

## 6. PERILLA AND THE TREATMENT OF ALLERGY— A REVIEW

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Perilla (*Perilla frutescens* Britt.), a traditional Chinese herb, has recently received special attention because of its beneficial effects in the treatment of some kinds of allergic reactions without the side effects associated with some other used antiallergy medicines. In this chapter, the authors present a review of the problem of allergy and the current favorable evidence for the use of Perilla products towards its resolution.

### THE ALLERGY PROBLEM

Allergy is an abnormal immune reaction of the body to allergens such as pollen, dust, certain foods, drugs, animal fur, animal pets, animal excretions, feathers, microorganisms, cosmetics, textiles, dyes, smoke, chemical pollutants and insect stings. Certain conditions such as cold, heat, or light may also cause allergic symptoms in some susceptible people. Some allergens are just specific to some individuals but not to others. Allergens may act via inhalation, ingestion, injection or by contact with the skin. The resulting allergy may cause the victim to have a medical problem such as hay fever (allergic rhinitis), or atopic dermatitis (eczema), or allergic asthma, with symptoms ranging from sneezing, rhinorrhea, nasal itch, obstruction to nasal air-flow, loss of sense of smell, watery and itching eyes as in allergic rhinitis; and skin itching, skin redness and skin lesion as in atopic dermatitis. Allergic patients suffer not only irritating symptoms but also an impairment of the quality of life.

In 1989 allergy diseases affected 10% of the world's population (Vercelli and Geha, 1989). Today, allergy is even more common. It is now the most wide spread immunological disorder in humans, and the most prevalent and rapidly increasing chronic health problem, particularly in the industrialized countries where allergy affects one in four individuals. Furthermore allergy also causes a socioeconomic problem resulting in huge economic losses. In the U.S. alone it costs billions of dollars per year (HayGlass, 1995).

In the U.S. an estimated 20% or more of its population is allergic to something (Lichtenstein, 1993). Allergic rhinitis alone affects 10–15% of the U.S. population (Broide, 1995). The incidence of allergic asthma in the U.S. rose by 60% between 1979 and 1989 (Bousquet *et al.*, 1994). In England an investigation showed that the reported prevalence of asthma had risen from 4.1% in 1964 to 10.2% in 1989, hay fever from 3.2% rose to 11.9%, and eczema from 5.3% rose to 12% in the same period (Rusznak *et al.*, 1994). In Central Europe, pollinosis alone affects 10 percent of its population (Puls and Bock, 1993). In Sweden, more than one in three adults and 40% of children suffer from allergy, and the number of allergy patients has doubled over the last ten years and

continues to increase (Ullenius *et al.*, 1995). In Finland, 20–30% of young adults have the allergic symptoms (rhinorrhea), and about 20% of aged 0 to 6 year children have the skin eruption symptom (Nuutinen, 1995; Syvänen, 1995). In Australia, asthma affects as many as 20% of children and 10% of adults (Sutherland, 1994). In Japan, an investigative data published by the Ministry of Welfare of Japan showed 34% of its population suffered from some kinds of allergies, and mostly among children from the age of 0 to 4 (Oyanagi, [Chapter 7](#), this book). One-third of infants born in Japan are diagnosed as atopic (Okuyama, 1992).

One main cause which contributed to the increase in allergy incidence is the change of living environment and the extension of air pollution which is becoming more and more serious all over the world. In Japan, allergic rhinoconjunctivitis was found to be more prevalent in individuals living near motorways than in cedar forests. A recent study in Finland showed that admissions to hospital with severe asthma correlated with atmospheric levels of nitrogen dioxide (Rusznak *et al.*, 1994). In China, the prevalence of asthma is greater in the more modernized area than in the less developed area (Zhong, 1994).

