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Efficacy of Flavonoids for Patients with Japanese Cedar Pollinosis

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1. Introduction

The worldwide prevalence of allergic diseases such as asthma, atopic dermatitis and allergic rhinitis has increased during the last two decades (Holgate, 1999; Eder et al., 2006). Allergic rhinitis now affects 400-500 million people worldwide (Greiner et al., 2011; Ozdoganoglu & Songu, 2012) and adversely affects social life, school performance, and work productivity (Bousquet et al., 2001). The first case of Japanese cedar pollinosis in Japan was reported in the mid-1960s (Horiguchi & Saito, 1964), but now half of the Japanese population have become sensitized to Japanese cedar pollens and 24-29% of the population is suffering from the disease (Kaneko et al., 2005), so that Japanese cedar pollinosis is now rated as one of the most common diseases in Japan (Okamoto et al., 2009). The complicated interaction between genetic and environmental factors is thought to cause the development of allergic diseases. Many genetic loci related to atopy, a genetic tendency to produce immunoglobulin E (IgE) in response to environmental allergens, have been identified through genome-wide association studies (Grammatikos, 2008). However, changes in the environment have made a more significant contribution than genetic factors to the recent increase in the prevalence of allergic diseases (Nolte et al., 2001; Ho, 2010), since it seems unlikely that genes would have changed during the last two decades. Dietary change has been proposed as one of the environmental factors responsible for the increasing prevalence or the worsening symptoms of allergic diseases (Devereux & Seaton, 2005; Devereux, 2006; Kozyrskyj et al., 2011; Nurmatov et al., 2011; Allan & Devereux, 2011). Indeed foods include both allergy-promoting and anti-allergic nutrients (McKeever & Britton, 2004), and flavonoids, which are plant secondary metabolites, can have powerful antioxidant, anti-allergic and immune-modulating effects (Hollman & Katan, 1999; Middleton et al., 2000; Manach et al., 2004). This review article introduces the anti-allergic properties and efficacy of flavonoids for patients with Japanese cedar pollinosis and discusses the possibility that an appropriate intake of

flavonoids may constitute an effective complementary and alternative medicine as well as a preventative strategy for allergic diseases.

2. Flavonoids possess anti-allergic activity

In the mid-1990s we evaluated the clinical efficacy of one kind of traditional vegetarian diet on adult patients with severely to moderately active atopic dermatitis. After a two-month treatment period, the severity of dermatitis had decreased from 49.9 to 27.4 based on the SCORAD index, a score of atopic dermatitis severity, in association with a reduction in the number of peripheral blood eosinophils and the amount of urinary secretion of 8-hydroxy-2'-deoxyguanosine, a marker of oxidative DNA damage (Kouda et al., 2000; Tanaka et al., 2001). What factor(s) led to this amelioration of dermatitis remained unknown but subsequently it was found that one of the characteristics of the remedy was a high daily intake of flavonoids.

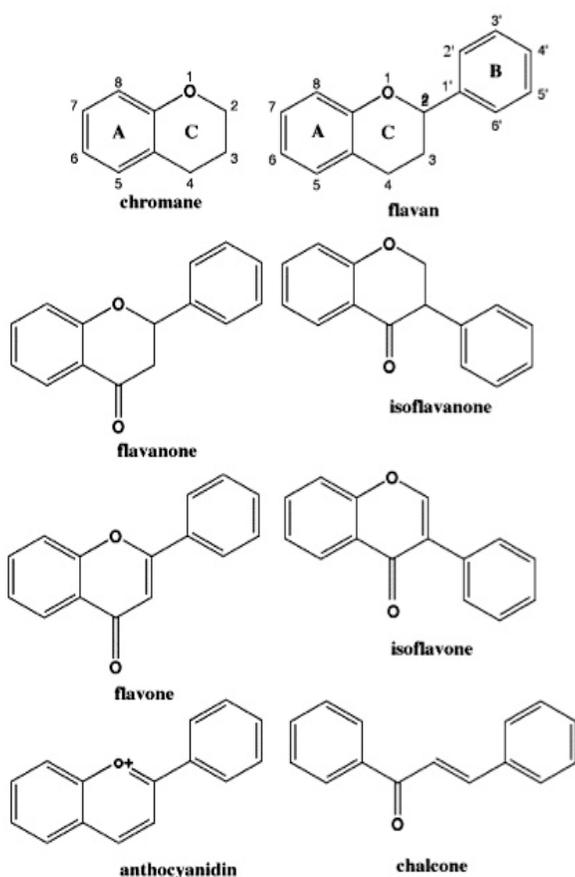


Figure 1. Structures of basic flavonoid skeletons

Flavonoids are comprised of a large group of low-molecular-weight polyphenolic secondary plant metabolites that are found in fruit, vegetables, cereals and beverages, and thus are common substances in the daily diet (Hollman & Katan, 1999; Middleton et al., 2000). Based on their skeleton, flavonoids are classified into eight groups: flavans, flavanones, isoflavanones, flavones, isoflavones, anthocyanidins, chalcones and flavonolignans (Fig. 1).

