

REVIEW

Dietary polyphenols in the prevention and treatment of allergic diseases

A. Singh, S. Holvoet and A. Mercenier

Allergy Group, Department of Nutrition & Health, Nestle Research Center, Vers-chez-les-Blanc, Lausanne, Switzerland

Clinical & Experimental Allergy

Summary

Allergic disorders encompass skin, food and respiratory allergies. Sensitization to a normally harmless allergen results in the immune system being biased to a predominant T-helper type 2 response. Re-exposure to the same allergen leads to a robust secretion of allergy-related mediators that eventually triggers symptoms. Our understanding of these disorders has enabled the search of therapeutic approaches that can either modulate the sensitization process or impact on allergic mediators, thus helping manage allergic symptoms. Polyphenols are one such class of compounds that are found in foods and plant sources and have been investigated for their anti-allergic effect in different disease models and in human clinical trials. Their anti-inflammatory profile is known to impact on the recruitment of immune cells to the skin and in preventing the development of secondary infections following disruption of the skin barrier. 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 inhibit mediator release, resulting in the alleviation of symptoms. In addition, their endogenous anti-oxidant ability limits the extent of cellular injury from free radicals during the allergic insult. Overall, polyphenols hold promise as anti-allergy agents capable of influencing multiple biological pathways and immune cell functions in the allergic immune response and deserve further investigation. The objective of the current review is to summarize the key findings and progress made in studying polyphenols as anti-allergic ingredients. Special emphasis is placed in this review to highlight key physiological, cellular and signalling pathways implicated in the mechanism of action of different polyphenols in the context of allergic disorders and their manifestations.

Correspondence:

Dr A. Mercenier, Allergy Group,
Department of Nutrition & Health,
Nestle Research Center, Vers-chez-les-
Blanc, CH-1000 Lausanne 26,
Switzerland.
E-mail: annick.mercenier@rdls.
nestle.com

Introduction

The incidence of allergic disorders has increased dramatically in the developed world and a variety of factors (environment, genetics, hygiene, diet, etc.) are known to impact on their development [1–3]. Allergies may start in predisposed individuals from early infancy i.e. atopic eczema, followed by the development of food allergies. Respiratory allergies [allergic rhinitis (AR) and asthma] occur later in life and complete the sequelae of allergic manifestations often termed as the 'Atopic March' [4–6]. Allergies represent a dysregulated immune response to a multitude of allergens normally present either in the environment (dust mite, grass pollen) or in food (milk, eggs, nuts, wheat) [7, 8]. Recent advances in the understanding of the pathophysiology of allergy have revealed a series of complex immune cell interactions that can be manipulated to influence either sensitization to the allergen (prevention) or help alleviate allergic manifestations (treatment) [9, 10].

A majority of therapeutic options available today for allergies (corticosteroids, anti-histaminics) are aimed at treating different allergic symptoms. While proven to be highly effective, numerous factors such as the dose and the route of administration account for the efficacy of these treatments, notwithstanding the adverse effects that are sometimes associated with a chronic use of these medicines [11, 12]. What would then be the ideal profile of an anti-allergic therapy? It should ideally be able to impact on allergic sensitization as well as alleviate allergic symptoms once sensitization to the allergen has occurred. The therapy should also be beneficial against different allergic disorders i.e. atopic eczema, food allergies, AR and asthma and ultimately be safe upon long-term administration.

Recent scientific evidence from pre-clinical studies and human clinical trials has highlighted different nutritional interventions such as probiotics, vitamins, lipids and dietary polyphenols as promising agents that can impact both allergic sensitization and alleviate allergic symptoms [13–15]. Dietary polyphenols are a class of bioactive

compounds that are found in abundance in plant (tea, cocoa, coffee, etc.) and fruit (apple, grapes, pomegranate, etc.) sources and have been studied extensively in numerous disease models [16–19]. The safety profile of dietary polyphenols and their presence in the daily diet suggest that these compounds should be evaluated further as anti-allergy agents [20–22].

Polyphenols modulate different phases of the allergic response

Polyphenols are classified mainly based on their chemical structure; the attachment of one or more hydroxyl groups to the aromatic ring (phenol groups) distinguishes them from other chemical compounds. Phenolic acids, flavanoids, hydroxycinnamic acid lignans and stilbenes are major classes of polyphenols that are commonly found and have been well characterized (Fig. 1). The flavanoid group comprises a mix of bioactive compounds that are the most abundant in plants and fruits and as a result constitute a majority of polyphenols that are consumed daily in our diet. The flavanoids can be further classified into different categories such as the flavones, flavonols, isoflavones, flavanones and the flavan-3-ols depending on the placement of the hydroxyl groups on the aromatic ring structures. Flavonols such as quercetin are widely present in different berries, apples and red onions and have been investigated for their anti-inflammatory and anti-cancer benefits. In relation to allergies, they have been studied with regard to their specific effect on mast cells (MC), which are effector immune cells involved in the allergic response [23–26]. Among the major flavanols are the catechins and epicatechin derivatives. These compounds are mainly found in green tea, cocoa and chocolate and have been investigated for their beneficial effects in improving cardiac function, as anti-cancer agents and for slowing the ageing process. Their efficacy in allergic disorders is just beginning to be unravelled and future research needs to be carried out to substantiate their role as anti-allergy agents. The major polyphenols known to have a beneficial effect on allergic disorders are listed along with their natural sources in Table 1.

Certain classes of polyphenols can influence the development of allergic immune responses at two critical stages, mainly during allergic sensitization and following re-exposure to the allergen (Fig. 2). During the sensitization phase, the ability of polyphenols such as caffeic and ferulic acid to form insoluble complexes with potentially allergenic proteins can render the protein hypoallergenic [27]. Polyphenols belonging to the flavanoid group are also known to have a direct effect on antigen presentation by dendritic cells (DC) by either inhibiting the cell surface expression of MHC-II and co-stimulatory molecules (CD80, CD86), resulting in inefficient antigen presenta-

tion, or impacting on DC function i.e. inhibiting cytokine production [28, 29].

In sensitized individuals, allergen re-exposure results in the differentiation and expansion of T-helper type 2 (Th-2) helper CD4 T cells that drive the adaptive immune response by secreting cytokine mediators characteristic of an allergic response that include IL-4, IL-5 and IL-13. These Th-2 cells are important in switching antibody production from B cells to predominantly IgE production as well as secreting chemokines that attract allergic immune cells such as MC and eosinophils to inflammatory sites. Polyphenols such as catechins and their derivatives can inhibit the production of Th-2 cytokines [30–33] and impact on the activation, proliferation and recruitment status of T cells [34–37]. B cell recruitment to inflammatory sites and IgE production were also reported to be inhibited via polyphenol consumption [32, 38–40]. A well-studied immunological effect of polyphenols such as quercetin with respect to allergies is their inhibitory effect on degranulation, particularly histamine release from MC and basophils [25, 26, 41, 42]. Two mechanisms are postulated: one where polyphenols impact allergen–IgE complex formation and another where they impact on the binding of this complex to their receptor (FcεRI) on MC and basophils [43–46].