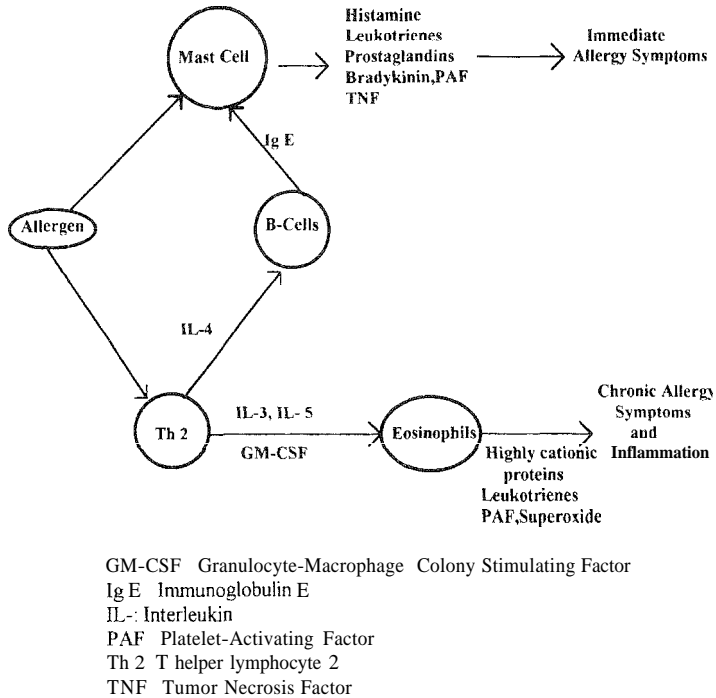
On the other hand, as a result of the affects of air pollution, the climatic change of global warming is likely to have significant effects on the distribution and abundance of allergenic plants. This impact on natural ecosystems is likely to be greatest in southern and Mediterranean Europe and in northern Scandinavia. These changes will alter the severity of pollen seasons and will have wide ranging implications for the incidence of pollinosis (Emberlin, 1994).

However, the prevalence of allergy in China is generally much lower than in western countries. Hay fever, the leading allergic disease in the West, is not common in China and some other Asian countries (Zhong, 1994; Leung, 1993; Rubenstein and Rubenstein, 1984). It is interesting to investigate whether this difference is due to racial predisposition or environmental factors; or may partly be attributed to the popularity of the application of traditional Chinese medicines in China.

## THE TREATMENT OF ALLERGY

The treatment of allergic diseases has benefited from the gradual understanding of allergy mechanisms. Allergic reaction is due to a change in the immunoreactivity of an individual. From current knowledge, its mechanism (Lichtenstein, 1993; Kay, 1993; International Rhinitis Management Working Group, 1994a; Cooper, 1994), is partly illustrated in [Figure I](#). When the allergen is presented to T-helper cells, B-lymphocytes will overproduce allergen-specific IgE antibodies. In the case of allergen contact, IgE bound to mast cells leads to mast cell activation and degranulation. As a result, mast cells release abnormal amounts of mediators such as histamine, PAF (platelet-activating factor), leukotrienes, prostaglandin D. These mediators will dilate blood vessels, increase permeability of small blood vessels, stimulate nerve endings, stimulate secretion of mucus in airways, or constrict bronchial airways, so as to induce local inflammation and cause various immediate symptoms or chronic symptoms.

## PERILLA AND THE TREATMENT OF ALLERGY



**Figure 1** Hypothesis on Partial Mechanisms of Allergy

In addition, cytokines such as TNF (Tumor Necrosis Factor) were recently found to be linked with allergic reaction. Indeed, plasma TNF levels are elevated in the serum of patients with atopic dermatitis, and the levels are tightly correlated with plasma histamine (Cooper, 1994; Sumimoto *et al.*, 1992). Furthermore, TNF will reversely stimulate the immune cells to produce more mediators (Yamazaki, 1993). It is now accepted that, allergy pathogenesis is involved in multifactors including hereditary, environmental, and immunological factors.

The treatment of allergic diseases is mainly based on allergen avoidance, public health education, the use of chemotherapy (therapy using any synthetic pharmaceutical compound), traditional herbal therapy, immunotherapy or an herbal immune regulator. In this chapter, Perilla is advanced as a herbal immune regulator.