Flavonols constitute a separate class of flavonoids that possess the 3-hydroxyflavone backbone. Typical flavonoids such as quercetin, kaempferol, fisetin and myricetin belong to flavonols while luteolin and apigenin are classified as flavones. Flavonoids have been found to exert several biological activities including antioxidant, anti-bacterial and anti-viral activities, and to have anti-inflammatory, anti-angiogenic, analgesic, hepatoprotective, cytostatic, apoptotic, estrogenic or anti-estrogenic and immune-modulating effects as well as anti-allergic properties (Harborne & Williams, 2000; Williams & Grayer, 2004; Chirumbolo, 2010; Visioli et al., 2011; Calderon-Montano et al., 2011; Russo et al., 2012). As a result, considerable interest has been paid to the role of flavonoids in the prevention of chronic diseases, including cardiovascular diseases, cancers, type 2 diabetes, neurodegenerative diseases, osteoporosis and allergic diseases (Sealbert et al., 2005).

Mast cells and basophils expressing the high-affinity IgE receptor (FcεRI) play an important role in allergic inflammation by releasing chemical mediators such as histamine and cysteinyl leukotrienes, cytokines and chemokines (Stone et al., 2010). As for the anti-allergic activities of flavonoids, Fewtress and Gomperts first identified the inhibition by flavones of transport ATPase in histamine secretion from rat mast cells (Fewtrell & Gomperts, 1997). Fisetin, quercetin, myricetin and kaempferol were found to inhibit histamine release while morin and rutin showed little effect. Subsequently, quercetin was reported to inhibit histamine release by allergen-stimulated human basophils (Middleton et al., 1981; Middleton & Kandaswami, 1992). Flavonoids such as apigenin, luteolin, 3,6-dihydroxy flavones, fisetin, kaempferol, quercetin, and myricetin, all with IC₅₀ values of less than 10 μM, were found to inhibit hexosaminidase release from rat mast cells (Cheong et al., 1998). In addition, flavonoids have also been shown to suppress cysteinyl leukotriene synthesis through inhibition of phospholipase A₂ and 5-lipoxygenase (Lee et al., 1982; Yoshimoto et al., 1983). As for the suppressive effect of flavonoids on cytokine expression, Kimata et al were the first to report that luteolin, quercetin and baicalein inhibited the secretion of granulocyte macrophage-colony stimulating factor by human cultured mast cells in response to cross-linkage of FcεRI (Kimata et al., 2000a) and subsequently showed that these compounds also inhibited IgE-mediated tumor necrosis factor (TNF)-α and interleukin (IL)-6 production by bone marrow-derived cultured murine mast cells (Kimata et al., 2000b). These findings thus indicate that flavonoids are inhibitors of chemical mediator release and cytokine production by mast cells and basophils. One of the characteristic features of allergic diseases is overproduction of IgE in response to environmental allergens. The differentiation of B cells into IgE-producing cells requires both the interaction of the CD40 ligand with CD40 and the action of IL-4 or IL-13 on B cells (Rosenwasser, 2011), which are provided with these signals by Th2 cells, basophils and mast cells (Gauchat et al., 1993). Basophils were then used to examine the effects of flavonoids on IL-4, IL-13 and CD40 ligand expression. It was found that fisetin suppressed in a dose-dependent fashion both IL-4 and IL-13 synthesis by allergen- or anti-IgE antibody-stimulated peripheral blood basophils and that the IC₅₀ value of fisetin for inhibition of IL-4 synthesis was 5.8 μM (Higa et al., 2003; Hirano et al., 2004). Fisetin also inhibited IL-4, IL-5 and IL-13 production by KU812 cells, a basophilic cell line, in response to the calcium ionophore, A23187 plus phorbol myristate acetate (PMA), but the suppressive effect of fisetin on IL-6, IL-8 and IL-1β synthesis was relatively weak (Higa et

al., 2003). In order to determine the basic structure of the flavonoids that accounts for their inhibition of IL-4 production and to identify more active compounds, 45 kinds of flavones, flavonols and their related compounds were screened (Hirano et al., 2004; Kawai et al., 2007).

