Flavonoids as complementary medicine for allergic diseases: current evidence and future prospects

T Tanaka¹,²*

Abstract

Introduction

During recent decades, various allergic diseases such as allergic rhinitis, asthma, atopic dermatitis and food allergy have become more prevalent globally. Dietary change has been proposed to be one of the environmental factors responsible for the increase in allergic diseases and worsening of allergic symptoms. If this continues to increase, complementary medicine or a preventive strategy for allergic diseases may be found in dietary management. In fact, complementary and alternative medicine in the form of natural products has been traditionally used worldwide, but no specific natural products or nutrients for any allergic diseases have been recommended yet. Flavonoids are low-molecular-weight polyphenolic secondary plant metabolites included in the daily diet. In addition, they are natural products with antioxidant, anti-inflammatory and anti-allergic properties as well as immune-modulating effects used as complementary and alternative medicine. Findings from numerous studies, both in vitro and in vivo, using allergic animal models have indicated the potential benefits of an appropriate intake of flavonoids as complementary medicine and a dietary strategy for the prevention of allergic diseases. The aim of this review was to discuss flavonoids as complementary medicine for allergic diseases.

Conclusion

Allergy is a disease of growing concern because of its already high and still increasing prevalence, and because it interferes with people's social life, school performance and work productivity, therefore it constitutes a major burden for society.

Discussion

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees associated to the institutions in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in the studies. Animal care was in accordance with the institutional guidelines.

Dietary changes and the growing prevalence of allergic diseases

The past two decades have witnessed a worldwide increase in allergic diseases, including atopic dermatitis, asthma, allergic rhinitis and food allergy. It is believed that several environmental factors interacting with genetic factors contribute to sensitisation to environmental allergens and to suffering from allergic diseases. In this context, it has been suggested that a change in dietary habits is one environmental factor, which is responsible for this increase and worsening of allergic symptoms, because food and beverages include either effective anti-allergic or allergy-promoting substances. However, because of limited evidence, no specific dietary management for allergic diseases has yet been established. Flavonoids are plant-derived nutrients, which possess antioxidant, anti-inflammatory, anti-allergic and immune-modulating properties. This review presents current findings associated to the biological action and beneficial effects of flavonoids in allergic animal models, as well as the results of epidemiologic and intervention studies of allergic diseases. These findings suggest that an appropriate intake of flavonoids may represent complementary medicine and a preventive strategy for allergic diseases.
Along with the growth in the prevalence of allergic diseases, the use of complementary and alternative medicine (CAM), for both allergic children and adults has also increased. The National Health Interview Survey performed in 2007 reported that 42%-49% of patients with asthma had used CAM during the previous 12 months. The National Centre for Complementary and Alternative Medicine (NCCAM) defines CAM as a group of diverse medical and health care systems, practices and products that are not generally considered part of conventional medicine. CAM practices are grouped into certain broad categories as follows: natural products, manipulative and body-based practices and others. Natural products include herbal medicines, omega-3 PUFAs, vitamins, minerals, probiotics and probiotics and are widely used by allergic patients in the belief that they can ameliorate allergic symptoms and maintain good health. However, the Cochrane Library and other systematic reviews regarding CAM for allergic diseases indicate that currently no specific natural products or nutrients can be recommended for allergic diseases mostly because of limited evidence of their effect. However, additional well-designed intervention studies involving humans may result in recommendations of some specific nutrients for allergic diseases. Flavonoids represent one of the natural substances for the prevention and treatment of allergic diseases.

Flavonoids may constitute complementary medicine for allergic diseases. Flavonoids, common substances in the daily diet, comprise a large group of low-molecular-weight polyphenolic secondary plant metabolites and are included in various vegetables, fruits and beverages. Flavonoids share a common structure consisting of two aromatic rings (A and B) that are bound together by three carbon atoms that form an oxygenated heterocycle (C) (Figure 1). They exert several biological benefits for humans, such as antioxidant, anti-inflammatory, antibacterial, anti-viral, anti-angiogenic, anti-allergic and immune-modulating effects. An appropriate intake of flavonoids may therefore be expected to prevent chronic diseases including allergic diseases.