### Allergen Avoidance

If the allergens can be identified, allergy may be treated simply by avoiding the offending agents. Allergen avoidance has always been seen as the first choice to be tried and the most effective treatment, but preventing exposure to some common environmental substances such as house dust mite, and pets allergens, is seldom possible. As mentioned

above the main cause of the allergic reaction is air pollution, therefore it is virtually impossible to prevent outdoor allergens exposure completely. Furthermore, even when an allergen, such as a pet is removed from a patient's environment, the benefit may take several weeks or months to be perceived (Bousquet *et al.*, 1994).

### Public Health Education

Public health educational campaigns are helpful in promoting self-medication and rational and economic treatment of allergy. For example, in Sweden the year 1995 was proclaimed as the Allergy year by five related national organizations for improving quality of life of allergy sufferers (Ullenius *et al.*, 1995) and in Finland, a similar campaign was undertaken by Finnish community pharmacists (Aaltonen and Kostiainen, 1995).

### Chemotherapy

As a main measure, medicine therapy plays an important role in allergy treatment. But with today's medicines such as antihistamine, corticosteroids, sodium cromoglycate and so on, it is still symptomatic (International Rhinitis Management Working Group, 1994b; Cooper, 1994). The symptoms of allergic diseases are caused by various factors and are different in individuals, and therefore therapy must be varied accordingly. Present medicines can cause side effects such as osteoporosis, diabetes, weight gain, ulcer and resistance to the corticosteroids. Although new application techniques have dramatically decreased the unfavorable side effects, some newer effective approaches to allergy treatment without side effects are still eagerly awaited by sufferers and physicians.

### Immunotherapy

Immunotherapy is a specific form of controlled allergen admission that changes immunoactivity into allergen tolerance. It has been used for more than 80 years but still represents a controversial treatment of allergic diseases (Mailing, 1994). It is appreciated that the efficacy of allergen immunotherapy is currently very low. Severe symptomatic reactions occasionally may occur, especially in asthmatic patients. In certain countries (the UK and the Scandinavian countries) the use of immunotherapy has been greatly curtailed due to adverse reactions (International Rhinitis Management Working Group, 1994b; HayGlass, 1995).

### Traditional Chinese Medicine (TCM)

With thousands of years of experience in treating diseases with natural materials, TCM still plays an important role in the health-care system of modern China and is officially recognized not only in China, but also in Japan and in some other eastern and south-eastern Asian countries which have the same cultural tradition (Zhu and Woerdenbag, 1995). People there still prefer to use traditional herbs for the treatment of allergy. There are several TCM prescriptions effective for allergic symptoms (Chen Yuh-Pan,

**Table 1** Some traditional Chinese herb prescriptions for allergy

<i>Condition</i>	<i>Prescriptions</i>
Allergic Rhinitis and Pollinosis	Minor Blue Dragon Combination Ophiopogon Combination Pueraria Combination Magnolia flower and Gypsum Combination Ephedra and Apricot Seed Combination Atractylodes Combination Ephedra Combination Minor Bupleurum Combination with Pinellia and Magnolia Combination (with <b>Perilla</b> ) Ephedra, Aconiti and Asarum Combination
Bronchial Asthma	Minor Blue Dragon Combination Minor Bupleurum Combination with Pinellia and Magnolia Combination (with <b>Perilla</b> ) Ephedra and Apricot Seed Combination Minor Bupleurum Combination with Ephedra and Apricot Seed Combination Ephedra and Magnolia Combination (with <b>Perilla</b> ) Hoelen and Schizandra Combination
Urticaria	Minor Blue Dragon Combination Pueraria Combination Bupleurum and Schizonepeta Combination
Atopic Dermatitis	Zemaphyte
Crab and fish poisoning	<b>Perilla</b> and Ginger Combination

Personal communication). Some of them are listed in Table 1. Among them, the Minor-Bupleurum-Combination with Pinellia-Magnolia Combination (Saibokuto), consisting of ten herbs including Perilla and the Ephedra-Magnolia-Combination containing Perilla, have been traditionally used for the treatment of bronchial asthma. Studies showed that Saibokuto, and Minor-Blue-Dragon-Combination (Syoseiryuto) clinically exhibit inhibitory effects on type I allergic reaction (Umesato *et al.*, 1984) and Saibokuto was found to inhibit histamine release and mast cell degranulation (Toda *et al.*, 1988).

