Food and Natural Materials Target Mechanisms to Effectively Regulate Allergic Responses

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Summary An immune hypersensitivity disorder called allergy is caused by diverse allergens entering the body via skin contact, injection, ingestion, and/or inhalation. These allergic responses may develop into allergic disorders, including inflammations such as atopic dermatitis, asthma, anaphylaxis, food allergies, and allergic rhinitis. Several drugs have been developed to treat these allergic disorders; however, long-term intake of these drugs could have adverse effects. As an alternative to these medicines, food and natural materials that ameliorate allergic disorder symptoms without producing any side effects can be consumed. Food and natural materials can effectively regulate successive allergic responses in an allergic chain-reaction mechanism in the following ways: [1] Inhibition of allergen permeation via paracellular diffusion into epithelial cells, [2] suppression of type 2 T-helper (Th) cell-related cytokine production by regulating Th1/Th2 balance, [3] inhibition of pathogenic effector CD4+ T-cell differentiation by inducing regulatory T cells (Treg), and [4] inhibition of degranulation in mast cells. The immunomodulatory effects of food and natural materials on each target mechanism were scientifically verified and shown to alleviate allergic disorder symptoms. Furthermore, consumption of certain food and natural materials such as fenugreek, skullcap, chitin/chitosan, and cheonggukjang as anti-allergics have merits such as safety (no adverse side effects), multiple suppressive effects (as a mixture would contain various components that are active against allergic responses), and ease of consumption when required. These merits and anti-allergic properties of food and natural materials help control various allergic disorders.

Key Words food and natural materials, anti-allergic activity, allergen permeation, Th2 response, degranulation

Allergy is an immune hypersensitivity disorder that develops when the immune system reacts to generally harmless substances present in the environment. Pollen, dust, animal dander, mites, bee stings, and certain foods and medications are commonly known allergens that cause allergic reactions via skin contact, injection, ingestion, and inhalation. These allergic responses may result in allergic disorders such as atopic dermatitis, asthma, anaphylaxis, and allergic rhinitis, which continue to increase every year. According to the World Health Organization, allergic asthma is one of the most common chronic diseases among children and affects around 235 million people worldwide (1).

For the prevention and treatment of these allergic disorders, many studies that aim at developing a number of drugs such as immunosuppressants, anti-histamines, and various steroids are currently underway. However, it has been reported that the long-term intake of these drugs has adverse side effects such as growth retardation, diabetes, hypertension, cataract, and osteoporosis (2). Thus, in recent years, food and natural materials have been continuously explored as alternatives to anti-allergic medicines owing to their safety and efficiency.

Allergic chain-reactions are initiated due to sensitization of the immune system because of allergen permeation into epithelial cells (3). The permeated allergens are phagocytosed by antigen-presenting cells such as macrophages and dendritic cells, which in turn display the allergen to CD4+ T cells. The CD4+ T cells are further functionally differentiated into T-helper (Th)2 cells, resulting in the production of the interleukins (IL) IL-4, IL-5, and IL-13. These Th2 interleukins/cytokines promote both the activation and proliferation of B cells and eosinophils, leading to the production of antigen-specific IgE by B cells. IgE can bind to FcεRI on the mast cells with strong affinity and cross-link with re-permeated allergens. Activation of mast cells due to interactions between IgE and allergens leads to their degranulation, resulting in the release of histamines, tryptases, and leukotrienes, which cause allergic symptoms (4).


Abbreviations: IgE, immunoglobulin E; IL, interleukin; Th, T-helper; TJ, tight junction; Treg, regulatory T; ZO, zonula occludens.

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Regulation of these target mechanisms in an allergic response can reduce the symptoms of allergic disorders (Fig. 1). For example, based on the above discussion, we earlier evaluated the anti-allergic activities of herbs and foods derived from 106 species, of which only nine edible species (black pepper, green tea, turmeric, fermented soybean, licorice, hawkweed, beefsteak plant, fenugreek, and skullcap) were selected based on their high activity and nontoxicity. Anti-allergic effects of the nine-species mixture (NPM-9) were verified against trimellitic anhydride-induced contact dermatitis (5). This evaluation of the anti-allergic activities might be effective because the anti-allergic response to each phase mechanism can be combined to improve efficacy.