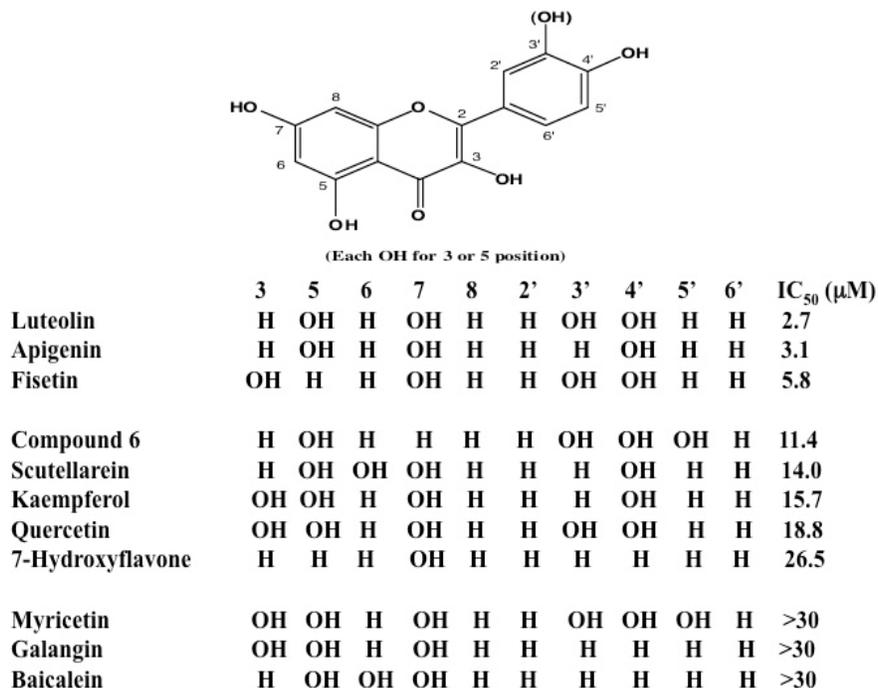


Figure 2. Basic structure of flavonoids for inhibitory activity of IL-4 synthesis by basophils

Luteolin, apigenin and fisetin were found to be the strongest inhibitors with an IC₅₀ value of 2.7-5.8 μM (Fig. 2). Quercetin and kaempferol are representative of flavonoids associated with a substantial daily intake and had an intermediate inhibitory effect on IL-4 synthesis with an IC₅₀ value of 15.7-18.8 μM, but myricetin showed no such effect. These analyses of structure-activity relationships revealed the fundamental structure required for the action. For maximal effect, hydroxylation in positions 7 and 4' is essential while the presence of OH in either position 3 or 5 is also required. In addition, luteolin, apigenin and fisetin were found to suppress CD40 ligand expression by activated basophils and KU812 cells in a dose-dependent manner, whereas myricetin even at 30 μM did not have such an effect (Hirano et al., 2006). These inhibitory properties indicate that flavonoids such as luteolin, apigenin and fisetin are natural IgE inhibitors.

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcriptional factor that mediates the toxic and biological actions of many aromatic environmental pollutants such as dioxins (Connor & Aylward, 2006). An AhR-based in vitro bioassay for the dioxin [2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)] revealed that the flavonoids, apigenin, luteolin, baicalein, quercetin, kaempferol and myricetin had noticeable inhibitory effects on AhR activation with an EC₇₀ value (equal to 70% of the maximal response to TCDD) of 1.9-5.1 μM, while marked AhR activation was displayed by daidzein, resveratrol, naringenin and baicalein at higher concentrations (Amakura et al., 2008). Moreover, it has recently been

shown that AhR is a regulator of differentiation of naïve CD4 positive T cells into effector T cell subsets (Marshall & Kerkvliet, 2010), suggesting that flavonoids modulate immune functions through their binding to AhR.

3. The relationship between flavonoid intake and the prevalence, incidence or severity of allergic diseases

As mentioned previously, flavonoids are contained in vegetables, fruit, cereals and beverages. Epidemiological studies have reported that a high intake of fresh fruit and vegetables may provide protection against asthma (La Vecchia et al., 1998; Butland et al., 1999). The Mediterranean diet, which has high antioxidant content because of the preponderance of fruit, vegetables, legumes, nuts and wholegrain cereals, has been associated with a reduced likelihood of asthma, wheezing and allergic rhinitis in cross-sectional studies of children (Chatzi et al., 2007; Garcia-Marcos et al., 2007; Tamay et al., 2007; De Batlle et al., 2008; Castro-Rodriguez et al., 2008). Shaheen et al reported that the results of a population-based case-control study of 607 cases and 864 controls in South London indicated that apple consumption and red wine intake were negatively associated with, respectively, asthma prevalence and severity, perhaps due to the protective effect of flavonoids (Shaheen et al., 2001), while the follow-up study made it clear that dietary intake of catechins, flavonols and flavones was not significantly associated with asthma prevalence and severity (Garcia et al., 2005). A cohort epidemiological study of 10,054 adults in Finland regarding the association between flavonoid intake and risk of several chronic diseases found that asthma incidence was lower for higher quercetin, naringenin, and hesperetin intakes (Knekt et al., 2002).

A study of 1,253 five-year-old children reported that maternal apple intake during their mothers' pregnancy was associated with beneficial results for ever wheeze, ever asthma and doctor-confirmed asthma (Willers et al., 2007). The Irish Lifeways Cross-Generation Cohort Study determined an association between high maternal fruit and vegetable intake during pregnancy and reduced likelihood of asthma in 632 three-year-old children (Fitzsimon et al., 2007). A third cohort study also demonstrated that wheeze and atopic sensitization in 460 children aged 6-7 years was less frequent if their mothers had followed a Mediterranean diet during pregnancy (Chatzi et al., 2008). Although there have been few reports of case-control or longitudinal studies examining direct associations between flavonoid intake and the prevalence or incidence of allergic diseases, the findings of the epidemiological studies mentioned here suggest that higher flavonoid intake is beneficial for protection against allergic diseases.

