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Alcohol Influence of polyphenols on allergic immune reactions: mechanisms of action

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The increased incidence of allergic disease seems to rely on many factors. Among them, the association between genetic variations of the immune response and environmental pressure by allergens, infectious agents and pollutants should be taken into consideration. In alternative to conventional treatments with corticosteroids and antihistaminics, nutraceuticals have been shown to act on allergic disease either during allergic sensitisation or on consolidated disease. In this review, special emphasis is placed on the effects of dietary polyphenols on three major allergic diseases, namely atopic eczema, food allergy and asthma. 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.

Allergy: T-helper cells: T-regulatory cells: Polyphenols: Wine

Incidence of allergic disease has tremendously increased within westernised countries and, in particular, asthma. For instance, an increase of 70.5% of asthma incidence in the period from 1996 to 2005 has been observed in the province of Ontario (Canada)⁽¹⁾. Many factors seem to account for allergy development⁽²⁾. Evidence has been provided that increase in allergic disorders seems to rely on the interaction between genetics (e.g. immune regulation and lung factors) and environment (allergens, infections, microbes, pollution and alcoholic drinks), which may be influenced by age or development^(2–5). Allergies start very early in high-risk infants who have a parent affected by an allergic disease. In this respect, atopic eczema and food allergies are precocious clinical manifestations which may be followed by respiratory allergies later in life^(4,6,7).

IgE antibody production represents the major event contributing to immediate hypersensitivity reactions based on the degranulation of basophils and mast cells with liberation of noxious mediators in various organs (lungs, intestine and skin)⁽⁸⁾. However, IgE antibodies play other important activities in protective immunity against parasites, also influencing the expression of their own receptors

FcεRI and CD23 as well as mast cell function homeostasis⁽⁸⁾. Besides IgE, the role of innate immunity has also been re-evaluated in the pathogenesis of allergic disease. Neutrophils and macrophages express encoded pattern recognition receptors, which recognise pathogen-associated molecular patterns or danger-associated molecular patterns⁽⁹⁾. For instance, endotoxins or bacterial lipopolysaccharides, as environmental contaminants, bind to Toll-like receptor 4 on neutrophils and macrophages, thus enhancing responses to inhaled allergens in a sensitised host⁽¹⁰⁾. Basophil functions have also been reconsidered since they produce cytokines, such as IL-4 and IL-13, which participate in the development of allergic disease⁽¹¹⁾. Moreover, in the mouse basophils act as antigen presenting cells, thus triggering T-helper (Th)-2-mediated responses⁽¹¹⁾. Eosinophils, whose presence has been documented in allergic inflammation, have recently received a re-appraisal. In fact, eosinophils are involved in tissue homeostasis and regulation of adaptive and innate immunity responses to microbes⁽¹²⁾. In this respect, there is the need to understand in what circumstances eosinophils may afford protection or become detrimental to the host.

Abbreviations: FGM, fermented grape marc; K, Koshu; IT, immunotherapy; N, Negroamaro; Th, T-helper; Treg, T-regulatory; OVA, ovalbumin.

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Epithelial cells of the airway have been considered as a protective barrier between the lung and the environment⁽¹³⁾. This initial view has recently been revised since epithelial cells have been shown to interact with environmental antigens such as rhinoviruses, interplaying with the innate immunity in the determination of the allergic inflammation⁽¹³⁾.