Polyphenols in the prevention and management of skin manifestations of allergy

The skin is the largest anatomical organ and is constantly exposed to the outside environment. Atopic eczema or dermatitis is an allergic disorder of the skin that usually occurs early in life in infants, starting around 3–4 months of age, and continues to peak till about 2 years of age [6]. The symptoms of eczema include dryness, itching, inflammation and erythema (redness). In most clinical cases, there is also an accompanying secondary infection with *Staphylococcus aureus* in the affected area, which arises mostly as a result of a loss of integrity of the skin barrier and the itching caused by the eczematous reaction. While several polyphenolic extracts have been described in the literature to have an impact on skin inflammation, which we have summarized in Table 2, we focus our discussion on those polyphenols where the suggested effect has a possible impact in relation to allergic skin disorders and where targeting future research could yield a specific benefit i.e. against pruritis or against staphylococcal association in atopic eczema.

Polyphenol-enriched extracts mitigate skin inflammation

A local inflammatory response is a critical component of allergic skin manifestations. Thus, polyphenols with an anti-inflammatory effect have the potential to be included

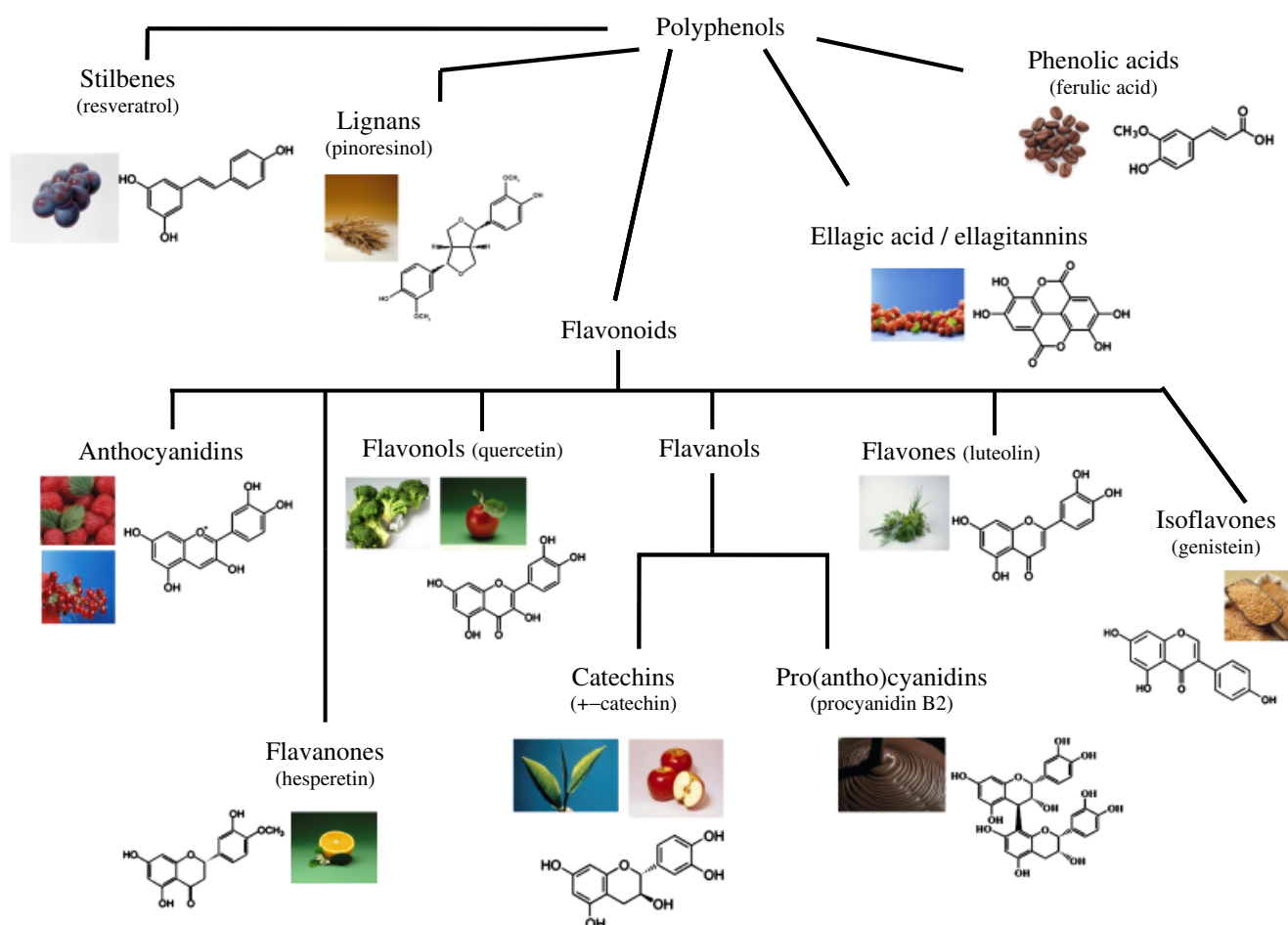


Fig. 1. Different classes of polyphenols, their known plant and fruit sources. Polyphenols are classified on the basis of their chemical structure; the attachment of hydroxyl groups to the aromatic ring structure (phenol groups) is characteristic of these chemical compounds. Phenolic acids, flavanoids, hydroxycinnamic acid lignans and stilbenes are major classes of polyphenols and these polyphenols can be found abundantly in plant and fruit sources.

both in the diet and as topical agents to alleviate allergic inflammation. Tea extracts have been studied for their efficacy in skin inflammation animal models [47–49]. Green tea extracts are particularly rich in flavanols such as catechins and epicatechin and their derivatives. Epigallocatechin gallate (EGCG) was found to be the active ingredient in green tea extracts that provided protection against cutaneous inflammation. The extract was applied topically and was found to have a dose-dependent protective effect [48]. EGCG has been well studied for its immunological effect using *in vitro* systems and it has been observed to suppress the production of the pro-inflammatory cytokine IL-12 [50]. Using skin explants and a contact hypersensitivity protocol, it has been demonstrated that the topical application of polyphenol-enriched white and green tea extracts is beneficial against photoprotection [47]. Green tea extracts also reduce hyperplasia and hyperkeratosis around inflamed skin sites [49]. So what potential do these compounds hold specifically for alleviating allergic inflammation in the skin?