Anti-allergic properties of flavonoids

Immunoglobulin E (IgE)-mediated immune responses consist of a sensitisation and an effector phase. Flavonoids have been shown to have an inhibitory effect in both phases by acting on several cells. First, interleukin (IL)-4 and IL-13 are known as class-switching factors for IgE, while kaempferol reportedly inhibits IL-4-induced activation of the signal transducer and activator of transcription (STAT) 6 by inhibiting Janus kinase (JAK) 3 activation. Second, low doses of several kinds of flavonoids, including apigenin, luteolin, baicalein, quercetin, kaempferol and myricetin, have been shown to inhibit activation of the aryl hydrocarbon receptor (Ahr), which is a ligand-activated transcriptional factor involved in the biological responses to planar aromatic hydrocarbons, such as dioxins. On the other hand, high concentrations of daidzein, resveratrol, naringenin and baicalein induce Ahr activation. Moreover, it has recently been demonstrated that Ahr is an important regulator for differentiation of naïve CD(4+) T cells into effector T cell subsets, which suggests that flavonoids can modulate acquired immune responses through their binding to Ahr. Third, the inhibitory effect of flavonoids on activation of high-affinity IgE receptor (FcεRI)-expressing cells, such as mast cells and basophils is well known, and was found to also inhibit histamine release and synthesis of leukotriene or other chemical mediators. We also found that flavonoids inhibit production of IL-4 and IL-13 as well as CD40 ligand expression by activated basophils. The fact that both the interaction of CD40 ligand with CD40 and the action of IL-4 or IL-13 on B cells, which are required for the differentiation of natural products used as traditional medicine or complementary and alternative medicine.

Flavonoids possess antioxidant, anti-allergic, anti-inflammatory and immune-modulating activities.

Administration of flavonoids are preventively or therapeutically efficacious for several allergic animal models.

Epidemiologic studies indicate that a high intake of vegetables and fruits may provide protection against asthma and allergic rhinitis, whereas there are few reports dealing with direct associations between flavonoid intake and allergic diseases.

A few clinical trials of flavonoids show beneficial effects on allergic rhinitis.

Figure 1: Summary of anti-allergic property of flavonoids.
B cells into IgE-secreting cells, has led to the notion that flavonoids are natural IgE inhibitors. Our analyses have demonstrated the existence of a hierarchy of inhibitory activity of flavonoids in IL-4 synthesis by activated basophils. Luteolin, apigenin and fisetin were identified as the most powerful inhibitors of IL-4 production with a half-maximal inhibitory concentration (IC_{50}) value ranging from 2.7–5.8 μM. Kaempferol and quercetin were found to have a moderate inhibitory effect with an IC_{50} value of 15.7–18.8 μM, whereas myricetin even with an IC_{50} value of 30 μM showed no such effect. Further, it has been shown that various flavonoids inhibit activation of nuclear factor-kappaB (NF-kB), which is one of the most important transcriptional factors to induce inflammatory responses and thus, to contribute to the development of asthma.

These anti-allergic, immune-modulating, antioxidant and anti-inflammatory activities of flavonoids strongly suggest that they may be effective dietary nutrients for the prevention and treatment of allergic diseases.

**Epidemiologic studies**

The findings of various epidemiologic studies indicate that a high intake of vegetables and fruit may provide protection against asthma and allergic rhinitis. However, few such studies have dealt with direct associations between flavonoid intake and allergic diseases. One cohort epidemiologic study in Finland, in which 10,054 adults were enrolled, found a reverse relationship between asthma incidence and higher flavonoid intake. Several recently established databases of the flavonoid content of major vegetables, fruits and beverages, such as those compiled by the US Department of Agriculture (USDA), the European BioActive Substances in Food Informative System (EuroFIR-BASIS) and Phenol-Explorer, will certainly facilitate epidemiologic studies and contribute to clarification of the relationship between the quantity and quality of flavonoid intake and the prevalence, incidence and severity of allergic diseases.