Major allergic diseases are represented by asthma, atopic dermatitis and food allergy as recently reviewed^(14–16). Asthma is a chronic lung airway inflammation characterised by a Th-2 response with a robust production of IL-4, IL-5 and IL-13, which initiate and perpetuate the disease status⁽¹⁷⁾. Elevated IgE responses, mast cell degranulation and eosinophilic inflammation are the consequences of the above-cited abnormal Th-2 responses^(17,18). Over recent years, the role of T-regulatory (Treg) cells in asthma has been investigated since they are able to inhibit both Th-1 and Th-2 responses⁽¹⁹⁾. Of note, two major subsets of Treg cells have been described, namely CD4+CD25^{high}FoxP3+ cells and IL-10 producing Treg cells both endowed with suppressive functions^(20,21). Atopic dermatitis is an early allergic manifestation characterised by structural abnormalities in the epidermis which may predispose to skin colonisation by *Staphylococcus aureus*⁽²²⁾. In turn, skin colonisation may account for the persistence of cutaneous lesions and refractoriness to conventional treatment. Atopic dermatitis is an example of barrier defects, which may lead to allergic sensitisation and asthma⁽²²⁾. Anaphylaxis is an acute IgE-mediated reaction that can be life-threatening as in the case of food allergies⁽²³⁾. For this reason, food allergies are the object of intensive investigation mostly in terms of antigenic composition of food and effective treatment.

Corticosteroids and antihistaminics represent the conventional treatment of allergies, even if several adverse effects have been reported following their administration⁽²⁴⁾. In this framework, much evidence has been provided that nutraceuticals, such as probiotics and prebiotics are able to influence allergic sensitisation as well as to mitigate clinical manifestation of allergy^(25,26). In this review, the main mechanisms of action of polyphenols on the immune-mediated reactions in allergic disease are elucidated.

Structure and function of polyphenols

Polyphenols are natural products largely present in fruit and vegetables. Structurally, they are characterised by the binding of one or more phenol groups to the aromatic ring⁽²⁵⁾. The main classes of polyphenols are represented by flavonoids (flavonols, flavones, isoflavones, flavanones and the flavan-3-ols) and non-flavonoid compounds such as the stilbene resveratrol. In Table 1, the natural sources of polyphenols are indicated.

Consumption of dietary polyphenols has been associated with pro host effects such as prevention or delay of age-related disease (CVD, Alzheimer's disease) and inhibition of neoplastic growth^(27–29).

Over recent years, we have studied the *in vitro* and *in vivo* effects of polyphenols from red wine or from

Table 1. Natural sources of major polyphenols

Polyphenols	Sources
Kaempferol, quercetin, myricetin, fisetin	Onions, leeks, broccoli, red grapes, berries, strawberries
Apigenin, luteolin	Parsley, celery
Daidzein, genistein	Soya and soya products
Hesperitin, naringenin	Citrus fruit, tomatoes, oranges, grapefruit
Catechin, epicatechin, epigallocatechin, epigallocatechin gallate	Green tea, red wine, chocolate, berries, apple
(3,5,4'-trihydroxystilbene) resveratrol	Red wine, red grapes, cocoa powder

fermented grape marc (FGM) on the human and animal immune responsiveness. For instance, red wine polyphenols in the absence of alcohol were able to activate human healthy mononuclear cells *in vitro*, thus determining release of NO, balancing the inflammatory/anti-inflammatory cytokine network and increasing the production of IgG and IgA antibodies^(30–32). Noteworthy, polyphenols were able in coculture experiments to interfere with lipopolysaccharide-mediated pro-inflammatory effects, switching-off the NF- κ B pathway⁽³³⁾. Also polyphenol-mediated inhibition of p38 expression in the presence of lipopolysaccharides seems to contribute to the interruption of the pro-inflammatory cascade⁽³³⁾. In all these experiments alcohol *per se*, used as control, did not have any significant effect⁽³²⁾.

The observed *in vitro* effects exerted by red wine polyphenols may play a beneficial role in the host⁽³⁴⁾ and, in particular, moderate wine consumption may exert protective effects⁽³⁵⁾. For instance, *in vivo* release of NO may inhibit platelet aggregation and reduce the influx of monocytes and LDL into the arterial walls, thus halting atherogenesis⁽³²⁾.