Allergic inflammation of the skin is characterized by an infiltration of T cells, MC, and eosinophils at inflamed sites; in a study examining the direct effect of green tea compounds on T cells *in vitro*, the green tea pigments (theaflavins) and polyphenols were found to inhibit the production of the T cell growth factor IL-2. In addition, the levels of Th-1 and Th-2 (IL-4 and IL-5) cytokines were inhibited [31].

EGCG is known to have an affinity binding to the CD4 molecule, thus limiting the interactions of the co-receptor with its known ligands [51]. Catechins and EGCG have been demonstrated to inhibit the up-regulation of adhesion molecules such as CD11b on circulating B and T cells, thereby inhibiting their migration to inflammatory sites [38, 52]. EGCG can also inhibit histamine release from MC and basophils. Using an *in vitro* assay that studies histamine release from a rat basophilic cell line (RBL-2H3), EGCG was shown to have a dose-dependent inhibitory effect on histamine release from cells stimulated both with a calcium ionophore and an IgE-antigen complex [42].

Table 1. Polyphenols, their sources and their effect on allergic disorders

Polyphenol	Source	Prevention vs. treatment	Strength of evidence
<i>Flavonols</i>			
Quercetin	Green vegetables, red onion, tea, apple, grapes	Treatment	Strong, especially well-characterized immune effect
Rutin	Citrus fruits, berries	Treatment	Weak, mostly from <i>in vitro</i> assays
<i>Flavanols</i>			
Catechin	Green tea, apples, cocoa, wine, chocolates	Prevention, Treatment	Good evidence especially on flavanol-rich extracts. Further characterization needed
Epicatechin			
Procyanidins			
EGCG	Green, white, oolong tea	Treatment	Further characterization is needed
<i>Flavanones</i>			
Naringenin	Grapefruit, tomato skin, citrus fruits	Treatment	Few studies with good results. More evidence needed
<i>Flavones</i>			
Luteolin	Thyme, rosemary, oregano	Treatment	Weak evidence, further studies required
<i>Phenolic acids</i>			
Chlorogenic	Coffee	Prevention	Promising <i>in vitro</i> . Further <i>in vivo</i> data required
<i>Others</i>			
Resveratrol	Grapes	Treatment	Well-known anti-inflammatory. More evidence required for allergies
Curcumin	Turmeric	Treatment	Few studies, further evaluation needed
Avenanthramides	Oats, walnuts	Treatment	Weak. More studies needed

EGCG, epigallocatechin gallate.

Other *in vitro* studies performed on basophils showed that EGCG impacts on the activation of basophils via the inhibition of FcεRI expression [44]. Oolong tea, a traditional Chinese tea, is reported to have anti-allergic activities [53]. In a clinical trial, oolong tea was found to reduce the severity of pruritis in subjects suffering from recalcitrant atopic dermatitis [54]. Apple polyphenols were also investigated in a pilot clinical trial with atopic eczema subjects; their consumption for 8 weeks at a dose of 10 mg/kg reduced the inflammation, lichenification and itching associated with the disease compared with the control group, where standard therapy was maintained [55].

Polyphenols have anti-itch activity and are required for optimal skin health

Itching or pruritis is one of the most disturbing symptoms of atopic eczema; it severely impacts on the quality of life (QOL) of the allergic subjects and leads to complications such as secondary infection. Avenanthramides are polyphenolic compounds that are found exclusively in oats and have been studied for their health benefits [56]. These polyphenols have been shown to mitigate inflammation in animal models of skin inflammation such as contact hypersensitivity and specifically act as anti-itch agents in a pruritogen-induced model [57]. Their effects on keratinocytes and immune cells were examined in *in vitro* systems. These polyphenol compounds are believed to inhibit nuclear factor κB (NF-κB) activation and decrease

pro-inflammatory cytokines such as TNF-α and IL-8. These findings are consistent with those obtained in different animal models of disease where these compounds have been evaluated [58, 59]. Quercetin and luteolin are two other polyphenols reported to be capable of inhibiting skin itching and flush reaction (increase in skin temperature) [60]. However, in a human clinical trial evaluating the efficacy of quercetin on skin irritation and skin barrier function, it was observed that the topical application of quercetin on irritated skin was without any effect [61]. In addition to their anti-inflammatory effect, polyphenols are likely to impact skin health via their anti-oxidant function. The effect of consuming both low- and high-dose cocoa drinks was evaluated on skin health and microcirculation in healthy women; it was reported that only high-dose oral consumption with cocoa rich in flavanols led to decreased water loss from the skin and an improvement in dermal blood circulation [62].

Role of polyphenols in the management of staphylococcal infection in atopic eczema

The skin of subjects with atopic eczema is often colonized with *S. aureus* bacteria; this association is speculated to contribute to the increased severity of symptoms associated with eczema [63, 64]. Management strategies to treat this secondary infection include mainly antibiotic therapy [65]. Polyphenols hold potential as a treatment option to help negate the virulence associated with

