Review paper

The role of flavonoids in asthma

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Abstract

Dietary change is considered to be one of the environmental factors that cause allergic diseases such as asthma, atopic dermatitis and allergic rhinitis. Epidemiological and animal asthma model studies have suggested that flavonoids may protect against asthma. These compounds have profound effects on the function of immune and inflammatory cells, as confirmed in a large variety of *in vitro* and *in vivo* studies. Flavonoids, ubiquitously present in fruits, vegetables, teas and wine, possess anti-allergic properties and ameliorate asthma symptoms.

Key words: flavonoids, asthma, allergic inflammation.

Introduction

Epidemiological studies conducted in different parts of the world clearly show an increase in the incidence of allergic diseases such as bronchial asthma, atopic dermatitis and allergic rhinitis in the past 2 decades. This problem is worrying, because the upward trend in the incidence of allergic diseases continues. An example that well illustrates the expansion of allergic disease is the allergy to cedar pollen in Japan. The first casuistic case of allergy to cedar was described in 1960, but currently it is estimated that half of Japanese people are allergic to the tree, and 24-29% show symptoms of allergy [1]. The increasing number of people with allergic diseases is explained by genetic predisposition and environmental influences. Environmental changes are considered to be the most important factor that directly affects the manifestation of allergies; it was also found that certain environmental factors may modify the genetic material of humans [2-4]. In addition to weather conditions, attention is paid to nutritional factors that also play an important role in the development of asthma. Foods containing large amounts of vitamins A, C, E and selenium, magnesium, and omega-3 polyunsaturated fatty acids act as a brake on the development of allergic diseases. A diet rich in omega-6 polyunsaturated fatty acids and sodium fosters the development of asthma. Very interesting observations were made by Tanaka *et al*. [5] in patients with atopic dermatitis (AD), who for 2 months were on a vegetarian diet. Rating the severity of the activity of AD showed a significant SCORAD, as much as 54% improvement after following a diet containing foods of plant origin. Further investigations revealed that the polyphenols contained in plants have a beneficial effect on many diseases, including allergic reaction [6].

Polyphenols are produced by plants. These compounds play an important role during plant growth, giving colour to individual elements and protecting plants against various pathogens. It is estimated that plants are able to produce up to 8000 different types of polyphenols, which occur in flowers, fruits, seeds, leaves and roots. These compounds cause plants to have a specific colour, taste and smell. Considering the chemical structure of polyphenols, flavonoids and phenolic acids (derivatives of benzoic and cinnamic acid) are distinguished. Flavonoids, in turn, are divided into flavones, flavanones, flavonols, flavanols, isoflavones, and anthocyanins (Fig. 1) [7].

Biological properties of flavonoids

The chemical structure of flavonoids means that they exhibit both hydrophobic and hydrophilic properties. Therefore, in contact with biological membranes flavonoids have the ability to connect with each two-layer structure of biological membranes and modify both the fluidity and the electrical potential of cell membranes [8]. Such interactions have further implications in the form of changes in membrane enzyme activity, the affinity of various types of ligands to membrane receptors, ion transport through biological membranes or changes in the