4. Efficacy of flavonoids in allergic models

The anti-allergic characteristics of flavonoids observed *in vitro* led to a study using NC/Nga mice to test whether intake of flavonoids might be effective for the prevention or the amelioration of allergic symptoms. NC/Nga mice spontaneously develop severe eczema, scratching behaviour and serum IgE elevation with aging under nonspecific pathogen-free

conditions (Matsuda et al., 1997). To determine the preventive effect of flavonoids, the mice were orally given astragalín, kaempferol 3'-glucoside (1.5 mg/kg), a major ingredient of flavonoid in persimmon leaf tea, or a control diet. Development of dermatitis with aging was observed in the control group and the severity of dermatitis was scored for evaluation. Oral intake of astragalín markedly prevented the appearance of the dermal symptoms, scratching behaviour and serum IgE elevation (Kotani et al., 2000). Moreover, when astragalín was administered to NC/Nga mice after the appearance of dermatitis, it significantly diminished its severity (Matsumoto et al., 2002). It was subsequently demonstrated with this mouse model that administration of extracts from petals of *Impatiens balsamina* L., which contains flavonoids such as kaempferol 3-rutinoside and 2-hydroxy-1,4-naphthoquinone as active gradients (Oku & Ishiguro, 2001), of apigenin (Yano et al., 2009), or of baicaléin (Yun et al., 2010) suppressed skin lesions. In an asthmatic mouse model sensitized with ovalbumin (OVA), it was demonstrated that oral administration of luteolin, even as little as 0.1 mg/kg, led to a significant suppression of bronchial hyperreactivity and bronchoconstriction (Das et al., 2003). It was also found that nobiletin, a polymethoxyflavonoid, when given intraperitoneally to OVA-sensitized rats at a dose of 1.5 or 5 mg/kg, reduced OVA-induced increases in eosinophils and eotaxin expression (Wu et al., 2006). In subsequent investigations, flavonoids such as quercetin, isoquercitrín, rutin, 3-O-methylquercetin 5,7,3',4'-O-tetraacetate, narirutín, apigenin, luteolin, sulfuretin, hesperidin, fisetín and kaempferol have been shown to suppress responses in various types of allergic animals (Makino et al., 2001; Fernandez et al., 2005; Rogerio et al., 2007; Jung et al., 2007; Jiang et al., 2007; Funaguchi et al., 2007; Yano et al., 2007; Cruz et al., 2008; Park et al., 2009; Choi et al., 2009; Li et al., 2010; Leemans et al., 2010; Shishebor et al., 2010; Song et al., 2010; Kim et al., 2011; Wu et al., 2011; Gong et al., 2012).

5. Efficacy of flavonoids for patients with allergic rhinitis

The aforementioned findings regarding the *in vitro* and *in vivo* anti-allergic properties of flavonoids strongly support the notion that an appropriate intake of flavonoids may constitute a complementary and alternative medicine and/or a preventive strategy for allergic diseases (Tanaka et al., 2003; Tanaka et al., 2004; Kawai et al., 2007; Tanaka et al., 2011; Singh et al., 2011). Indeed, the results of previous clinical trials using flavonoid extracts suggest that flavonoids have beneficial effects on allergic rhinitis (Takano et al., 2004; Kishi et al., 2005; Enomoto et al., 2006; Segawa et al., 2007; Yoshimura et al., 2007). The extracts examined were *Perilla frutescens* enriched with rosmarinic acid, apple polyphenols including procyanidins, or apple condensed tannin, catechin, epicatechin, phlorizin, and chlorogenic acid, hop water extract including quercetin and kaempferol glycosides, and tomato extract including mainly naringenin chalcone. However, the direct effect of flavonoids on allergic symptoms has remained unknown.

Enzymatically modified isoquercitrín (EMIQ) is a quercetin glycoside that consists of isoquercitrín and its maltooligosaccharides, and is manufactured from rutin through an enzymatic modification (Fig. 3) (Salim et al., 2004), which markedly enhances the absorption rate through the intestine.