**Intervention studies in allergic animal models**

To examine the efficacy of flavonoids for allergic diseases, we examined the preventive and therapeutic effects of astragalin, kaempferol 3'-glucoside in an NC/Nga atopic dermatitis mouse model, which spontaneously developed eczema, scratching behaviour and serum IgE elevation. Oral administration of astragalin before the onset of dermatitis prevented the development of these symptoms and IgE elevation and also had a therapeutically beneficial effect on dermatitis. It was also shown that apigenin and baicalene, respectively contributes to the prevention and amelioration of skin lesions in NC/Nga mice. Moreover, in an ovalbumin-sensitized asthma mouse model, orally administered luteolin suppressed both bronchial hyperreactivity and bronchoconstriction. Subsequent investigations have demonstrated the benefits of various kinds of flavonoids, administered orally, or injected intraperitoneally or intravenously, in asthma, atopic dermatitis, food allergy and anaphylactic animal models. These flavonoids include fisetin, kaempferol, quercetin, isoquercitrin, rutin, 3-O-methylquercetin, 5,7,3',4' O-tetraacetate, nobiletin, narirutin, sulforufin and hesperidin.

**Intervention studies in humans**

The findings described above strongly support the notion that an appropriate intake of flavonoids may constitute complementary medicine or a preventive dietary strategy for allergic diseases. Indeed, it has been reported that various natural products, in which flavonoids are thought to be the main ingredients that account for their anti-allergic effects, and several kinds of traditional medicines, such as herbal and kampo medicines, which include substantial amounts of flavonoids, are efficacious for allergic rhinitis, pollinosis, atopic dermatitis and asthma. However, the direct effects of flavonoids on allergic symptoms have remained unknown.

We therefore examined whether flavonoids might be effective for symptoms associated to Japanese cedar pollinosis (JCP). The flavonoid used in our study was enzymatically modified isoquercitrin (EMIQ), which is a mixture of quercetin glycosides and consists of isoquercitrin and its maltooligosaccharides. It is approved as a food additive in Japan and as a substance generally recognised safe by the Food and Drug Administration. In three different, parallel-group, double-blind and placebo-controlled studies, which were performed between 2007 and 2009, it was demonstrated that EMIQ (100–200 mg/day, 4–8 weeks) is significantly effective for reducing symptoms caused by JCP. Present evidence regarding anti-allergic property of flavonoids is summarised in Figure 1.

**Conclusion**

Allergy is a disease of growing concern because of its already high and still increasing prevalence and because it interferes with people's social life, school performance and work productivity and therefore, constitutes a major burden for society. Along with the increasing rate of incidence of allergic diseases, the use of CAM has expanded among patients with such diseases. Establishment of effective strategies to...
end the increase in the prevalence of allergies and improve allergic symptoms is therefore of major importance. Dietary change has been suggested as one of the environmental factors that cause the increasing prevalence and worsening of allergic symptoms. If this is the case, improvement in dietary habits may ameliorate allergic symptoms, while dietary management during pregnancy, lactation or infancy may also prevent the onset of allergic diseases in infants. In view of this expectation, various in vitro and in vivo studies are in progress to investigate the effects on allergic diseases of antioxidants, minerals, omega-3 PUFAs, probiotics and natural products used in traditional medicine or CAM. However, because of the limited evidence, current findings have not yet resulted in specific recommendations of any of these substances for prevention of the development of allergic diseases or amelioration of allergic symptoms. In addition to the above mentioned substances, flavonoids are also potentially beneficial for allergic diseases. However, further epidemiologic and intervention studies as well as clarification of mechanisms through which flavonoids are effective for allergic diseases are essential for achievement of the goal of prevention and therapeutic efficacy, which is shown in Figure 2.

**Abbreviations list**

Ahr, aryl hydrocarbon receptor; CAM, complementary and alternative medicine; EMIQ, enzymatically modified isoquercitrin; IC_{50}, half-maximal inhibitory concentration; Ig, immunoglobulin; IL, interleukin; JCP, Japanese cedar pollinosis; PUFA, polyunsaturated fatty acids.

**References**


Licensee OA Publishing London 2013. Creative Commons Attribution Licence (CC-BY)

**For citation purposes:** Tanaka T. Flavonoids as complementary medicine for allergic diseases: current evidence and future prospects. OA Alternative Medicine 2013 May 01;1(2):11.