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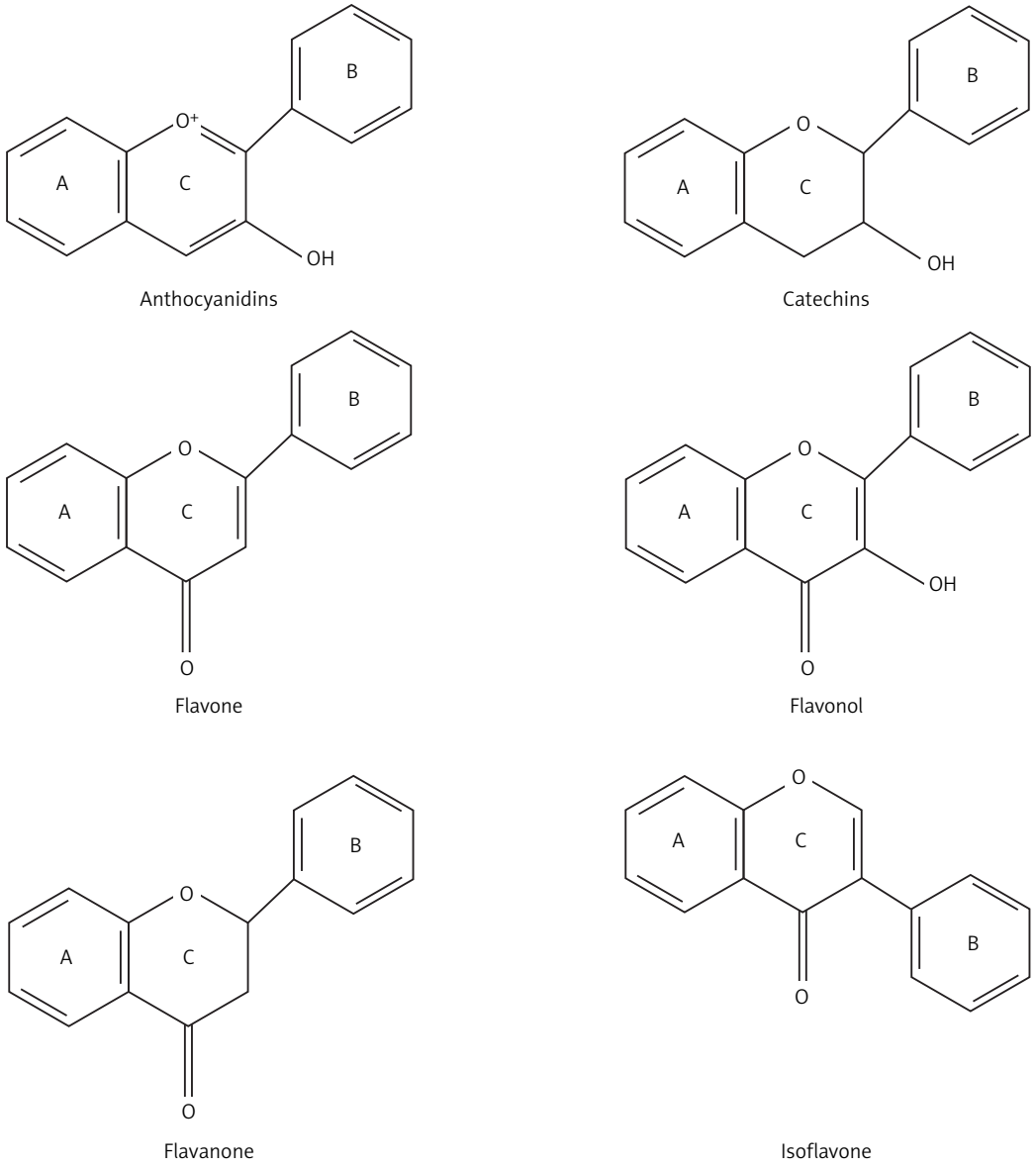

Fig. 1. Flavonoids structure

activity of protein kinases. In addition, flavonoids have the ability to neutralize various types of free radicals of aerobic origin [9].

It has been proven that flavonoids are important factors governing the activity of many cellular enzymes of man. The most frequently emphasized action of flavonoids is the impact on oxygen free radicals. Galleano *et al*. [10] have shown that flavonoids belonging to the catechins are direct inhibitors of NADPH oxidase and thereby reduce the production of oxygen radicals in mitochondria.

Many authors also indicate the ability of flavonoids to modulate cellular metabolism. This action is done by influencing the activity of enzymes involved in purine metabolism, such as ATPase, various kinases, reverse transcriptase, xanthine oxidase, DNA polymerase, RNase and DNA ligase, resulting in changes of gene expression [11].