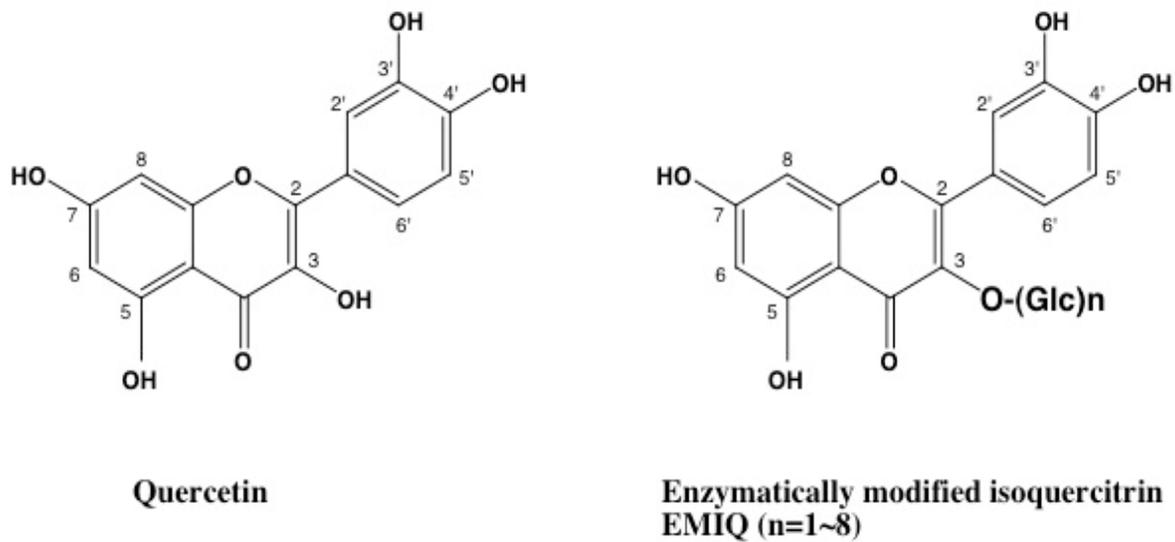


Figure 3. Enzymatically modified isoquercitrin is a quercetin glycoside.

This flavonoid is approved as a food additive in Japan and is used as an antioxidant for various commercially available food products such as beverages. Tests were performed in 2007, 2008 and 2009 to determine whether intake of EMIQ was effective for Japanese cedar pollinosis (Kawai et al., 2009; Hirano et al., 2009). Japanese cedar pollinosis is defined as an immunological response modulated by IgE and a seasonal (intermittent) allergic rhinoconjunctivitis caused by Japanese cedar pollen, characterized by nasal symptoms such as sneezing, rhinorrhea and nasal congestion and by ocular symptoms such as lacrimation, ocular itching and congestion (Okamoto et al., 2009).

In a parallel-group, double-blind, placebo-controlled study, volunteers with Japanese cedar pollinosis took two capsules of 50 mg EMIQ or a placebo daily for 8 weeks during the pollen season. Severity of subjective symptoms was evaluated by a scoring system (Baba et al, 2002) with some modifications. The study in 2007 began after the pollen had dispersed and thus aimed at examining the therapeutic effect of EMIQ. During the entire study period, ocular symptom+medication and ocular symptom scores for the EMIQ group were significantly lower than those for the placebo group (Fig. 4), while symptom+medication and symptom scores were significantly reduced at week 4-5 compared to those for the placebo group (Kawai et al., 2009).

To examine the preventive effect of EMIQ on symptoms of pollinosis the next study in 2008 began 3 weeks before the first day of pollen dispersion. Ocular symptom+medication and ocular symptom scores were also significantly suppressed during the entire period and symptom+medication and symptom scores were also reduced at week 5-6 (Fig. 5) (Hirano et al., 2009).

Although these two studies did not show a statistically significant ameliorative effect on nasal symptoms, the 2009 study using 200 mg/day of EMIQ for 4 weeks clearly demonstrated efficacy of EMIQ for reducing nasal symptoms (Fig. 6).