Inhibition of Allergen Permeation via Paracellular Diffusion into the Epithelial Cells

Allergens mainly permeate across the epithelial cells via paracellular diffusion. The tight junction (TJ) protein complexes in the epithelial cells regulate paracellular diffusion and are located around the apical end of the lateral cell membrane. Modulation of TJs can control the permeability of allergens via paracellular diffusion pathways. TJs are formed by specific interactions between various intracellular proteins and transmembrane proteins. The three main transmembrane proteins involved are occludins, claudins, and JAM and the major intracellular proteins involved are zonula occludens (ZO): ZO-1, ZO-2, ZO-3, cingulin, and 7H6 (6). These intracellular proteins maintain the structure and function of TJs by interacting with transmembrane proteins. The up-regulatory effects of food and natural materials on the expression and assembly of TJ proteins could inhibit allergen permeation, thereby enhancing the barrier function of the epithelium. For example, skullcap (Scutellaria baicalensis) extract inhibits OVA permeation across Caco-2 cell monolayers by up-regulating the expression of occludins, ZO-1, and JAM proteins (7). Furthermore, kaempferol has been reported to enhance the assembly of ZO-1, ZO-2, occludins, claudin-1, claudin-3, and claudin-4 and the expression of ZO-2 and claudin-4 (8). The up-regulation of TJ proteins by food and natural materials not only mitigates allergic disorders but also inflammatory diseases, as the up-regulation of TJ proteins could also block the permeation of pathogens and toxins into the tissues from the external environment.

Suppression of Th2-Related Immune Response by Regulating the Functional Differentiation of Th Cells

Generally, the immune system maintains a balance between Th1 and Th2 responses. For example, under allergic conditions, the Th2 response is enhanced, while
The Th1 response is suppressed. In contrast, the Th1 response increases under inflammatory conditions, while the Th2 response is decreased. Many studies suggest that food and natural materials could reduce the symptoms of allergic disorders such as allergic contact dermatitis, asthma, and food allergies, by maintaining the Th1/Th2 balance. For example, fenugreek, which is used as a spice in curry preparations, and chitin/chitosan, which is obtained from crustaceans, are known to increase the Th1 response and decrease the Th2 response, respectively, thereby alleviating symptoms of allergic contact dermatitis, asthma, and food allergies (9, 10). Although enhancement of the Th1 immune response could decrease the allergic Th2 immune response, induction of Treg cells could also result in a reduction of all other responses by effector T cells, including those of Th2 cells. Therefore, the induction of Treg cells mediated by food and natural materials could be effective in suppressing allergic hypersensitivity.

Food-derived phytochemicals such as naringenin, quercetin, curcumin, and resveratrol induce differentiation of Treg cells, resulting in suppression of the Th2 cell response (11). Recently, it has been reported that various probiotics may cause induction of Treg cells. Kwon et al. studied a 5-probiotic mixture (IRT-5) that showed anti-allergic and anti-inflammatory activities in atopic dermatitis and colitis by enhancing the induction of Treg cells (12). These effects of food and natural materials could contribute in ameliorating the symptoms of not only allergic disorders but also autoimmune diseases such as inflammatory bowel diseases, rheumatoid arthritis, lupus, and psoriasis, by suppressing the effector Th1/Th2/Th17 cells.

**Suppression of Histamine Release by Inhibiting Degranulation in Mast Cells**

Mast cells are granulocytes that play a key role in allergic immune responses. Degranulation of mast cells caused by cross-linking between IgE and allergens leads to the release of allergic inflammatory mediators such as histamines, leukotrienes, tryptases, and prostaglandins. The release of these mediators could result in various allergic disorders, especially allergic asthma due to bronchoconstriction, airway hyperresponsiveness, eosinophilic infiltration, and mucus hypersecretion. Intake of certain food and natural materials could alleviate allergic symptoms and ameliorate allergic disorders like asthma. For example, *cheonggukjang* (13) (called natto in Japan), a traditional Korean fermented soy product, and *Anemarrhena asphodeloides* (14) extract treatments lead to alleviation of allergic asthma symptoms and result in suppression of the anaphylactic reaction by decreasing Ca\(^{2+}\) influx into mast cells, leading to subsequent reduction of degranulation and histamine release from them. Although, many drugs like anti-histamines have been used to treat allergic symptoms, their side effects cannot be ignored. Therefore, intake of food and natural materials that have been characterized as being safe may help to alleviate allergic symptoms without causing any adverse side effects.

The use of food and natural materials for the treatment of allergies has three main advantages: [1] the consumer feels more secure because these materials are non-toxic and have no adverse side effects, [2] food and natural materials are a mixture of various components that possibly have multiple targets, allowing the suppression of different allergic mechanisms, and [3] they can be consumed at any time because of their easy availability in the environment.

**REFERENCES**