Furthermore, there has been increasing interest in western countries for TCM. British scientists achieved impressive results with a TCM prescription (Zemaphyte) containing 10 Chinese herbs for the treatment of severe atopic eczema (Latchman *et al.*, 1995; Sheehan and Atherton, 1994; Cooper, 1994; Sheehan *et al.*, 1992; Harper *et al.*, 1990). Dr. Allan indicated in the FIP-CPA'93 (International Pharmaceutical Federation—Chinese Pharmaceutical Association) that most western medicines are single substances intended for a single well-defined disease. Complex diseases like eczema were not well served by western medicine but are often successfully treated with TCM (Hardman, 1993). Cooper indicated that the mechanism of action of Chinese herbal mixtures and their toxicities

require further investigation, but may reveal hitherto unconsidered avenues (Cooper, 1994). Therefore, traditional herbs are a potential valuable source for obtaining effective medicines for the treatment of allergy.

### Herbal Immune Regulators

In recent years, many researchers have been interested in elucidating the function of TCM as biological response modifiers or immune regulators. It has also been confirmed that some common vegetables or herbs contain nonnutritive components that may provide protection against chronic diseases including allergy and even some forms of cancer. (Haranaka *et al.*, 1985; Chen and Chen, 1989; Kawakita *et al.*, 1990; Yamazaki, 1992; Imaoka *et al.*, 1993).

A research team led by Prof. Yamazaki of Teikyo University, Japan, reported about the screening of vegetables with immune regulating activity. Experiments *in vivo* and *in vitro* found that among 18 kinds of vegetables, Perilla and ginger were the most active in reducing TNF production and its activity, which is linked with the allergy and inflammation as mentioned above (Yamazaki, 1992). Based on these findings, Kosuna and Yamazaki have developed the new application of Perilla in the treatment of allergy (Kosuna, 1993). On the other hand, it has also been found that Perilla seed oil rich in n-3 fatty acid ( $\alpha$ -linolenic acid) is also said to have some benefit in the treatment of allergy and this is dealt with later in this chapter (Ito *et al.* 1992; Watanabe *et al.*, 1994).

Interestingly, these findings agreed with earlier reports on the application of Perilla and ginger mixture for the clinical treatment of asthma and chronic bronchitis (Jiangsu New Medical College, 1977). Further reports trace back to the traditional use of Perilla leaf and seed for hundreds of years in the treatment of asthma (Chen, [Chapter 4](#)) and some symptoms associated with what is now known as allergy. Also, the traditional method of cooking crab or shellfish with Perilla leaves, in order to prevent so called "poisoning" existing in crab etc., might be re-evaluated as an effective way of preventing food allergy (IgE-mediated allergy) (Ortolani and Vighi 1995; Burks, 1995).

### APPLICATION OF PERILLA LEAF EXTRACT FOR ALLERGY

The manufacturing process of Perilla extract and the safety of the products were reported by Kosuna in [Chapter 8](#) of this book. In addition to the factory made Perilla products, several other methods for Perilla preparation are available in the folklore of China and Japan (Yamazaki, 1994; Kozo, 1994; Xu, 1983). The application of home made Perilla extract is also used for the treatment of allergy. However, the removal from the extract of agricultural chemicals and perillaldehyde, which might be allergens to some individuals is important (Kosuna, [Chapter 8](#)).

### Administration of Perilla Leaf Extract

Dr. Oyanagi *et al.* reported their experiences in treating allergy patients with Perilla products (Oyanagi, 1993; Yamagata, 1992; Mitsuki, 1992; Kabaya, 1994). According to

the different symptoms and the condition of the patients administration may be singly or combined (Oyanagi, 1993; Yamagata, 1992; Mitsuki, 1992).