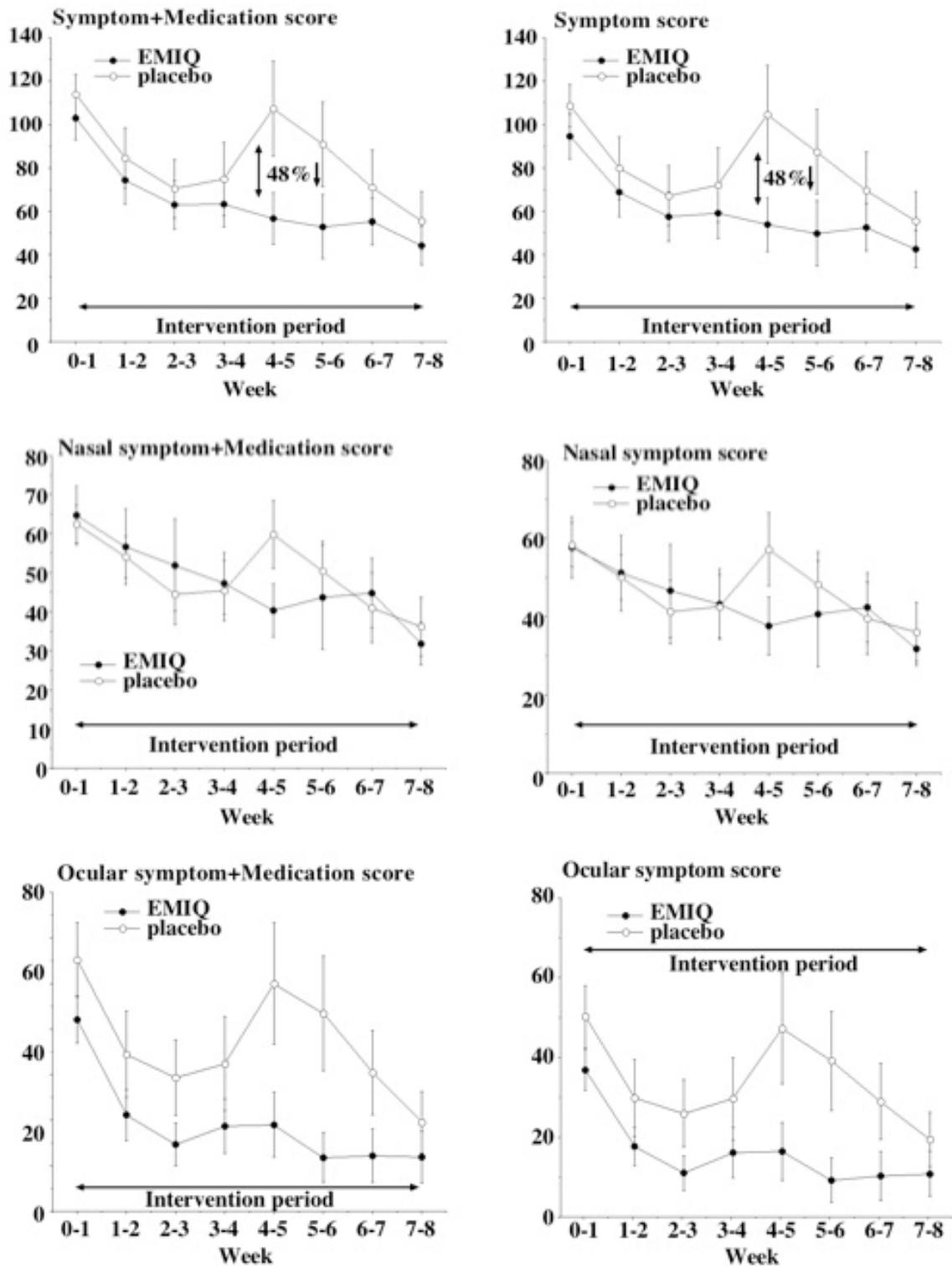


Figure 4. Efficacy of EMIQ on allergic symptoms caused by Japanese cedar pollinosis in 2007. The ameliorative effect was evaluated by total symptom (nasal+ocular symptom)+medication, total symptom, nasal symptom (sneezing, rhinorrhea and nasal obstruction)+medication, nasal symptom, ocular symptom (ocular itching, lacrimation and ocular congestion)+medication and ocular symptom scores.