From the perspective of clinical research, the reports of Mackenzie *et al*. [12, 13] and Verstraeten *et al*. [14], documenting the impact of flavanols on transcription factors, are very important. It was proved that polyphenols of this type inhibit NFκB and block the space of the κB receptor of DNA. This action of flavonols inhibits the development of inflammation and, in the case of some lymphomas, may inhibit carcinogenesis.

Flavonoids and bronchial asthma

The guidelines developed by experts, GINA, which relate to asthma, draw attention to two aspects of the diet of patients with bronchial asthma. The first and most important points to foods as allergens which can lead to exacerbations of asthma in sensitized patients, and preservatives, especially sulfites, which can also trigger serious bouts of breathlessness. The second aspect of the diet which is analysed by the GINA document is the role of fruits, vegetables, and polyunsaturated fatty acids n-3 and n-6 in the development of atopic diseases and asthma. The recently observed consumption of processed foods results in a lower intake of fresh vegetables and fish, which in turn contributes to increased prevalence of allergic diseases [15, 16].

The main drugs used in asthma therapy are corticosteroids, β_2-agonists, inhaled anticholinergics, leukotriene modifiers and anti-IgE. Biological treatment is reserved for the treatment of severe asthma [17].

Bearing in mind the recommendations of GINA, it is worth considering whether in patients with asthma, dietary modification can favourably affect the course of the disease.

Studies on the effects of individual chemical compounds naturally occurring in plants on the course of asthma are difficult, and information on the mechanisms of action of substances of vegetable origin is derived mainly from studies conducted in animal models and *in vitro*.

Research conducted by Leemans *et al*. [18] shows the beneficial effect of a diet containing omega-3 polyunsaturated fatty acids and luteolin – a flavonoid belonging to the flavonols (Fig. 2) – on asthma induced in experimental animals. According to the authors, the addition of omega-3 polyunsaturated fatty acids and luteolin to the diet reduces inflammation in the bronchial epithelium and reduces bronchial hyper-reactivity [18].

Of interest seems to be the effect of another flavonoid, apigenin (Fig. 3). Apigenin is a flavone found in fruits and vegetables, and an especially large amount of this compound is found in onions, parsley, citrus fruits, tea and wheat germ [19]. Studies conducted *in vitro* have shown that apigenin, through inhibiting the transcription factor NFκB, has an anti-inflammatory effect, and inhibits the production of cytokines such as IL-6, IL-8, and certain prostaglandins [20].