#### *Oral administration*

For the concentrated products of Perilla extract, the dose was 0.3–2 ml/50–100 ml water or other drink, 2–3 times daily dependent on the age. With home made or diluted extract, the dosage varied with the concentration and methods of preparation.

#### *Nasal application*

To relieve the symptoms of an itching or running nose, the Perilla extract was applied inside the nostrils using a cotton bud.

#### *Topical application of Perilla extract*

Application to the skin was helpful in relieving the itching and redness.

#### *Topical use of Perilla cream and soap*

For some atopic dermatitis, Perilla cream and soap were recommended (Oyanagi, Chapter 7).

Following treatment with Perilla, some patients experienced effects just after use, others after some days to one week, or in some cases up to three months. A therapy period usually occupied three months. In some cases, at the beginning of the treatment, the symptoms seemed to be more serious than before. This reflects an action of Perilla. Usually after one week, the symptoms are less and thereafter the patient continues to improve. Only a small number of patients (about 2–3%) will experience worse symptom even after ten days. For these, the Perilla extract is discontinued (Oyanagi, 1993; Yamagata, 1992; Mitsuki, 1992).

### **Evaluation of Usefulness of Perilla Leaf Extracts**

Perilla leaf extract has been available as a "health product" rather than as a medicine. There are no published reports of controlled clinical trials. Even so, there are many reports of open (uncontrolled) studies from physicians and from patients-completed questionnaires, to support the beneficial use of Perilla leaf extract in the treatment of allergy. Rigorous double-blind placebo-controlled trials are doubtlessly needed before Perilla leaf extract can be accepted as an antiallergy medicine in the West.

#### *Out-patients evaluated by physicians*

Dr. Oyanagi reported his results of open studies in the treatment of more than one hundred allergy cases of children with atopic dermatitis. After three months of therapy

**Table 2** Conditions of 78 cases who were effective after using Perilla extracts for allergy treatment

<i>Conditions</i>		<i>Cases</i>	<i>%</i>
Gender	Female	52	62.8
	Male	26	37.2
Age (years)	0–10	24	30.8
	11–20	13	16.6
	21–30	12	15.4
	31–40	10	12.8
	41–50	11	14.1
	51–60	6	7.7
	61–70	1	1.3
	71–80	1	1.3
Allergic history (years)	0–3	14	17.9
	4–6	13	16.7
	7–9	6	7.7
	10–15	6	7.7
	16–30	7	9
	Unknown	32	41
Allergic diseases	Pollinosis	20	25.6
	Rhinitis	21	26.9
	Atopic	36	46.2
	Asthma	1	1.3

using a Perilla extract cream formulation, 80% of the patients showed varying degrees of improvement in the degree of itching, skin lesion, and eruption (Oyanagi, 1993, Yamazaki, 1994). No side effects were observed in any of the cases.

Dr. Takiguchi (1993) reported from his open studies that 20 allergic patients, using Perilla cream topically and Perilla extract orally, after two months, showed an improvement in 90% of the patients. Among these, 30% of the patients got significant benefit, 25% of the patients got some benefit and the rest got little benefit. All these patients ceased other medicine while using the Perilla products. Dr. Takiguchi concluded that Perilla is effective for allergy treatment without side effects.

#### *Self evaluation by patients*

In the Japanese magazines "My Health" (No. 9, 156–168, 1992; No. 8, 142–145, 1993; No. 3, 192–206, 1993; No. 2, 145–149, 1994), "Anshin" (No. 7, 171–191, 1992; No. 7 139–155, 1993; No. 7, 258–267, 1994) several special issues about the evaluation, of the use of Perilla extract for allergy were published. Many allergic patients reported their satisfying results after using Perilla leaf extracts or its products such as Perilla cream, Perilla soap and Perilla drink. From these the following data is derived.