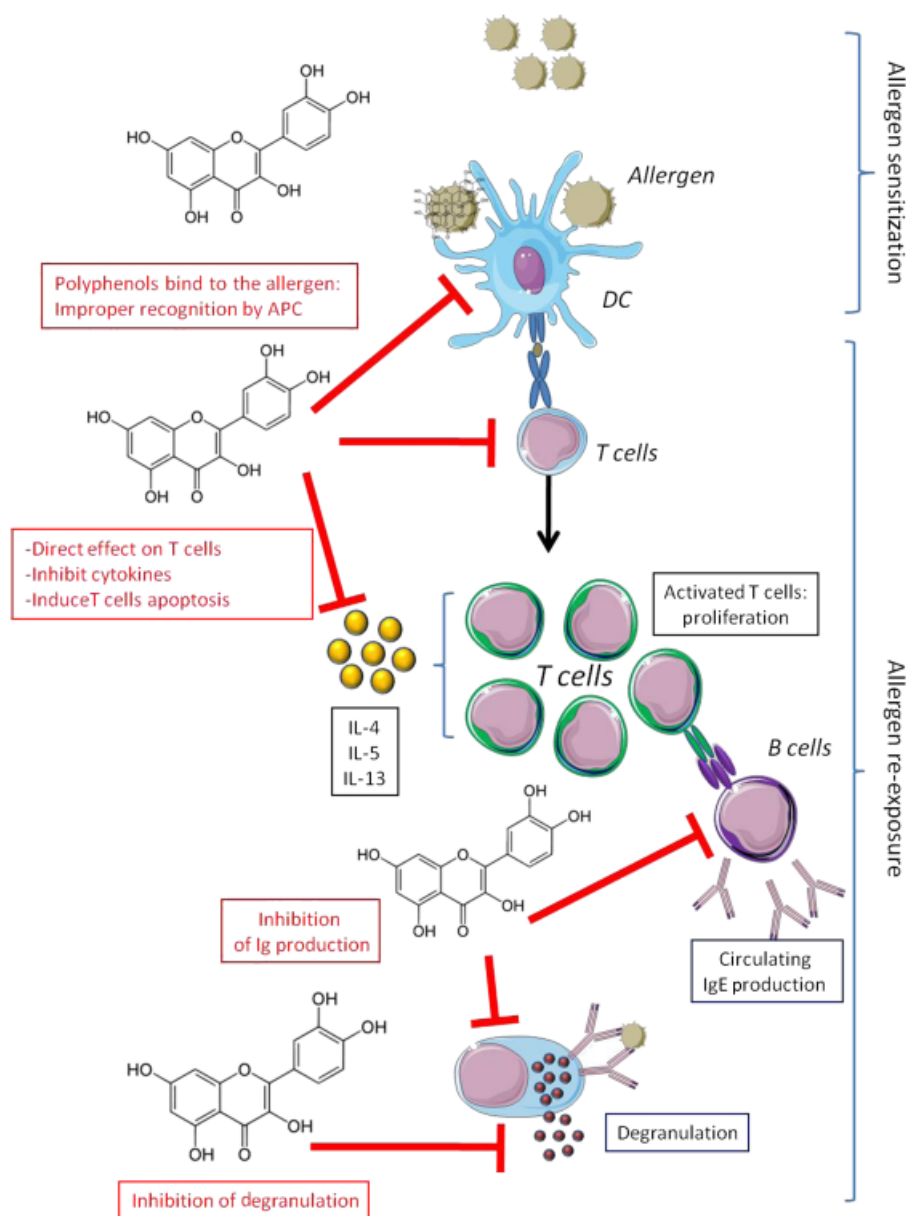


Fig. 2. Mechanism of action of polyphenols in allergic disorders. Polyphenols can impact the development of allergic immune responses at two critical stages: allergic sensitization and during re-exposure to the allergen. Polyphenols can form insoluble complexes with allergenic proteins and render them hypoallergenic. This leads to inefficient antigen presentation by specialized cells such as dendritic cells (DCs). Polyphenols can also directly modulate DC maturation and function. During re-exposure, polyphenols can inhibit T cell proliferation and cytokine production and also impact on antibody production via B cells. Polyphenols such as quercetin can inhibit mediator release from allergic effector cells such as mast cells.

S. aureus in atopic eczema patients. In particular, apple polyphenols have been described to inhibit the biological activity of staphylococcal enterotoxins [66, 67]. In these studies, the ability of both commercially available apple juices as well as polyphenol-enriched apple extracts was examined. Apple condensed tannins (ACT) and hop bract tannins (HBT) were found to be effective *in vitro* in neutralizing the enterotoxin activity. In addition, HBT preparations inhibited skin inflammation in *in vivo* models [66]. Similar observations were made in another study where staphylococcal enterotoxin A (SEA)-induced mur-

ine splenocyte proliferation was inhibited via polyphenol-enriched apple extracts. Using an innovative *in vitro* approach to quantify the binding of the enterotoxin to the polyphenolic components, it was demonstrated that the polyphenols bind irreversibly to the enterotoxin, rendering it inactive [67]. The polyphenols had no effect on the viability of the splenocytes. These are important observations that first of all provide evidence for the use of polyphenols as a management strategy for skin inflammatory conditions and secondly support their integration within food matrices for the neutralization of

Table 2. Effect of polyphenols on skin-allergic responses

Polyphenol	Source	Study	Observations
Catechin derivatives, EGCG [47, 49, 53, 54]	Green, white and oolong tea	<i>In vivo</i> and <i>ex vivo</i> effect of tea polyphenols applied topically or given orally on passive cutaneous anaphylaxis and skin inflammation Oolong tea administered (10 g tea bags three times daily) to subjects with recalcitrant atopic eczema ($n = 118$). Regular treatment maintained in an open trial [54]	Protection conferred by topical application of green and white tea extracts Moderate improvement in 2/3rd of subjects after 1 month of consumption. No statistical significance
Avenanthramides [57]	Oats	Topical application of the polyphenols in an oxazolone-induced murine model of contact hypersensitivity	Effect on the NF- κ B signalling pathway in keratinocytes. Inhibition of edema and itching at inflammatory sites
Apple condensed tannins (ACT) and polyphenols [66, 67] (flavanols and flavanoids)	Apple	<i>In vitro</i> ability of apple juices and polyphenol extract to bind to enterotoxins and effect on enterotoxin-induced T cell proliferation	Inhibition of biological activity of enterotoxins by apple polyphenols.
Luteolin [60]	Pure isolated polyphenols	Niacin-induced flush <i>in vivo</i> model. Luteolin given i.p. (4.3 mg per animal)	Luteolin blocked the increase in inflammatory mediators such as prostaglandins
Quercetin [61]	Pure isolated polyphenols	Contact dermatitis was induced in human subjects ($n = 15$). Quercetin applied topically for 5 days. Skin water loss and erythema evaluated	No benefit observed of the topical application of the polyphenol compared with the control
Flavanols [62] (catechin, epicatechin, procyanidins)	Cocoa	Crossover human trial ($n = 10$), healthy women consumed a low- (27 mg) or a high- (329 mg) dose cocoa-rich drink	High-dose cocoa drink consumption decreased skin water loss and improved dermal blood circulation

EGCG, epigallocatechin gallate; NF- κ B, nuclear factor κ B; i.p., intraperitoneally.

staphylococcal enterotoxins that are often contaminants in food products and have been implicated as adjuvants in promoting food-allergic immune responses in animal models [68, 69].

Polyphenols in the prevention and management of food allergy

Food allergies are common in children and occur in around 2–5% of all children [70]. These allergies are often linked to the subsequent development of respiratory allergies such as rhinitis and asthma [1, 5]. As such, intervention strategies that target both prevention of sensitization to food allergens as well as help negate allergic symptoms associated with food allergies are likely to have an additional impact later on in life in lowering the risk of developing AR or allergic asthma. Preventing food allergy requires that the causative allergen be eliminated from the diet. This, however, does not take away the risk associated with accidental exposure to the allergen that can trigger severe allergic reactions in susceptible subjects. Polyphenols in the diet can impact on both allergic sensitization to food allergens as well as inhibit adaptive immune responses that lead to allergic symptoms. Table 3 summarizes studies that have been reported in the scientific literature with regard to food allergy and different polyphenol extracts.