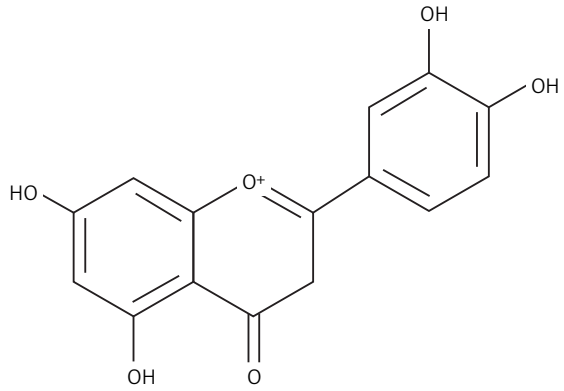

Fig. 2. Structural formula of luteolin

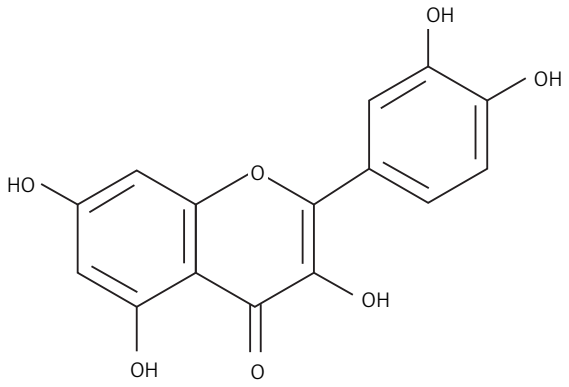

Fig. 4. Quercetin structure

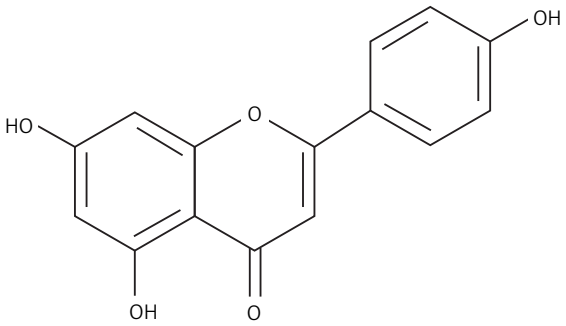

Fig. 3. Apigenin structure

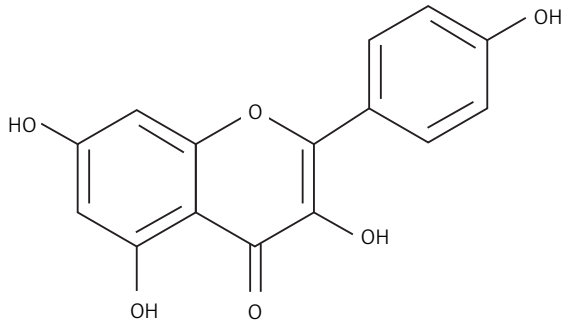

Fig. 5. Kaempferol structure

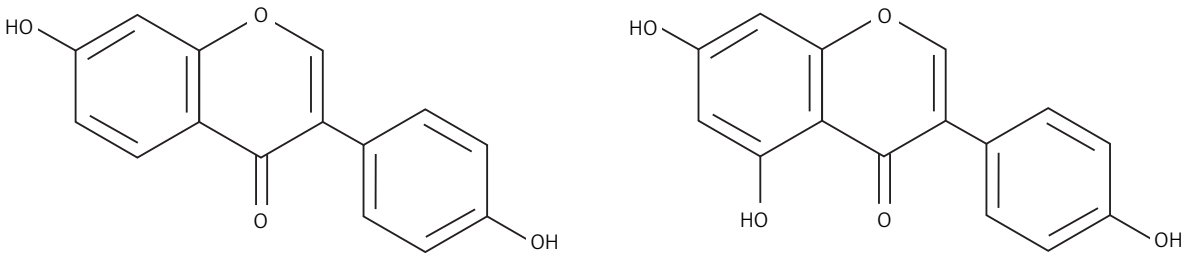

Fig. 6. Genistein and daidzein structure

Pang *et al*. [21] and Choi *et al*. [22] have shown in animal studies that apigenin inhibits allergic inflammation in the bronchial tree. The authors have shown that apigenin, by blocking the transcription factor GATA 3, reduces the population of Th2 cells and the production of IL-4. However, the analysis of washings obtained from the bronchial tree showed a significantly lower number of lymphocytes and especially eosinophils, which in turn is explained by the inhibition of the adhesion molecules ICAM-1 and VCAM-1 by this compound [23]. Previous studies by Yoon *et al*. [24] conducted *in vitro* and in animal models have shown that apigenin inhibits maturation of dendritic cells and thus modulates the initial development stages of inflammation.

The study of bronchial reactivity in test animals showed a significantly lower tendency to bronchial obstruction after apigenin. This flavonoid may affect the remodelling of the bronchial tree in asthma. Indeed it was found that apigenin inhibits the activity of metalloproteinases 2 and 9 (MMP-2, MMP-9) [22].

It is worth noting that there are reports discussing the effect of apigenin on tumour cells, which show that this compound inhibits the growth of leukaemic cells, breast cancer and colorectal cancer [23].

Studies on the effects of flavonoids on bronchial asthma also relate to the world's most widespread plant flavone – quercetin (Fig. 4). This compound most commonly occurs in combination with sugars – rhamnose and rutinose. The largest amounts of these flavonoids are in onions (particularly red onion), apples, red wine, tea (especially white and green tea), ginkgo biloba, hawthorn, horse chestnut, and dark chocolate [25].

