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Mini Review

Polyphenols and their Mechanism of Action in Allergic Immune Response

Abstract

Mini review article deals with the most studied group of chemical compounds – polyphenols – predominantly flavonoids in relation to their allergic immune response. There is clarified and discussed their mechanism of action as well. We emphasized on the strongest inhibitors of allergic reactions - luteolin, fisetin and apigenin, but in the second part the currently studied flavonoids have been summarized as well.

Introduction

The prevalence of allergic diseases has increased all over the world during the last two decades. Dietary change is considered to be one of the environmental factors that cause this increase and worsen allergic symptoms [1]. One of the major questions in food allergy research is therefore which impact nutrition and food processing may have on allergenicity of food and perhaps on sensitization [2].

The anti-inflammatory activities of some triterpenenic acids, sesquiterpene lactones, and polysaccharides may be due to their immunomodulating activities on the complement and/or T-lymphocyte populations, respectively. As the antiallergic and antiasthmatic compounds are effective also thiosulfates [3]. Nowadays, the preventive effects of polyphenols, carotenoids, polysaccharides, and non-digestible oligosaccharides and amines on allergic diseases are discussed [4,5].

Polyphenolic compounds have and continue to attract the interest of numerous scientists due to possible relations between their content in diet and lower incidence of cancer or cardiovascular diseases [6,7]. Their antimutagenic, anticarcinogenic and anti-inflammatory effects have been confirmed as well [8-11].

Recent evidence has brought to the spotlight plant-derived polyphenols as a promising tool to prevent allergy. Phenolic acids and flavonoids, are the best studied natural substances known to possess an anti-inflammatory and anti-allergic potential [12]. Polyphenols represent such class of compounds that are found plant sources and have been investigated for their anti-allergic effect in different disease models and in human clinical trials [13].

1. They are capable of influencing multiple biological pathways and immune cell functions in the allergic immune response.
2. The interaction of polyphenols with proteins can modulate the process of allergic sensitization and their direct effect on allergic effector cells, such as mast cells, inhibits mediator release, resulting in the alleviation of symptoms
3. Endogenous anti-oxidant ability can limit the extent of cellular injury from free radicals during any reaction [12].

Mechanism of selected polyphenols action in allergic immune response

We distinguish at least 4 types of allergic immune responses induced by drugs and allergens but the most studied is type is type by T- helper cells. Type-1 allergic diseases consist of two phases. An inductive phase comprises IgE formation to allergens based on the immune system being based to predominant T-helper type 2 responses. In a triggering phase allergic symptoms are triggered due to a robust secretion of mediators from mast cells and other cells after re-exposure to the same allergen [14]. Interference of polyphenols with T-helper 2 activation seems to be the main mechanism of their inhibitory effects on allergy development. Moreover, deficits of T-regulatory cells seem to play a pathogenic role in allergic disease and, therefore, these cells may represent a major target of polyphenol activity [15].

The most studied group of polyphenols are flavonoids. A variety of *in vitro* and *in vivo* experiments have shown that selected flavonoids possess anti-allergic, anti-inflammatory, antiviral and antioxidant activities. They possess potent inhibitory activity against a wide array of enzymes, but of particular note is their inhibitory effects on several enzyme systems intimately connected to cell activation processes such as protein kinase C, protein tyrosine kinases, phospholipase A (2), and other. The stimulated activities of numerous cell types, including mast cells, basophils, neutrophils, eosinophil's, T & B lymphocytes, macrophages, platelets, smooth muscle, hepatocytes, and others, can be influenced by particular flavonoids [16].

Intake of representative polyphenols - flavonoids (flavones, flavone-3-ols, catechins, anthocyanidins, flavanones, procyanidins) can improve a skewed Th1/Th2 (T – helper type 1/ T – helper type 2) balance and suppress antigen-specific IgE antibody formation [17].

Flavonoids inhibit the activation of mast cells and basophils and

therefore suppress the release of chemical mediators, synthesis of Th2 type cytokines such as interleukin (IL)-4 and IL-13, and CD 40 ligand expression. They also reportedly inhibit IL-4-induced signal transduction and affect the differentiation process of naïve CD4+ T cells into effector T cell subsets [18]. Except for inhibition of (IL)-4 and IL-13 synthesis, flavonoids inhibit histamine release and CD40 ligand expression by basophils. The inhibitory activity of flavonoids on IL-4 and CD40 ligand expression was possibly mediated through their inhibitory action on activation of nuclear factors of activated T cells and AP-1 [1].

Among all studied polyphenols luteolin, fisetin and apigenin were found to be the strongest inhibitors of both IL-4 [1,19] and IL-13 production by basophils but did not affect leukotriene C4 synthesis [20].

The luteolin is able to inhibit CD40 ligand expression in human basophils.

Luteolin did not suppress Syk or Lyn phosphorylation in basophils, nor did suppress p54/46 SAPK/JNK, p38 MAPK, and p44/42 MAPK activation by a basophilic cell line, KU812 cells, stimulated with A23187 and PMA. However, luteolin did inhibit phosphorylation of c-Jun and DNA binding activity of AP-1 in nuclear lysates from stimulated KU812 cells [19]. The flavone luteolin is also a strong inhibitor of human autoimmune T cells [21].