Polyphenol–protein interactions: reduced allergenicity of common food allergens via polyphenols as a preventive approach against food allergies

Polyphenol and protein interactions have been studied in detail [71, 72]. Polyphenols form soluble and insoluble complexes with proteins and can render them hypoallergenic by either changing the structure of the allergenic protein or rendering it less bioavailable. Polyphenols of the phenolic acid category that include caffeic, ferulic and chlorogenic acids have been evaluated for their ability to bind to the main allergens present in peanuts, Ara h 1 and Ara h 2. In these interesting studies, it was demonstrated that polyphenols bind irreversibly to the allergens in peanuts and reduce the allergenicity of peanut butter and peanut extracts [27]. Polyphenols such as ellagic acid that are found in common allergic foods such as walnuts have also been shown to be effective in binding to allergenic proteins within the food matrix [71, 73]. Our observations in an *in vivo* food allergy murine model with polyphenol-enriched apple extracts also support the hypothesis that one of the mechanisms by which polyphenols may exert a beneficial effect is due to their affinity to bind to the causative allergen i.e. ovalbumin (OVA). We observed that complexing OVA with apple polyphenols led to a dose-dependent reduction in allergenicity and the polyphenol–OVA complexes were inferior in triggering mediator

Table 3. Effect of polyphenols on the prevention and treatment of food allergies

Polyphenol	Source	Study	Observations
Phenolic acids [27,33,71] (ferulic, caffeic, gallic, chlorogenic)	Pure compounds	<i>In vitro</i> binding of major allergenic peanut proteins to phenolic compounds and IgE-binding capability of the complexes	Formation of insoluble complexes by phenolic compounds with allergenic proteins. Reduced IgE-binding of the complexes
Apple condensed tannins (ACT) and polyphenols [33,74] (phloridzin, catechins and derivatives, quercetin)	Apple	Investigation into preventive [74] (given in drinking water at doses of 0.1–1%) and treatment [33] effect (1% in diet) on food allergy	ACTs have a preventive effect on allergic sensitization. Protection correlates to an increase in TCR $\gamma\delta$ T cells in the gut [74]. Polyphenol enriched extract inhibits symptoms of food allergy upon challenge in sensitized mice and decreases immune parameters such as mMCP-1 and Th2 cytokines[33]
Luteolin, rosmarinic acid and rutin [76]	Thyme, rosemary, tarragon	<i>In vitro</i> model to study intestinal permeability by investigating OVA permeation through Caco-2 monolayer's	Inhibitory effect of the isolated polyphenols on OVA permeability
Quercetin [23–25]	Pure isolated polyphenols	Direct <i>in vitro</i> effect of the polyphenol on mast cell activation (CD23 expression) and mediator release (histamine)	Inhibition of CD23 expression and histamine release. Decreased Ca^{2+} influx by quercetin [23]

mMCP-1, mouse mast cell protease-1; OVA, ovalbumin; Th2, T-helper type 2; TCR, T cell receptor.

release from RBL-2H3 cells *in vitro* compared with native OVA protein [33]. A word of caution to this approach must be mentioned, particularly in relation to allergen detection systems; the high polyphenol content within the food matrix can mask the detectable levels of allergen. Further research is needed in order to validate this hypothesis and to generate hypoallergenic foods via polyphenol treatment.

Polyphenols modulate food-allergic manifestations and impact gut morphology and function

Polyphenols have been investigated by various research groups for their ability to modulate intestinal Th2 responses. ACT from unripe apples were shown to inhibit sensitization to an orally fed antigen in a murine model. This beneficial effect correlated with an increase in $\gamma\delta$ T cells among the intestinal intraepithelial lymphocyte cell population in the group of animals that received the ACT in their daily diet [74]. Using a murine model of food allergy, we have also investigated the effect of a polyphenol-enriched apple extract on the development of allergic manifestations in sensitized animals. In this model, a challenge with a high dose of the allergen in sensitized mice induces allergic symptoms that include itching, diarrhoea, immobility and, in extreme cases, food-induced anaphylaxis. The group of animals that received a 1% incorporation of the polyphenol extract in their diet had significantly reduced allergic symptoms following the challenge as well as reduced systemic levels of mMCP-1, an immune marker of allergic inflammation [33].

Polyphenols can decrease the cell surface expression of adhesion molecules such as CD11b on pro-inflammatory

monocytes, but simultaneously increase its expression on immune regulatory T cell populations [35]. This suggests a balancing effect of polyphenols on the immune system, where the migration of regulatory immune cells to sites of inflammation takes precedence over the recruitment of pro-inflammatory cells. Transcription of genes coding for pro-inflammatory mediators is also repressed; apple polyphenols target pro-inflammatory signalling pathways such as NF- κ B and modulate the expression of transcription factors such as STAT-1 and IRF-1. In these studies, the relative gene expression levels of pro-inflammatory chemokines such as IP-10, CXCL10 and enzymes like COX-2 and CYP3A4 were also reduced; this effect was mostly due to the presence of flavan-3-ol (procyanidins) polyphenols in the apple [75].

Luteolin, rutin and quercetin polyphenols have been reported to inhibit the permeation of the antigen in a Caco-2 cell monolayer *in vitro* model [76]. These compounds may play a role in maintaining intestinal barrier integrity. The influence of apple and red wine polyphenols on gut health and development has been studied in weaning piglets by incorporating either apple or red-wine pomace into the piglet starter diet. Polyphenol incorporation increased crypt size in the colon as well as reduced gut-associated lymphoid tissue activation in Peyer's patches, suggesting a faster immune development around weaning with polyphenol consumption [77]. MC that secrete histamine are often the first intermediaries at intestinal sites due to increased intestinal permeability that promotes food-allergic immune responses [78, 79]. Polyphenols such as quercetin can regulate Ca^{2+} entry into MC and inhibit their activation and cytokine production; also, the role of quercetin and polyphenols obtained

from apple and grapes in inhibiting MC degranulation has been well documented using *in vitro* systems such as the RBL-2H3 assay [23–25, 80–82].

Gut metabolites of polyphenols and the interaction of polyphenols with gut commensals

Our understanding of how polyphenols impact intestinal allergic inflammation and gut morphology is incomplete without a closer examination of their absorption status as intact ingredients ingested via food or their interaction with the intestinal microbiota that leads to the breakdown of polyphenols into metabolites in the gut. Several studies studying this aspect of polyphenol biology have largely agreed on the fact that a vast majority of polyphenol absorption occurs in the colon segment of the large intestine [83–86]. Experimental systems that include *in vitro* assays, animal models and human clinical trials have attempted to understand the process of the generation of the metabolites of polyphenols as well as their bioavailability and functional effects.