The first reports that pointed to quercetin as a factor inhibiting the activity of basophils appeared about 30 years ago [26, 27]. Subsequent studies have shown that this compound is able to inhibit 5-lipoxygenase and phospholipase A2, and inhibit the release of leukotrienes [28].

Rogerio *et al*. [29] evaluated the effect of quercetin in experimental animals in which allergic inflammation of the bronchial tree was induced. As in the case of other flavonoids, quercetin showed inhibitory inflammation in the bronchial tree. It was also found that administration of quercetin solution to experimental animals with food results in blocking NFκB, reduces the expression of P-selectin in lung tissue, reduces the number of eosinophils and reduces the concentration of IL-4 and IL-5 in broncho alveolar lavage fluid (BALF) in test animals. Research conducted by these authors compares the potency of quercetin to dexamethasone. According to Rogerio, quercetin, like dexamethasone, reduces the secretion of mucus in the bronchial tree, blocking NFκB slightly less, but more effectively than the examined glucocorticoid inhibiting the expression of P-selectin [28]. Other studies, conducted on a similar experimental model, showed that quercetin used in inhalation decreases by as much as 68-73% BALF eosinophils, and inhibits the production of mRNA for MMP-9 and GATA-3. Also proven was the inhibitory effect of quercetin on the activity of Th2 cells [30].

Another very popular polyphenol is kaempferol (Fig. 5), a flavonoid, which naturally occurs in conjunction with rhamnose, galactose and glucose. The highest content of kaempferol is in green tea leaves and broccoli [31]. Medeiros *et al*. [32] in experimental studies in animal models have shown that kaempferol acts as a brake on the two most important components of asthma pathogenesis; namely it reduces infiltration in the epithelium of bronchial inflammation and inhibits bronchial hyperreactivity. The principal effect of this flavonoid is seen by the authors in its inhibition of Th2 lymphocytes, and in reducing expression of CD40 on basophils and mast cells. In addition, kaempferol blocked the production of IL-5 and IL-13, key cytokines in allergic inflammation in the bronchi of patients with bronchial asthma. These studies of Medeiros *et al*. [32] compare the effectiveness of kaempferol with dexamethasone and show that this compound has a significant effect on allergic inflammation in the bronchial tree, and only a slightly lower activity than dexamethasone. The beneficial effects of flavonoids in the prevention of many diseases, including asthma, were shown in epidemiological studies conducted in Finland in the years 1966-1972 on a group of 62,440 subjects. Precise analysis showed that quercetin and kaempferol con-

sumed in large quantities significantly reduce the risk of developing asthma. The authors of this study highlight the anti-free radical effects of flavonoids and use this mechanism to explain the beneficial effect on health of a diet containing flavonoids [33].

Very interesting biological properties are exhibited by isoflavones. Representatives of this group of plant polyphenols are genistein and daidzein (Fig. 6), compounds that are present in the greatest quantities in soya bean seeds. Due to the strong similarity to oestrogens and affinity to oestrogen receptors for ERα and ERβ, they are also called phytoestrogens.

It has been proven that a diet containing soya isoflavones reduces the risk of developing breast cancer and diseases associated with atherosclerosis of blood vessels. Soya and genistein and daidzein were the subject of surveys by Miyake *et al*. [34], who decided to determine the impact of these factors on the symptoms of allergic rhinitis in 1002 pregnant women. These studies have shown that consuming soya products (tofu, cooked soya beans, soya miso), abundant in isoflavones, significantly reduces symptoms of allergic rhinitis in the first four months of pregnancy. Genistein and daidzein belong to inhibitors of tyrosine kinases, enzymes which are involved in transmitting signals from membrane to the nucleus. Wong *et al*. [35] demonstrated in experimental studies that genistein inhibits the release of mediators of anaphylaxis and bronchial smooth muscle contraction. This effect is explained by the influence of genistein on protein kinases, blocking calcium channels in bronchial smooth muscle and inhibitory effects on the production and release of leukotriene LTD4.