FGM from Negroamaro (N) and Kosu (K) grape *Vitis vinifera*, enriched in a mix of bioactive flavonoids, was *in vivo* administered to mice with experimental colitis⁽³⁶⁾. In comparison with untreated colitis mice, K- but not N-FGM-administered mice underwent a marked attenuation of colitis, e.g. abrogation of colon length reduction⁽³⁶⁾. This morphological finding was supported by the evidence that in colon homogenates from K-FGM-treated mice levels of pro-inflammatory cytokines (IL-1 β and TNF α) were considerably diminished in comparison with the untreated counterpart⁽³⁶⁾. These data confirm the anti-inflammatory activity of polyphenols and their potential beneficial effects in the case of human inflammatory bowel disease. In the context of the above studies, also in experimental asthma, there is evidence of an increased release of IL-1 β and CXC chemokines, which may represent potential drug targets⁽³⁷⁾.

The major effects of red grape polyphenols are summarised in Table 2.

Table 2. *In vitro* and *in vivo* immunomodulation exerted by polyphenols from red grape

a. Polyphenols extracted from red wine (<i>V. vinifera</i> Negroamaro (N))
<ul style="list-style-type: none"> • Release of NO from circulating human monocytes⁽³⁰⁾. • Release of inflammatory mediators such as IL-1β and TNFα as well anti-inflammatory cytokines (e.g. IL-10) from circulating human lymphomonocytes⁽³¹⁾. • Production of both IgG and IgA antibodies from circulating human B-cells⁽³¹⁾. • Inhibition of lipopolysaccharide-effects <i>via</i> a reduced activation of NF-κB pathway in co-culture experiments in the presence of circulating human lymphomonocytes⁽³³⁾.
b. Polyphenols contained in fermented grape marc (FGM) from Koshu (K) and N <i>V. vinifera</i>
<ul style="list-style-type: none"> • Abrogation of colon length reduction in K-FGM but not N-FGM-treated colitis mice when compared with untreated colitis controls⁽³⁶⁾. • Reduction of IL-1β and TNF-α content in colon homogenates of K-FGM but not of N-FGM-treated colitis mice⁽³⁶⁾.

Polyphenols in the prevention and treatment of allergic disease

In a recent report, Singh *et al.*⁽³⁸⁾ have efficaciously reviewed the effects of polyphenols on two critical phases of allergic responses, namely sensitisation to a given allergen and re-exposure to it. At least two major mechanisms elicited by polyphenols seem to be effective in allergic sensitisation.

1. Phenolic compounds, such as caffeic and ferulic acid, have been shown to reduce allergenicity of peanut extracts and liquid peanut butter, forming insoluble complexes with allergenic proteins⁽³⁹⁾.
2. Flavonoids are able to modulate dendritic cell functions either dampening MHC-II and co-stimulatory molecule expression or inhibiting cytokine production, thus hampering the antigen presentation process⁽⁴⁰⁾.

During re-exposure to allergen in sensitised individuals, tea polyphenols have been demonstrated to inhibit the activation, proliferation and function of Th-2 cells⁽³⁹⁾. Th-2 cytokines, such as IL-4, IL-5 and IL-13 are important key players in allergic reactions either in IgE production or in attracting mast cells and eosinophils to inflammatory sites⁽⁴¹⁾. Also consumption of polyphenols attenuates the allergenic re-exposure by inhibition of adhesion and migration of peripheral B-cells, suppression of IgE and IgG1 levels and abrogation of Th-2 cytokines in sensitised mice^(42–44).

In the following paragraph, the effects of polyphenols on atopic eczema, food allergy and asthma will be described.

Atopic eczema

Atopic eczema is an allergic disease complicated by secondary infections⁽⁴⁵⁾. One of the major symptoms of atopic eczema is the itching that predisposes to infection of the

skin. Polyphenols and, in particular, avenanthramides from oat have been found to act on keratinocytes, attenuating skin inflammation, also reducing itching in a pruritogen model⁽⁴⁶⁾. Polyphenols inhibit NF- κ B activation and decrease production of TNF- α and IL-8, as seen in *in vitro* models⁽⁴⁷⁾.