Polyphenols obtained from pomegranates such as punicalagins were examined *in vitro* using pH-controlled fermentation systems [87]. Culture of fecal bacteria obtained from distal segments of human large intestines with polyphenols led to the generation of a series of metabolites called urolithins. The polyphenols in turn promoted the growth of *Bifidobacterium* and *Lactobacillus* bacterial species, which have often been studied for their health-promoting effects, but did not impact on the growth of potentially harmful species such as *Clostridium* spp. Similarly, grape polyphenols were evaluated for their direct effect on the growth curve kinetics of *Lactobacillus acidophilus* CECT 93 strain in liquid cultures. These polyphenols were able to significantly increase the biomass of this particular strain [88]. Also, in another study, it was observed that the oral administration of a grape skin extract rich in polyphenols that was fermented in the presence of a *Lactobacillus plantarum* strain exerted a beneficial effect on allergic responses, while the non-fermented extract had no effect [89]. Rutin and phloridzin polyphenols have also been reported to enhance the adherence of a probiotic strain *Lactobacillus rhamnosus* to Caco-2 cells [90]. Studying the effect of tea polyphenols such as catechins and epicatechin and their metabolites on the growth of fecal bacteria, another group reported the ability of these polyphenols to inhibit the growth of certain pathogenic bacteria; however, no impact on the growth of *Bifidobacterium* and *Lactobacillus* species was observed [91]. Metabolites of flavan-3-ols such as procyanidins were directly evaluated for their immune profile on human PBMC cells that were stimulated with LPS; these metabolites had an anti-inflammatory property and could inhibit the production of pro-inflammatory cytokines such as TNF- α and IL-6 [92].

It should, however, be kept in mind that metabolite generation from polyphenols could differ between different individuals based on the composition and function of colonic microbiota [93].

Polyphenol consumption alleviates respiratory allergy manifestations

The incidence of AR, an allergic disease of the upper airways, and allergic asthma, which is an inflammatory disorder of the lower airways, has increased drastically over the last 20 years [1, 5, 94]. AR is characterized by symptoms such as nasal obstruction, runny nose, sneezing and pruritis. Often ocular symptoms like watery red eyes and itching in eyes manifest along with nasal symptoms. These symptoms can either be seasonal (pollen) or perennial [house dust mite (HDM), pet dander]. The major hallmarks of allergic asthma include inflammation, broncho-constriction that leads to wheezing, mucus production and increased lung hyper-reactivity. There is growing evidence in both animal models and in clinical trials with individuals suffering from respiratory allergies that polyphenol consumption has beneficial effects. Table 4 summarizes the various studies that have evaluated their role in the context of respiratory allergies.

Polyphenols inhibit airway inflammation and tissue eosinophilia

Airway inflammation in respiratory allergies is characterized by lung infiltration of lymphocytes and eosinophils. Using animal models of allergic airway disease, polyphenols have been shown to inhibit Th-2-driven allergic inflammation. Naringenin chalcone, a polyphenol extracted from the skin of red tomatoes, is effective in inhibiting eosinophilic recruitment around the airways in a murine model of allergic asthma. IL-4 and IL-5 production from *in vitro* stimulated splenocytes in the group receiving the polyphenol was also suppressed [30]. Resveratrol, a polyphenol from grapes, and a polyphenolic extract isolated from marine red algae (*Laurencia undulata*) have both been shown to have anti-asthmatic potential as their administration decreased levels of the Th-2 cytokines, IL-4 and IL-5, in bronchoalveolar lavage of sensitized animals [95, 96]. Dietary flavones such as apigenin may have potential in the prevention of allergic sensitization. When incorporated into the diet during the sensitization process, the polyphenol inhibited mRNA synthesis of IL-4 and IL-13 cytokines in splenocytes [32]. In an interesting study evaluating the direct effect of polyphenols on endogenous proteases present in environmental allergens such as HDM, it was reported that polyphenol components, mainly EGCG and myricetin, inhibit the enzymatic activity of these proteases and thus hold potential in preventing

Table 4. Effect of polyphenols on respiratory allergies

Polyphenol	Source	Study	Observations
Naringenin chalcone [30, 109]	Tomato	Mice sensitized and challenged with allergen (OVA). Polyphenol given orally (0.8 mg/kg) for the entire duration of the protocol	Decreased pulmonary eosinophilia, reduced Th2 cytokine production in re-stimulated cells
		Double-blinded placebo-controlled clinical trial ($n = 33$), subjects given orally either tomato extract (360 mg daily) or placebo for 8 weeks	Decreased total symptom scores, significant decrease in sneezing. Quality-of-life improvement in subjects taking tomato extract
Resveratrol [96]	Grape	Polyphenol given to sensitized mice in the OVA-asthma model	Decreased Th2 cytokine levels in the lungs and plasma. Mucus production and airway hyperresponsiveness inhibited in the treatment group
Quercetin [121, 122] and isoquercitrin [123, 124]	Pure isolated polyphenols	Quercetin (10 mg/kg and Isoquercitrin (15 mg/kg) for 5 days orally to sensitized mice in a murine asthma model. Clinical trials ($n = 24$) with isoquercitrin (100 mg twice daily) for 8 weeks on Japanese cedar pollinosis symptoms in adults	Decreased eosinophilia in broncho-alveolar lavage (BAL) in the polyphenol-treated groups
			Significant improvement in ocular itching and quality-of-life score. No effect on Th2 cytokines
Flavanols [94] (catechin, epicatechin, ECG, EGCG)	Green tea, pure isolated polyphenols	<i>In vitro</i> and <i>in vivo</i> effect of flavonols on the protease activity of Df-protease isolated from house dust mite was evaluated. <i>In vitro</i> inhibitory effect of flavonols on allergic effector cells such as mast cells and basophils	EGCG was the most effective in inhibiting protease activity
Chlorogenic and caffeic acid [125, 126]	Coffee	OVA-asthma model, mice administered phenolic acids i.p. for 5 days	Inhibition of pulmonary eosinophilia and reactive oxygen species. Chlorogenic acid decreased specific IgE and Th2 cytokines
Apple condensed tannins (ACT) and polyphenols [107, 108] (phloridzin, catechins, epicatechin, quercetin)	Apple	Two clinical trials on seasonal ($n = 36$, 500 mg daily for 12 weeks vs. placebo) and perennial allergic rhinitis ($n = 33$, placebo, low dose 50 mg and high dose 100 mg for 4 weeks)	Significant improvement in sneezing scores in both the trials. Nasal discharge inhibited in the high-dose group in perennial rhinitis
Curcumin [105]	Turmeric	OVA-sensitized mice were challenged with aerosolized OVA; curcumin (200 mg/kg) was given both i.p. and via the oral route for 3 weeks	Curcumin administration decreased airway hyperresponsiveness and lung inflammation. Inhibition of NF- κ B activation
Provinol [103, 106]	Red wine	<i>In vitro</i> and <i>in vivo</i> effect on tracheal smooth muscles reactivity in sensitized guinea-pigs	Bronchodilator effect of provinol administration via nitric oxide (NO) metabolism

ECG, epicatechin gallate; Epigallocatechin gallate; NF- κ B, nuclear factor κ B; i.p., intraperitoneally.

sensitization to airborne allergens [97]. It is likely that in addition to their anti-inflammatory effect on immune cells, polyphenols can limit inflammation via their anti-oxidant role. The generation of reactive oxygen and nitrogen species in chronic inflammation such as asthma can trigger inflammatory mediators such as leukotrienes and prostaglandins. Polyphenols may inhibit the generation of these compounds via their neutralization effect on reactive oxygen and nitrogen species [97–99].