Summary

Research on flavonoids quite convincingly shows the beneficial effects of these compounds on the course of allergic diseases. It emphasizes the ability of flavonoids to inhibit the production and release of IL-4, IL-13 and transcription factors, or the direct effect on the cells that initiate allergic reactions. In addition, these compounds may reduce airway hyper-responsiveness [36]. Additional benefits of flavonoids are their ability to inhibit free radicals and their anti-infective activity, particularly against viruses. The properties of flavonoids presented here encourage researchers to recommend a diet rich in plants containing these compounds. Especially large quantities of flavonoids are contained in onions, kale, lettuce, broccoli, parsley, strawberries, celery, citrus fruit and tea leaves. Pleasant sources of flavonoids include red wines [37].

References

1. Kaneko Y, Motohashi Y, Nakamura H, et al. Increasing prevalence of Japanese cedar pollinosis: a meta-regression analysis. Int Arch Allergy Immunol 2005; 136: 365-71.
2. Holgate ST. Genetic and environmental interaction in allergy and asthma. J Allergy Clin Immunol 1999; 104: 1134-46.
3. Palgan K, Bartuzi Z. Genetic aspects of food allergy. Adv Dermatol Allergol 2011; 28: 103-6.
4. Duczmal E, Bręborowicz A, Duczmal T. Marsz alergiczny w okresie dzieciństwa. Post Dermatol Alergol 2010; 27: 231-7
5. Tanaka T, Kouda K, Kotani M, et al. Vegetarian diet ameliorates symptoms of atopic dermatitis through reduction of the number of peripheral eosinophils and of PGE2 synthesis by monocytes. J Physiol Anthropol Appl Human Sci 2001; 20: 353-61.
6. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev 2000; 52: 673-751.
7. Pałgan K. Flawonoidy w medycynie. Post Hig Med Dosw 1994; 48: 589-601.
8. Annaba F, Kumar P, Dudeja AK, et al. Green tea catechin EGCG inhibits ileal apical sodium bile acid transporter ASBT. Am J Physiol Gastrointest Liver Physiol 2010; 298: G467-73.
9. Verstraeten SV, Mackenzie GG, Oteiza PI. The plasma membrane plays a central role in cells response to mechanical stress. Biochim Biophys Acta 2010; 1798: 1739-49.
10. Galleano M, Verstraeten SV, Oteiza PI, Fraga CG. Antioxidant actions of flavonoids: thermodynamic and kinetic analysis. Arch Biochem Biophys 2010; 501: 23-30.
11. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev 2000; 52: 673-751.
12. Mackenzie GG, Delfino JM, Keen CL, et al. Dimeric procyanidins are inhibitors of NF-kappaB-DNA binding. Biochem Pharmacol 2009; 78: 1252-62.
13. Mackenzie GG, Oteiza PI. Modulation of transcription factor NF-kappaB in Hodgkin's lymphoma cell lines: effect of (-)-epicatechin. Free Radic Res 2006; 40: 1086-94.
14. Verstraeten SV, Mackenzie GG, Oteiza PI, Fraga CG. Epicatechin, catechin, and dimeric procyanidins inhibit PMA-induced NF-kappaB activation at multiple steps in Jurkat T cells. Free Radic Res 2008; 42: 864-72.
15. Wood LG, Gibson PG. Reduced circulating antioxidant defences are associated with airway hyper-responsiveness, poor control and severe disease pattern in asthma. Br J Nutr 2010; 103: 735-41.
16. Global Initiative for Asthma 2010. Available at: http://www.ginasthma.org/.
17. Lazarus SC. Clinical practice. Emergency treatment of asthma. N Engl J Med 2010; 363: 755-64.
18. Leemans J, Cambier C, Chandler T, et al. Prophylactic effects of omega-3 polyunsaturated fatty acids and luteolin on airway hyperresponsiveness and inflammation in cats with experimentally-induced asthma. Vet J 2010; 184: 111-4.
19. Duthie G, Crozier A. Plant-derived phenolic antioxidants. Curr Opin Clin Nutr Metab Care 2000; 3: 447-51.
20. Hougee S, Sanders A, Faber J, et al. Decreased pro-inflammatory cytokine production by LPS-stimulated PBMC upon in vitro incubation with the flavonoids apigenin, luteolin or chrysin, due to selective elimination of monocytes/macrophages. Biochem Pharmacol 2005; 69: 241-8.
21. Pang LL, Li RR, Zhou LF. Inhibitory effects of apigenin on the expression of GATA-3 and Th2 cytokines in asthmatic mice. Zhongguo Zhong Xi Yi Jie He Za Zhi 2010; 30: 383-7.