Secondary infections have been shown to complicate the clinical course of atopic eczema and are usually treated by antibiotics^(48,49). However, recent findings have demonstrated that polyphenols are able to hamper the toxicity of Staphylococcal α -toxin from *S. aureus*, which colonises the skin of atopic eczema-affected patients. Both apple juice and polyphenol-enriched apple extracts were able to inhibit the enterotoxigenic activity as well as skin inflammation in *in vivo* models^(50,51). Quite interestingly, binding of polyphenols to enterotoxin was irreversible.

Food allergy

True food allergy is an early disorder more frequent in infants and children than in adults^(50–52). Its clinical manifestations are variegated according to the organ involved, e.g. skin (atopic eczema and urticaria), respiratory tract (laryngedema and bronchial obstruction), digestive tract (mucosal lesions from mouth to the anus)^(53,54). From an immunological point of view, the perinatal⁽⁵⁰⁾ period is very critical in the induction of food allergy⁽⁵⁴⁾. Development of oral tolerance is a mechanism of immune suppression towards innocuous antigens, such as food proteins⁽⁵⁵⁾. Treg cells maintain the condition of oral tolerance in the gut and their induction is mediated by dietary vitamin A converted to retinoic acid by dendritic cells and macrophages^(56,57). Any alteration of this homeostatic mechanism leads to food allergy caused by the uncontrolled activation of Th-2 cells. A series of experimental studies have provided evidence that polyphenols are able to modulate intestinal immune responses. For instance, apple condensed tannins inhibited sensitisation to an oral antigen by increasing intestinal γ - δ T-cells⁽⁵⁸⁾. Furthermore, polyphenols could decrease adhesion molecules on monocytes, while increasing their expression on Treg cells⁽⁵⁹⁾. In other studies, it has been reported that procyanidins in the apple reduced gene expression levels of pro-inflammatory cytokines, thus suggesting the beneficial role to human health following ingestion of this flavonoid⁽⁶⁰⁾. The majority of polyphenols are absorbed at colon level and this may explain their ability to promote growth of good bacterial strains such as *Bifidobacterium* and *Lactobacillus* bacterial species but not of harmful species, such as *Clostridium* spp.⁽⁶¹⁾. Catechins and epicatechins as well as their metabolites have been reported to affect the intestinal microbiota inhibiting the growth of pathogenic bacteria, while preserving *Bifidobacterium* and *Lactobacillus* spp.⁽⁶²⁾. Taken together, the interaction of polyphenols with the intestinal microbiota seems to represent another protective mechanism in the host, also contributing to the maintenance of the oral tolerance mechanism.

Asthma

Asthma is a chronic disorder of the lung airways which react to inhaled allergens, thus provoking airflow

obstruction of different degree. The lung is very much exposed to microbial attacks, and viral infections in early childhood may represent a risk factor for the development of asthma⁽⁶³⁾. Also epigenetic mechanisms have been invoked in the promotion of asthma phenotypes such as exposure to methyl-rich diets which can affect asthma risk in offspring⁽⁶⁴⁾. From an immunological point of view, asthma is characterised by a hyperactivation of Th-2 cells, IgE production and eosinophilia⁽⁶⁵⁾. Besides secretion of conventional cytokines, such as IL-4, IL-5 and IL-13, release of IL-17 from Th-17 cells gives rise to respiratory neutrophilic inflammation in the asthmatic patients^(65,66). Treg cell deficits have been discovered in atopic allergic diseases, even including asthma⁽⁶⁷⁾. Therefore, enhancement of Treg cell function in allergic disease seems to represent a novel therapeutic intervention to be pursued.

Increase of asthma prevalence in western countries has been associated with the change of antioxidant intake⁽⁴⁾. In particular, in childhood asthma a reduced maternal intake of vitamin E, vitamin D, selenium, zinc and PUFA has been invoked to explain the development of this allergic condition⁽⁴⁾. In this direction, two studies have suggested that dietary PUFA administration during pregnancy may reduce the likelihood of developing asthma^(68,69). However, further trials are required to confirm these results.