Seventy eight cases reported effective benefit after using Perilla extract. Two thirds of them were female and one third of them were male. They included various age groups, but nearly 50% were under the age of twenty. The allergy history of these cases, varied from months to thirty years. A strong familial tendency could be seen. Among these 78 cases, 36 cases were included in 14 families and heredity was implicated. Among the cases, about half suffered from pollinosis or allergic rhinitis, and half had atopic dermatitis. Only one case was an asthma sufferer (Table 2). Those were allergic to pollen had allergy in Spring and Summer, and some also in Autumn. With Perilla treatment all these patients got some relief from their allergy symptoms and their quality of life was significantly improved.

Few cases suffering from asthma benefited from using Perilla extract. This might be attributed to the fact that plasma TNF- $\alpha$  concentration in bronchial asthma cases was not increased or only slightly increased (Sumimoto *et al.*,1992). Whereas the action of Perilla extract was mainly due to its inhibition of TNF overproduction (See Figure 1 and Chapter 5, this book).

Since 1990 Perilla extract has been widely recommended for the treatment of allergy and some details are given from case studies:

A lady aged 30 years, had allergic reaction since infancy. Every spring when the trees were budding or in late summer when some plants were in bloom, she would have allergic rhinitis, recurrent sneezing, watery nose and eye, itching nose and eye. At that time her medication was ineffective, and she was also concerned about the side effects of the medication. Her child, aged 6, also suffered from allergic rhinitis and atopic dermatitis. After using Perilla extract only a few times, her allergic symptoms were reduced significantly. Her child was also treated topically with Perilla extract for his eczema and obtained as good results as his mother. Since Perilla extract has no side effects, they took Perilla extract as a drink (5-6 drops in a cup of water) twice daily, in order to prevent their symptoms (Mizumoto, 1992).

Another lady, aged 42 years, and a beautician, could not work very well due to pollinosis. Her history of allergy was short but the symptoms were serious with recurrent sneezing, nasal itching, face and eye itching, and running nose requiring a full box of tissues every day. After using Perilla extract for one week the running nose stopped and her quality of life was markedly improved (Inaba, 1992).

A man, aged 62 years, suffered from allergic rhinitis, associated with change in the weather, such as rain or strong wind. After using Perilla extract for three months, his allergic symptoms were much reduced (Tajiri, 1993).

#### *Self-completed questionnaires*

In Finland, Perilla extract was launched on the market in 1993. Investigation of the usefulness of Perilla products for allergy was carried out by self-completed questionnaires. These included age, gender, allergy history, symptoms, specific allergen, time of allergy, medicines used before, dosage, and evaluation of the effectiveness. The latter was self-evaluated according to the reduction of symptoms and the quality of life. The investigation is continuing in some other European countries. In one group in Helsinki city forty cases had accepted questionnaires, among them female 50 %, male 50 %.

Investigation showed all the cases were allergic to pollens, about half of the cases were also allergic to some foods or animal pets. All the cases had allergy in spring time and about 40% of the cases, had the trouble all year round. Of the allergy cases investigated, 30% reported Perilla products were highly effective, 35% reported effective, 20% less effective and 15% ineffective.

One example: A young man was allergic to dogs and cats experiencing eye itching and running nose. He took Perilla capsules, 2 or 3 capsules daily, for two weeks before his friend arrived with his dog to spend holiday with him and he had no allergic reaction during their stay (Yu, 1996).

## USE OF PERILLA OIL FOR ALLERGY

Bjorneboe *et al.* (1989) reported that dietary modifications involving supplementation with fish oil (rich in n-3 fatty acids) slightly favored the experimental group over the control group in the case of atopic dermatitis. Dietary Perilla oil, rich in n-3 fatty acids (which contain 54–64% linolenic acid) was also found to have some benefit in atopic dermatitis (Ito *et al.*, 1992).