22. Choi JR, Lee CM, Jung ID, et al. Apigenin protects ovalbumin-induced asthma through the regulation of GATA-3 gene. Int Immunopharmacol 2009; 9: 918-24.
23. Wang W, Heideman L, Chung CS, et al. Cell-cycle arrest at G2/M and growth inhibition by apigenin in human colon carcinoma cell lines. Mol Carcinog 2000; 28: 102-10.
24. Yoon MS, Lee JS, Choi BM, et al. Apigenin inhibits immunostimulatory function of dendritic cells: implication of immunotherapeutic adjuvant. Mol Pharmacol 2006; 70: 1033-44.
25. Dixon RA, Pasinetti GM. Flavonoids and isoflavonoids: from plant biology to agriculture and neuroscience. Plant Physiol 2010; 154: 453-7.
26. Middleton E Jr, Drzewiecki G, Krishnarao D. Quercetin: an inhibitor of antigen-induced human basophil histamine release. J Immunol 1981; 127: 546-50.
27. Middleton E Jr, Drzewiecki G. Flavonoid inhibition of human basophil histamine release stimulated by various agents. Biochem Pharmacol 1984; 33: 3333-8.
28. Middleton E Jr, Kandaswami C. Effects of flavonoids on immune and inflammatory cell functions. Biochem Pharmacol 1992; 43: 1167-79.
29. Rogerio AP, Dora CL, Andrade EL, et al. Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. Pharmacol Res 2010; 61: 288-97.
30. Park HJ, Lee CM, Jung ID, et al. Quercetin regulates Th1/Th2 balance in a murine model of asthma. Int Immunopharmacol 2009; 9: 261-7.
31. Park JS, Rho HS, Kim DH, Chang IS. Enzymatic preparation of kaempferol from green tea seed and its antioxidant activity. J Agric Food Chem 2006; 54: 2951-6.
32. Medeiros KC, Faustino L, Borduchi E, et al. Preventive and curative glycoside kaempferol treatments attenuate the Th2-driven allergic airway disease. Int Immunopharmacol 2009; 9: 1540-8.
33. Knekt P, Kumpulainen J, Järvinen R, et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002; 76: 560-8.
34. Miyake Y, Sasaki S, Ohya Y, et al. Soy, isoflavones, and prevalence of allergic rhinitis in Japanese women: the Osaka Maternal and Child Health Study. J Allergy Clin Immunol 2005; 115: 1176-83.
35. Wong WS, Koh DS, Koh AH, et al. Effects of tyrosine kinase inhibitors on antigen challenge of guinea pig lung in vitro. J Pharmacol Exp Ther 1997; 283: 131-7.
36. Garcia V, Arts IC, Sterne JA, et al. Dietary intake of flavonoids and asthma in adults. Eur Respir J 2005; 26: 449-52.
37. Kawai M, Hirano T, Higa S, et al. Flavonoids and related compounds as anti-allergic substances. Allergol Int 2007; 56: 113-23.