Polyphenols alleviate mucus production and impact on airway hyperresponsiveness

Polyphenols can act as anti-hypersecretory agents, limiting the amount of mucus production in respiratory

allergies. The effect of epicatechin gallate (ECG) on mucus-associated genes in a nasal epithelial cell line was investigated using an experimental system where the generation of reactive oxygen species (ROS) is achieved by stimulation with H_2O_2 . This results in an over-expression of mucus-associated genes; ECG inhibited the generation of ROS and MUC5AC expression in epithelial cells [100]. Another study evaluated the effect of polyphenols such as EGCG, quercetin, gingerol and curcumin on ciliary movements and MUC5AC expression in human airway epithelial cells activated via the pro-inflammatory cytokine IL-1 β . EGCG, quercetin and gingerol inhibited MUC5AC expression at different concentrations and had no effect on cell proliferation or ciliary movements [101]. Resveratrol, belonging to the stilbenes class of polyphenols and found in grapes, has been shown to be a

mucolytic agent and to inhibit mucus over-production when administered to mice suffering from allergic airway disease [96]. Also, curcumin, a polyphenol present in turmeric, was found to decrease mucus formation around the airways in a similar murine asthma model. Both these polyphenols also reduce the oxidative stress, which can inhibit inflammatory pathways such as NF- κ B and are thus valuable dietary agents to modulate airway inflammation in chronic diseases such as asthma in cases where corticosteroids are no longer effective [102]. Moreover, polyphenols have a broncho-dilatory effect and can improve physiological lung function [30, 95, 96, 103–105]. Polyphenols such as provinol, which are found in red wine were shown to inhibit tracheal smooth muscle reactivity, were shown to inhibit tracheal smooth muscle contraction. Further investigation confirmed the effect of provinol in alleviating tracheal reactivity to mediators such as histamine and this mechanism involved nitric oxide production [103, 106].

Human clinical trials support the integration of polyphenols into the management of respiratory allergies

Human clinical trials to support the efficacy of polyphenols as an anti-allergy ingredient were primarily conducted in subjects suffering from respiratory allergies. A placebo-controlled trial evaluating the effect of both a low- and a high-dose consumption of apple polyphenols in subjects with persistent AR to HDM showed that the high dose could help alleviate symptoms such as sneezing and runny nose. Nasal examination in the polyphenol-treated group of subjects showed decreased swelling of the nasal turbinates [107]. A study conducted in Japan on subjects sensitized to cedar pollen showed that the administration of apple polyphenols to the subjects 2 weeks before the start of the pollen season, and continued through the season, helped to significantly reduce the reported incidence of sneezing in allergic subjects when compared with the placebo group [108]. The efficacy of a polyphenol-rich tomato extract containing naringenin chalcone was evaluated in subjects with perennial AR. Oral administration of the extract for 8 weeks to the subjects relieved sneezing and improved the QOL of the subjects. Nasal discharge and obstruction also showed a decreased trend [109].

Future direction in polyphenol research for allergy benefits

The study of polyphenols is clearly an upcoming and exciting field of scientific research. In relation to their efficacy for different allergic disorders, several missing links need to be addressed before recommending them for the prevention and treatment of allergies. We propose an integrated scientific approach that should include:

(1) Studying the bioavailability of polyphenols in the context of allergic animal models or human subjects. Bioavailability of polyphenols remains a major consideration and several studies have been conducted to better understand this aspect [20, 110–113]. Strategies are needed that help improve the bioavailability of polyphenols and ultimately enhance their beneficial effect [114].

(2) Use of cutting-edge biochemical tools to identify active components within the different polyphenol extracts to understand which particular polyphenol correlates to the different anti-allergic effect [115–118]. It will also be important to correlate polyphenol metabolites in the systemic compartment (blood, urine) to their immune and physiological function benefits. These tools can help in the standardization of polyphenolic extracts with respect to batch-to-batch production, depending on the variety of fruit and plant sources selected for polyphenol enrichment and ultimately when the extracts are integrated into either a therapeutic formulation or a food matrix [119, 120].

(3) A better understanding of the cellular impact of polyphenols on immune cells in different anatomical locations (gut vs. blood) and their interaction with commensal bacteria is needed. These interactions may even result in improved bioavailability or the generation of metabolites that are responsible for the protective effects. While progress has been achieved with respect to studying certain polyphenols such as quercetin and their specific effect on MC, more of these cell-specific interactions with polyphenols need to be explored.

(4) Polyphenols need to be further evaluated with regard to their route of administration (oral vs. topical) and intervention window (prevention vs. treatment) for different allergic manifestations. For skin allergy, it will be important to test both topical and oral efficacy, for food and respiratory allergy oral consumption may suffice.

(5) Whether used as therapy or as dietary interventions, their long-term safety profile needs to be addressed in different age groups i.e. in children, adults and the elderly. The polyphenol content and the safety profile of extracts from different suppliers can differ; as such, these studies are needed and will only strengthen the general concept that polyphenols are safe [20, 21, 110, 111].

(6) There is an urgent need for more human clinical trials to substantiate the effect of specific polyphenols for the alleviation of different allergic manifestations. These clinical trials should include investigations into bioavailability, metabolite generation and safety studies in addition to addressing the efficacy of the polyphenols for different allergy-related benefits.

Acknowledgements

Images from Servier Medical Art were used with permission to illustrate Fig. 2 in the manuscript. We would like to

thank Laura Poquet, Lucas Actis Goretta and Fabiola Dionisi from the Bioavailability research group at the Nestle Research Center for their help with the figures.

Conflict of interest statement: All co-authors are employees of Nestec S.A.