Recent studies have indicated that the dietary  $\alpha$ -linolenate/linoleate balance affected on the development of some chronic diseases including allergy (Okuyama, 1992). Okuyama proposed that the excessive intake of linoleic acid and the changes in the essential fatty acid balance of diets have made our bodies hyperreactive to various allergens. The increase in the intake of Perilla oil will inhibit the production of leukotrienes which is another important mediator causing allergy (Figure 1). Therefore taking Perilla oil might be beneficial for the prevention and treatment of allergy.

Some recent patents have been published about the efficacy of Perilla oil for the treatment of allergy (Jpn. Patent Kokai Tokkyo Koho JP 290822, 1992; JP 290812, 1990). In one study (Table 3) twenty four patients with atopic dermatitis patients (male 18, female 6, aged 5–32 years) were divided into four groups each taking different kinds of oil, 2–3 grams. The different oil groups had different ratios of n-6/n-3 fatty acids. After three months those taking Perilla oil had benefited significantly (Jpn. Patent Kokai Tokkyo Koho JP 290822, 1992). Ito *et al.* (1992) also reported a pilot study on 6 atopic dermatitis outpatients treated with Perilla oil. These patients were given  $\alpha$ -linolenic acid-enriched diet reducing the n-6 fatty acid (linoleic acid and arachidonic acid) intake and increasing the n-3 fatty acid (Perilla oil). After 40 days treatment the dermatitis improved in 3 patients. Results suggested that daily meals containing  $\alpha$ -linolenic acid-enriched diet may have some benefit in the treatment of allergic diseases.

## THE POSSIBLE MECHANISMS OF PERILLA IN THE TREATMENT OF ALLERGY

Although the precise mechanisms of Perilla treatment for allergy are not yet well elucidated, recent researches on the various phytochemicals and their pharmacological properties have also revealed some mechanisms of Perilla action in allergy. Kosuna (1995) recently published a review on anti-inflammatory active compounds in Perilla.

**Table 3** Efficacy of Perilla oil in allergy

Patient Group	Intake Oil	n6/n3	Improvement % after		
			one month	two months	three months
1	Perilla oil 100%	0.22	33	50	83
2	Sesame 100%	105.76	17	33	33
3	Safflower oil 100%	382.5	0	0	17
4	Perilla oil 80% Sesame oil 20%	0.4	50	83	83

Several active components contained in Perilla have been found to be linked with antiallergy and anti-inflammatory actions. These include elemicine,  $\alpha$ -pinene, caryophyllene, myristicin,  $\beta$ -sitosterol, apigenin, phenylpropanoids and also some flavonoids which act as anti-inflammatory agents (Martin *et al.*, 1993). From current knowledge, the mechanisms of allergy treatment by Perilla may involve the following aspects which are linked to the regulation of the condition by the immune system.

### Perilla Leaf Extract

#### 1. TNF inhibition

Relevant to this section is the Perilla leaf extract which contains active components of molecular weight less than 10000. As mentioned above, Yamazaki reported that Perilla extract was shown to be active in inhibiting TNF production (Chapter 5). Kosuna proposed that more than ten active components contained in the Perilla leaf extract were active in inhibiting TNF production which plays an important role in controlling allergic reaction (Figure 1) (Kosuna, Chapter 8, this book). Sumimoto *et al.* (1992) reported that plasma TNF- $\alpha$  concentration was increased in atopic dermatitis and the magnitude of the increase was correlated with the severity of the dermatitis. Also a significant correlation was found between plasma TNF- $\alpha$  and plasma histamine concentrations in atopic dermatitis. Therefore, it seemed to be reasonable that Perilla was useful in treatment of atopic dermatitis and some other allergic reactions. However, TNF- $\alpha$  concentration was not or only slightly increased in plasma from bronchial asthma patients. This may explain why Perilla extract is less effective in asthma patients.

#### 2. IgE inhibition

For the Perilla leaf extract which contains active components with a molecular weight more than 10000, Imaoka *et al.* (1993) indicated that immunosuppressive effects of this kind of Perilla leaf extracts are preferentially on IgE production and that may be useful for the suppression of IgE antibodies in certain allergic disorders (Figure 1).