Fisetin suppressed the induction of IL-4, IL-13, and IL-5 mRNA expression by A23187-stimulated KU812 cells and basophils in response to cross-linkage of the IgE receptor. Fisetin reduced IL-4, IL-13, and IL-5 synthesis (inhibitory concentration of 50% [IC(50)] = 19.4, 17.7, and 17.4 micromol/L, respectively) but not IL-6 and IL-8 production by KU812 cells. In addition, fisetin inhibited IL-4 and IL-13 synthesis by anti-IgE antibody-stimulated human basophils (IC(50) = 5.1 and 6.2 micromol/L, respectively) and IL-4 synthesis by allergen-stimulated basophils from allergic patients (IC(50) = 4.8 micromol/L) [22].

Apigenin is promising flavone for atopic and chronic allergy [12]. Apigenin exhibited an anti-inflammatory activity, switching the immune response to allergens toward the Th1 profile in a murine asthma model [23]. Apigenin contained in the diet of NC/NGa mice reduced atopic dermatitis. The flavone alleviated the development of skin lesions, accompanied by lower serum immunoglobulin IgG1 and IgE levels and reduction of IFN-γ mRNA expression level in spleen cells [24].

Among another flavonoids, kaempferol and quercetin showed substantial inhibitory activities in cytokine expression but less so than those of fisetin [22].

Park et al. [25], compared the effect of six flavonoids (astragalin, fisetin, kaempferol, myricetin, quercetin, and rutin) on the mast cell-mediated allergic inflammation. Fisetin, kaempferol, myricetin, quercetin, and rutin inhibited IgE or phorbol-12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-mediated histamine release in RBL-2H3 cells. These five flavonoids also inhibited elevation of intracellular calcium. Gene expressions and secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1beta, IL-6, and IL-8 were assessed in PMACI-stimulated human mast cells (HMC-1). Fisetin, quercetin, and rutin decreased gene expression and production of all the pro-inflammatory cytokines after PMACI stimulation. Fisetin inhibited PMACI-induced phosphorylation of p38 mitogen-activated protein kinase, extracellular-regulated kinase, and c-Jun N-terminal kinase [26]. Myricetin attenuated TNF-alpha and IL-6 but not IL-1beta and IL-8. Fisetin, myricetin, and rutin suppressed activation of NF-kappaB indicated by inhibition of nuclear translocation of NF-kappaB, NF-kappaB/DNA binding, and NF-kappaB-dependent gene reporter assay.

Chrysin has recently attracted the attention for its protective effects on allergic inflammation. This compound possesses *in vivo* anti-inflammatory and anti-nociceptive potential, which are supported in silico by an interaction with COX-2 binding site [27].

Helioscopinin-A extracted from *Euphorbia helioscopia* showed a certain inhibitory activity on capillary permeability in passive cutaneous anaphylaxis responses of rats and also on antigen-induced bronchial constriction in an experimental asthma model of guinea pigs. The compound at a high concentration weakly inhibited histamine release from isolated mast cells [28].

The objective of the work of Aswar et al. [29], was to evaluate anti-allergic effects of intranasal administration of type-A procynidines polyphenols (TAPP) based standardized hydro alcoholic extract of *Cinnamomum zeylanicum* bark (TAPP-CZ) in ovalbumin (OVA)-induced experimental allergic rhinitis (AR) in BALB/c mice. Treatment with TAPP-CZ (10 and 30 µg/kg in nostril) showed significant attenuation in OVA-induced alterations of the nasal (number of nasal rubbing and sneezing), biochemical markers (serum IgE and histamine), haematological, morphological (relative organ weight of spleen and lung) and histopathological (nasal mucosa and spleen) parameters.

Compound 2((-)-epigallocatechin-7-gallate), 3(-)-5,7, 3',4',5'-pentahydroxyflavan), and 5((-)-tetra hydroxyflavan-7-gallate) isolated from *Pithecellobium clypearia* showed significant inhibition effect on histamine release [30]. In experiment Lee et al. [31] three gallotannins from *Euphorbia* such as 1,2,3,4,6-penta-O-galloyl-beta-D-glucose, 1,2,6-tri-O-galloyl-beta-D-allopyanose, and 1,2,3,6-tetra-O-galloyl-beta-D-allopyranose suppressed the gene expression and secretion of pro-inflammatory cytokines in a dose-dependent manner. In addition, these three gallotannins blocked the activation of NF-kappaB as indicated by an NF-kappaB-dependent gene reporter assay.

Recent advances in allergology have reported that quercetin is more effective than chromolyn in blocking mast cell cytokine release [32]. In food allergies i tis very important inhibition of dendric cells function. Quecretin together eith kaempferol, isoflavones are able to regulate mucosal immunity during hypersensitivity reaction [33].

Among other types of allergic reactions induced by flavonoids we can mention the inhibition of mast cell degradation by hesperetin as a main naturally component of citrus fruits. Another flavanone, naringenin suppressed contact hypersensitivity (CHS), a T cell-mediated immune reaction, by inhibiting activation and migration

of macrophages. Naringenin potently suppressed picryl chloride-induced contact hypersensitivity by inhibiting the proliferation and activation of T lymphocytes. Both of the activated hapten-specific Th2 cells and the Th2 cells stimulated with anti- CD3/anti-CD28 showed growth arrest *in vitro* after naringenin treatment [12].

Conclusion

Flavonoids play an important role in allergic imunne response. Interference of polyphenols with T-helper 2 activation seems to be the main mechanism of their inhibitory effects on allergy development. Nowadays the mostly studied flavonoids are quercetin, luteolin, fisetin and apigenin.

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