 2001.
64. Haraguchi, H., Aldose reductase inhibitors in higher plants, *Recent Res. Devel. Agric. Biol. Chem.,* 1, 147, 1997.
65. Sakai, I. et al., Presence of aldose reductase inhibitors in tea leaves, *Jpn. J. Pharmacol.,* 85, 322, 2001.
66. Yoshikawa, M. et al., Antidiabetic principles of natural medicines. II. Aldose reductase and alpha - glucosidase inhibitors from Brazilian natural medicine, the leaves of *Myrcia multiflora* DC. (Myrtaceae): structures of myrciacitrins I and II and myrciaphenones A and B, *Chem. Pharmaceut. Bull.,* 46, 113, 1998.
67. Matsuda, H. et al., Study on anticataract drugs from natural sources. II. Effects of Buddlejae Flos on *in vitro* aldose reductase activity, *Biol. Pharmaceut. Bull.,* 18, 463, 1995.
68. Okada, Y. et al., Search for naturally occurring substances to prevent the complications of diabetes. II. Inhibitory effect of coumarin and flavonoid derivatives on bovine lens aldose reductase and rabbit platelet aggregation, *Chem. Pharmaceut. Bull.,* 43, 1385, 1995.
69. Aida, K. et al., Isoliquiritigenin: a new aldose reductase inhibitor from Glycyrrhizae Radix, *Planta Med.*, 56, 254, 1990.
70. Yang, X.B. et al., Antidiabetic effect of *Oenanthe javanica* flavone, *Acta Pharmacol. Sinica*, 21, 239, 2000.
71. Croft, K.D., Antioxidant effects of plant phenolic compounds, in Basu, T.K., Temple, N.J., and Garg, M.L., Eds., *Antioxidants in Human Health*, CABI Publishing, Wallingford, U.K., 1999, 109.
72. Exner, M. et al., Genistein prevents the glucose autoxidation-mediated atherogenic modification of low-density lipoprotein, *Free Rad. Res.*, 34, 101, 2001.
73. Vedavanam, K. et al., Antioxidant action and potential antidiabetic properties of an isoflavonoid-containing soyabean phytochemical extract (SPE), *Phytother. Res.,* 13, 601, 1999.
74. von Schonfeld, J., Weisbrod, B., and Miller, M.K., Silibinin, a plant extract with antioxidant and membrane stabilizing properties, protects exocrine pancreas from cyclosporin A toxicity, *Cell. Molecular Life Sci.*, 53, 917, 1997.
75. Chang, C.H. et al., Effects on antilipid peroxidation of *Cudrania cochinchinensis* var. *gerontogea, J. Ethnopharmacol.*, 44, 79, 1994.
76. Mahabusarakam, W. et al., Inhibition of lipoprotein oxidation by prenylated xanthones derived from mangostin, *Free Rad. Res.*, 33, 643, 2000.
77. Blostein–Fujii, A. et al., Short term citrus flavonoid supplementation of type II diabetic women: no effect on lipoprotein oxidation tendencies, *Free Rad. Res.*, 30, 315, 1999.
78. Ceriello, A. et al., Red wine protects diabetic patients from meal-induced oxidative stress and thrombosis activation: a pleasant approach to the prevention of cardiovascular disease in diabetes, *Eur. J. Clin. Invest.*, 31, 322, 2001.
79. Saucier, C.T. and Waterhouse, A.L., Synergetic activity of catechin and other antioxidants, *J. Agric. Food Chem.*, 47, 4491, 1999.
80. Sanders, R.A., Rauscher, F.M., and Watkins, J.B., Effects of quercetin on antioxidant defense in streptozotocin-induced diabetic rats, *J. Biochem. Molecular Toxicol.,* 15, 143, 2001.
81. Thompson, K.H. and Godin, D.V., Micronutrients and antioxidants in the progression of diabetes, *Nutr. Res.,* 15, 1377, 1995.
82. McCune, L.M. and Johns, T., Antioxidant activity in medicinal plants associated with the symptoms of diabetes mellitus used by the indigenous peoples of the North American boreal forest, *J. Ethnopharmac.*, 82, 197, 2002.
83. McCune, L.M. and Johns, T., Symptom-specific antioxidant activity of boreal diabetes treatments, *Pharmaceut. Biol.*, 41, 362, 2003.
84. Scartezzini, P. and Speroni, E., Review on some plants of Indian traditional medicine with antioxidant activity, *J. Ethnopharmacol.*, 71, 25, 2000.

85. De las Heras, B. et al., Anti-inflammatory and antioxidant activity of plants used in traditional medicine in Ecuador, *J. Ethnopharmacol.,* 61, 161, 1998.
86. Kumar, S.K.C. and Müller, K., Medicinal plants from Nepal: II. Evaluation as inhibitors of lipid peroxidation in biological membranes, *J. Ethnopharmacol*., 64, 135, 1999.
87. Denke, M.A., Nutritional and health benefits of beer, *Am. J. Med. Sci*., 320, 320, 2000.
88. Dreosti, I.E., Antioxidant polyphenols in tea, cocoa and wine, *Nutrition,* 16, 692, 2000.
89. Ford, E.S. and Mokdad, A.H., Fruit and vegetable consumption and diabetes mellitus incidence among U.S. adults, *Prev. Med.,* 32, 33, 2001.
90. Facchini, J.S. et al., Relation between insulin resistance and plasma concentrations of lipid hydroperoxides, carotenoids, and tocopherols, *Am. J. Clin. Nutr.*, 72, 776, 2000.
91. Popkin, B.M., Horton, S., and Kim, S., The nutrition transition and prevention of diet-related diseases in Asia and the Pacific, *Food Nutr. Bull*., 22, S58, 2001.
92. Kuhnlein, H.V. and Receveur, O., Dietary change and traditional food systems of Indigenous Peoples, *Annu. Rev. Nutr*., 16, 417, 1996.

Index

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z