### 3. Antioxidative activity

As reported by Kosuna (Chapter 8) and Fujita (Chapter 10) and some other scientists, Perilla leaf extracts contain a lot of active constituents showing antioxidative activity such as flavonoids, anthocyanins, phenolics (rosmarinic acid, caffeic acid, caffeates, protocatechuic aldehyde etc.). Venge (1995) reported that oxygen radicals may also play an important role in allergy. Studies indicated that the cells involved in the allergic inflammation are potent producers of various oxygen metabolites. These cells produced large amounts of oxygen radicals which related to the allergic symptoms. From this point of view, it could be suggested that some antioxidants present in Perilla leaves *may* be involved in its action in the treatment of allergy.

### Perilla Essential Oil

Perilla seed, leaf and stem contain a total amount of essential oil about 0.5%. In addition to perillaldehyde, which was removed from the Perilla leaf extract products for its potential allergen property (Kosuna, Chapter 8), several other constituents contained in Perilla essential oil showed pharmacological activity. It was reported (Ke, 1982) that in animal experiments, one of the constituent in the essential oil,  $\beta$ -caryophyllene, showed relaxing action to the windpipe of guinea pig. Also it showed significantly suppressing action to citric acid or acrylaldehyde induced cough. It may partially explain the action of Perilla on anticough and antiasthma. Another constituent, *l*-menthol showed antiitching action thus making Perilla helpful in the treatment of some allergic skin diseases (Yin and Guo, 1994).

Martin *et al.* (1993) have proved the anti-inflammatory activity of  $\alpha$ -pinene and  $\beta$ -caryophyllene in the rat edema model induced by carrageenin or by PGE<sub>1</sub>. Hashimoto and Fujita (1994) reported that elemicin was found to exhibit an inhibitory action on 5-lipoxygenase (5-LOX) which is the first enzyme in the conversion of arachidonic acid to leukotriene. Elemicin also had a suppressing action in the rat homologous PCA (passive cutaneous anaphylaxis) test which is the most commonly used bioassay to evaluate anti-allergic effects on type I allergy.

### Perilla Seed Oil

Earlier, it was proposed that the n-6 and n-3 polyunsaturated fatty acids in diets were importantly involved in allergy (Hashimoto *et al.*, 1988). Recent studies have indicated that the dietary  $\alpha$ -linolenate/linoleate balance affected on the development of some chronic diseases including allergy and that raising the (n-3) to (n-6) ratios of diets would be effective in reducing the severity of immediate-type allergic hypersensitivity (Okuyama, 1992; Watanabe *et al.*, 1994). It was hypothesized that if taking more n-3 fatty acid, resulted in a lowering of n-6 fatty acid uptake, this would lead to the inhibition of leukotriene production which is another important mediator causing allergy (Figure 1). Therefore taking Perilla oil (contains mainly n-3 polyunsaturated fatty acid) might be beneficial for the prevention and treatment of allergy.

Ito *et al.* (1992) reported a pilot study on atopic dermatitis patient treated with Perilla oil. In his study, patients treated with Perilla oil, in the phospholipid fraction in serum, the n-3:n-6 ratio and the EPA:AA ratio were significantly increased. Leukotriene C4 release from polymorphonuclea leukocytes by zymosan and fresh autologous serum was significantly decreased. This results might support the hypothesis that increasing  $\alpha$ -linolenic acid could inhibit release of some chemical mediators (leukotrienes) linked with allergy.

## CONCLUSION

Allergy has become a serious problem affecting health and social economy. New approaches to the treatment of allergy have been studied and developed. Based on the long-term use as a traditional Chinese herbal medicine, food spice and garnish; Perilla has now been confirmed in limited trials to have beneficial effects in the treatment of some allergy diseases such as hay fever and atopic dermatitis in children and adults, apparently without side effects. Preliminary mechanism studies support the use of Perilla products in the treatment of allergy and these are promising candidates for use in clinical double-blind, placebo-controlled trials.

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