The effects of polyphenols in asthma have been investigated by different groups. For instance, naringenin chalcone, a polyphenol present in the skin of red tomatoes, suppressed in mice allergic asthma inhibiting Th-2-type cytokine production⁽⁷⁰⁾. Administration of catechin from *Albizia lebeck* to mice could inhibit histamine release and cytokine expression of antigen-IgE-activated mast cells⁽⁷¹⁾. Lee *et al.*⁽⁷²⁾ have explored in an allergic mouse model the effect of resveratrol administration on Th-2 responses to ovalbumin (OVA). The observed reduction of lung eosinophilia was likely dependent on the decreased levels of Th-2 cytokines. Reduced airway response to methacholine and mucus hypersecretion by airway goblet cells were other additional effects of resveratrol treatment. Tan and Lim⁽⁷³⁾ have reported that *trans*-resveratrol treatment of human eosinophils abrogated their activation and degranulation, inhibiting p38 and extracellular-signal-regulated kinase 1/2 activation after Ca ionophore, cytochalasin B and C5a exposure.

Our group has recently reported that N- and K-FGM exert anti-allergic activities either *in vitro* or *in vivo*. N-FGM but not K-FGM was able to inhibit *in vitro* degranulation of RBL-2H3 cells (a rat basophilic cell line)⁽⁷⁴⁾. Especially, quercetin contained in high amounts in N-FGM was responsible for this inhibitory effect⁽⁷²⁾. In contrast, K-FGM but not N-FGM, orally administered to Balb/c mice primed with OVA, decreased serum IgE levels and numbers of eosinophils in the bronchial alveolar lavage fluid⁽⁷⁵⁾.

In a passive cutaneous anaphylaxis reaction, Balb/c mice were intradermally sensitised with anti-OVA IgE serum and challenged intravenously with OVA containing Evans blue at 24 h after IgE sensitisation. Oral administration of K-FGM but not N-FGM at 30 min before OVA challenge significantly suppressed passive cutaneous anaphylaxis reaction⁽⁷⁵⁾.

Quite interestingly, *in vitro* treatment of normal human CD4+ cells with both N-FGM and K-FGM led to the increased expression of FoxP3, a marker of Treg cells⁽⁷⁶⁾. This finding was also supported by the increased levels of IL-10 detected in the supernatants of N-wine polyphenol-treated peripheral normal human T-cells⁽²⁸⁾. In relevance to these data, evidence has been provided for defects of peripheral blood CD4+CD25+FoxP3+ cells in asthmatics⁽⁷⁷⁾. Therefore, in asthma patients as well as in other allergic diseases functional deficits of Treg cells may be corrected by the assumption of dietary polyphenols in alternative to other treatments such as corticosteroids, allergen immunotherapy (IT), vitamin D₃ and long-acting β agonists.

Conclusion

As described in the previous paragraphs, manipulation of mucosal tolerance still represents the best approach to prevent or treat allergic disorders. In fact, antigen-specific IT is the only treatment that can afford long-lasting protection against allergic disease after therapy is finished⁽⁷⁸⁾. However, IT has been shown to be very effective in the treatment of rhinitis and insect venom allergy but less beneficial in allergic asthma^(78–80).

Just recently, evidence has been provided that increased proportions of Treg cells have been found in grass pollen allergics after IT⁽⁸¹⁾ and in IT-treated hay fever patients⁽⁸²⁾. This last evidence coupled to the ability of polyphenols to induce Treg cell activation may lead to the formulation of a combined therapy by IT and polyphenols for the treatment of those allergic diseases which are less responsive to IT treatment alone.

Conclusively, maintenance of immune homeostasis at mucosal levels via activation of Treg function seems to represent one of the major exploitable approaches for the therapy of human allergy.

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