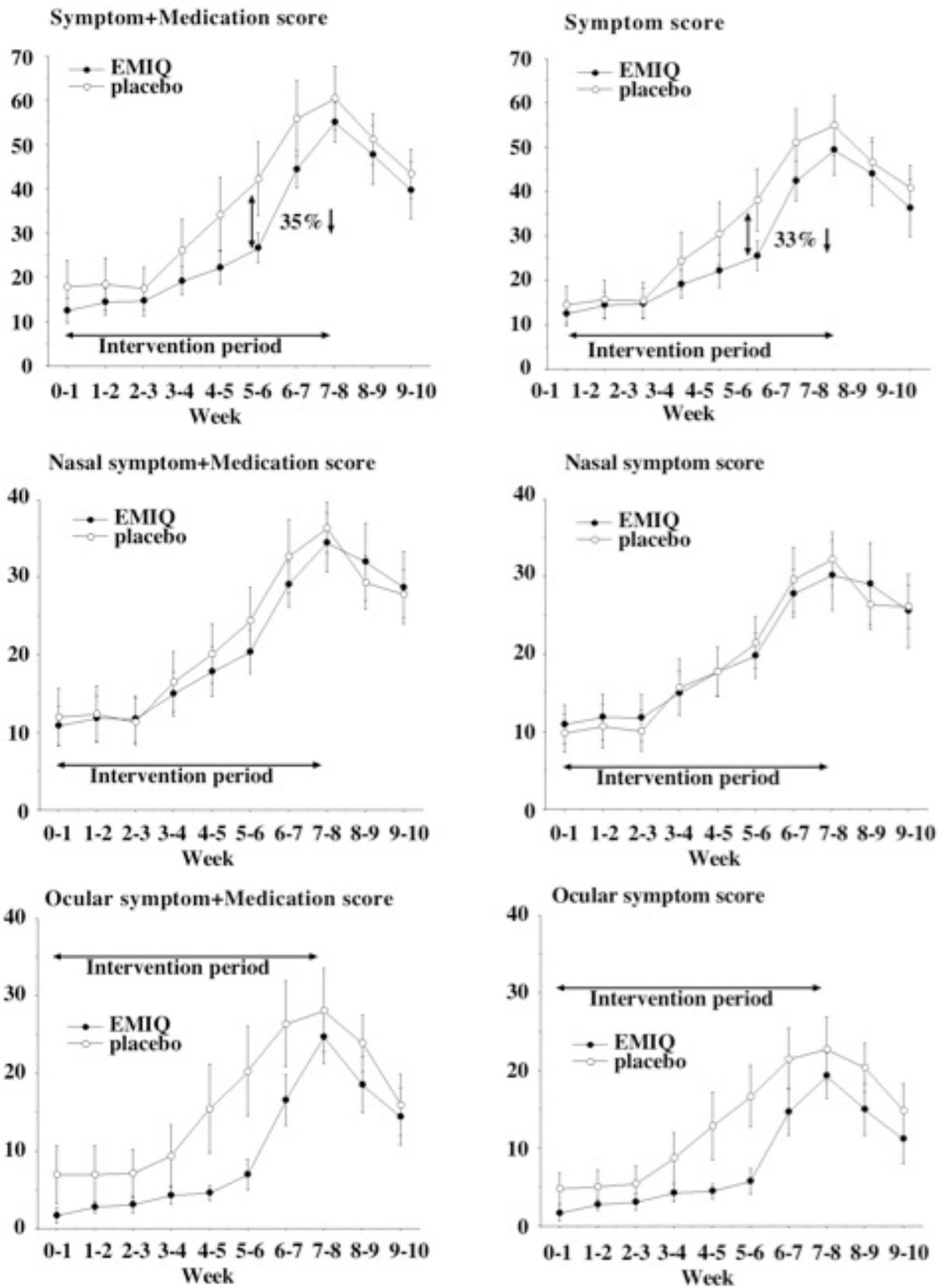


Figure 5. Efficacy of EMIQ on allergic symptoms caused by Japanese cedar pollinosis in 2008.

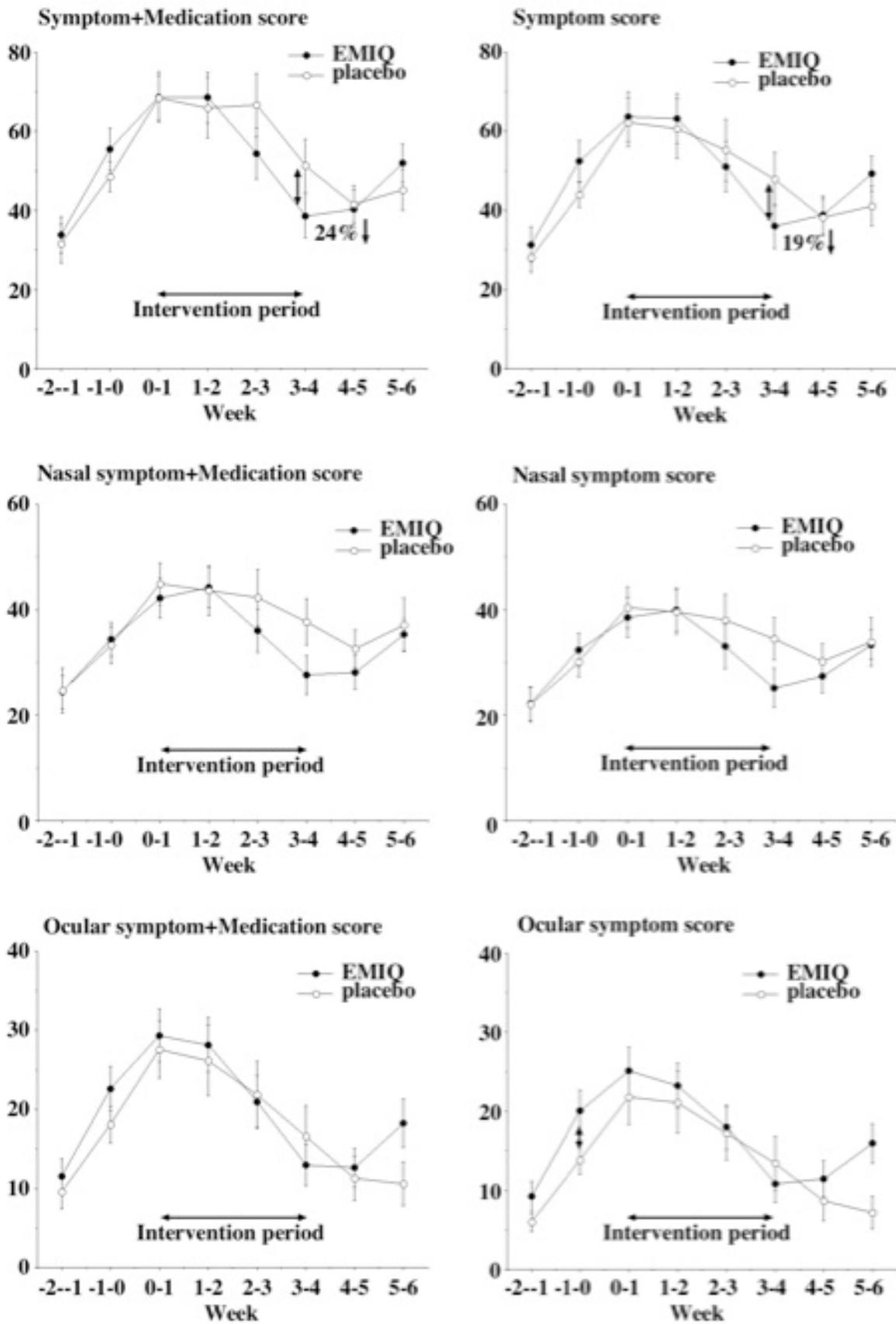


Figure 6. Efficacy of EMIQ on allergic symptoms caused by Japanese cedar pollinosis in 2009.

Moreover, a recent study showed the beneficial action of silymarin on allergic rhinitis symptoms (Bakshae et al., 2011), and clinical trials of pycnogenol, derived from the bark of the European coastal pine tree, including proanthocyanidines (Wilson et al., 2010), and of benifuuki green tea containing *O*-methylated catechin (Maeda-Yamamoto et al., 2009) demonstrated their ameliorative effects on seasonal allergic rhinitis symptoms.

6. Flavonoid daily intake and content of foods

Clinical trials of EMIQ involving patients with Japanese cedar pollinosis demonstrated that a daily intake of 100-200 mg of EMIQ is effective for the amelioration of symptoms. 100 mg of EMIQ, a glycosylated quercetin, is equivalent to 34 mg of quercetin. Results for the daily intake of flavonols plus flavones calculated in terms of the amounts of quercetin, kaempferol and myricetin, and, in some studies, with the addition of luteolin, apigenin and fisetin, have been reported in several countries (Tanaka et al., 2004). The total amount of these flavonoids varied from 2.6 to 68.2 mg/day in the European Union, USA and Japan. The major flavonoid was quercetin, ranging from 14 to 100% of the total amount of flavonoids, followed by kaempferol and myricetin with an average intake of 0.1 to 5.9 mg/day. An amount of 34 mg/day of quercetin is therefore tolerable and indeed there were no adverse events in the clinical trials. Recently, the U.S. Department of Agriculture (USDA) database for the flavonoid content of selected foods was published (USDA database, release 3, 2011). The database contains values for 500 food items and for 28 predominant monomeric dietary flavonoids that include quercetin, kaempferol, myricetin, apigenin and luteolin. It should be pointed out that most of the compounds in food are present in glycosylated forms, but this database converted the glycoside values into aglycone forms using conversion factors based on the molecular weight of the specific compounds to make data consistent across the database. EuroFIR-BASIS (European Food Information Resource - Bioactive Substances in Food Information System) is another database currently developed for bioactives that covers original content values for various polyphenols in plant-based foods (Gry et al., 2007). The more recently published Phenol-Explorer database includes content data for 502 polyphenols, flavonoids, phenolic acids, lignans, and stilbenes (Neveu et al., 2010; database URL: <http://www.phenol-explorer.eu/>; Perez-Jimenez et al., 2010). Over 60,000 composition data published since 1969 have been systemically collected, evaluated, and stored in this database and it contains information on glycosides and esters, whereas the USDA database pertains to data on aglycones. The Phenol-Explorer database was used to examine the intake of all individual polyphenols by a total of middle-aged 4,942 men and women in France (Perez-Jimenez et al., 2011). Mean total intake of flavonoids including proanthocyanidins, catechins, anthocyanins, flavonols, flavones, flavanones, theaflavins and dihydroflavonols was estimated at 506 mg/day, with nonalcoholic beverages, fruit, alcoholic beverages, cocoa products, vegetables and cereals contributing 114, 172, 73, 90, 26 and 28 mg/day, respectively. Mean total intake of flavonols and flavones was 51 and 33 mg/day, which is equivalent to 34 and 18 mg/day of aglycones, respectively. The findings obtained with these databases are sure to make a significant contribution to the development of dietary treatment for allergic rhinitis.

7. Conclusion

Allergy, a common disease worldwide, is the subject of growing concern because of its increasing rate of prevalence (Holgate, 1999; Eder et al, 2006). It has been suggested that dietary changes may contribute to this increase (McKeever & Britton, 2004; Devereux & Seaton, 2005; Devereux, 2006; Kozyrskyj et al., 2011; Nurmatov et al., 2011; Allan & Devereux, 2011). Flavonoids have antioxidant, anti-allergic and immune-modulating properties and recent clinical trials have shown their beneficial effect on allergic rhinitis. Several extensive databases for the flavonoid content of major vegetables, fruit, cereals and beverages can thus be expected to contribute to the dietary management of allergic rhinitis. Whether an appropriate intake of flavonoids can ameliorate respiratory or dermal allergic symptoms and prevent the onset of allergic diseases thus constitutes an important issue for future studies.

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