References

- Devereux G. The increase in the prevalence of asthma and allergy: food for thought. *Nat Rev Immunol* 2006; **6**: 869–74.
- Kemp A, Bjorksten B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. *Pediatr Allergy Immunol* 2003; **14**:74–80.
- Tai A, Volkmer R, Burton A. Prevalence of asthma symptoms and atopic disorders in preschool children and the trend over a decade. *J Asthma* 2009; **46**: 343–6.
- MacDonald TT, Di SA. The immunologic basis for gastrointestinal food allergy. *Curr Opin Gastroenterol* 2009; **25**:521–6.
- Schroeder A, Kumar R, Pongracic JA *et al.* Food allergy is associated with an increased risk of asthma. *Clin Exp Allergy* 2009; **39**:261–70.
- Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. *Immunol Allergy Clin North Am* 2010; **30**:269–80.
- Tang M, Kemp A, Varigos G. IL-4 and interferon-gamma production in children with atopic disease. *Clin Exp Immunol* 1993; **92**:120–4.
- Campbell DE, Hill DJ, Kemp AS. Enhanced IL-4 but normal interferon-gamma production in children with isolated IgE mediated food hypersensitivity. *Pediatr Allergy Immunol* 1998; **9**:68–72.
- Prescott SL, Jones CA. An update of immunotherapy for specific allergies. *Curr Drug Targets Inflamm Allergy* 2002; **1**:65–75.
- Varga EM, Nouri-Aria K, Till SJ, Durham SR. Immunomodulatory treatment strategies for allergic diseases. *Curr Drug Targets Inflamm Allergy* 2003; **2**:31–46.
- Coureau B, Bussieres JF, Tremblay S. Cushing's syndrome induced by misuse of moderate- to high-potency topical corticosteroids. *Ann Pharmacother* 2008; **42**:1903–7.
- Kirby B. A review of the rational use of corticosteroids. *J Int Med Res* 1989; **17**:493–505.
- Kalliomaki M, Antoine JM, Herz U, Rijkers GT, Wells JM, Mercenier A. Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of allergic diseases by probiotics. *J Nutr* 2010; **140**:713S–21.
- Laitinen K, Isolauri E. Management of food allerg: vitamins, fatty acids or probiotics? *Eur J Gastroenterol Hepatol* 2005; **17**:1305–11.
- O'Flaherty JT. Lipid mediators of inflammation and allergy. *Lab Invest* 1982; **47**:314–29.
- Bravo L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr Rev* 1998; **56**:317–33.
- Hounsborne N, Hounsborne B, Tomos D, Edwards-Jones G. Plant metabolites and nutritional quality of vegetables. *J Food Sci* 2008; **73**:R48–65.
- Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 2004; **79**:727–47.
- Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. *Am J Clin Nutr* 2005; **81**:215S–7.
- Akazome Y, Kametani N, Kanda T, Shimasaki H, Kobayashi S. Evaluation of safety of excessive intake and efficacy of long-term intake of beverages containing apple polyphenols. *J Oleo Sci* 2010; **59**:321–38.
- Mennen LI, Walker R, Bennetau-Pelissier C, Scalbert A. Risks and safety of polyphenol consumption. *Am J Clin Nutr* 2005; **81**:326S–9.
- Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. *Annu Rev Nutr* 2002; **22**:19–34.
- Fewtrell CM, Gomperts BD. Quercetin: a novel inhibitor of Ca²⁺ influx and exocytosis in rat peritoneal mast cells. *Biochim Biophys Acta* 1977; **469**: 52–60.
- Lee EJ, Ji GE, Sung MK. Quercetin and kaempferol suppress immunoglobulin E-mediated allergic inflammation in RBL-2H3 and Caco-2 cells. *Inflamm Res* 2010; **59**:847–54.
- Pearce FL, Befus AD, Bienenstock J. Mucosal mast cells. III. Effect of quercetin and other flavonoids on antigen-induced histamine secretion from rat intestinal mast cells. *J Allergy Clin Immunol* 1984; **73**:819–23.
- Scheller S, Dworniczak S, Pogorzelska T, Rajca M, Shani J. Effect of quercetin, caffeic acid and caffeic acid phenylethyl ester, solubilized in non-ionic surfactants, on histamine release in vivo and in vitro. *Arzneimittelforschung* 2000; **50**:72–6.
- Chung S-Y, Elaine T. Reducing the allergenic capacity of peanut extracts and liquid peanut butter by phenolic compounds. *Food Chem* 2009; **115**: 1345–9.
- Gong J, Chen SS. Polyphenolic antioxidants inhibit peptide presentation by antigen-presenting cells. *Int Immunopharmacol* 2003; **3**:1841–52.
- Kim JY, Kina T, Iwanaga Y, Noguchi H, Matsumura K, Hyon SH. Tea polyphenol inhibits allostimulation in mixed lymphocyte culture. *Cell Transplant* 2007; **16**:75–83.
- Iwamura C, Shinoda K, Yoshimura M, Watanabe Y, Obata A, Nakayama T. Naringenin chalcone suppresses allergic asthma by inhibiting the type-2 function of CD4 T cells. *Allergol Int* 2010; **59**:67–73.
- Tomita M, Irwin KI, Xie ZJ, Santoro TJ. Tea pigments inhibit the production of type 1 (T(H1)) and type 2 (T(H2)) helper T cell cytokines in CD4(+) T cells. *Phytother Res* 2002; **16**:36–42.
- Yano S, Umeda D, Yamashita T *et al.* Dietary flavones suppresses IgE and Th2 cytokines in OVA-immunized BALB/c mice. *Eur J Nutr* 2007; **46**:257–63.
- Zuercher AW, Holvoet S, Weiss M, Mercenier A. Polyphenol-enriched apple extract attenuates food allergy in mice. *Clin Exp Allergy* 2010; **40**:942–50.
- Aires V, Adote S, Hichami A, Moutairou K, Boustani ES, Khan NA. Modulation of intracellular calcium concentrations and T cell activation by prickly pear polyphenols. *Mol Cell Biochem* 2004; **260**:103–10.

- 35 Graff JC, Jutila MA. Differential regulation of CD11b on gammadelta T cells and monocytes in response to unripe apple polyphenols. *J Leukoc Biol* 2007; 82:603–7.
- 36 Hernandez P, Rodriguez PC, Delgado R, Walczak H. Protective effect of *Mangifera indica* L. polyphenols on human T lymphocytes against activation-induced cell death. *Pharmacol Res* 2007; 55:167–73.
- 37 Schoene NW, Kelly MA, Polansky MM, Anderson RA. A polyphenol mixture from cinnamon targets p38 MAP kinase-regulated signaling pathways to produce G2/M arrest. *J Nutr Biochem* 2009; 20:614–20.
- 38 Kawai K, Tsuno NH, Kitayama J, Sunami E, Takahashi K, Nagawa H. Catechin inhibits adhesion and migration of peripheral blood B cells by blocking CD11b. *Immunopharmacol Immunotoxicol* 2010; doi: 10.3109/08923973.2010.522195.
- 39 Takano F, Takata T, Yoshihara A, Nakamura Y, Arima Y, Ohta T. Aqueous extract of peanut skin and its main constituent procyanidin A1 suppress serum IgE and IgG1 levels in mice-immunized with ovalbumin. *Biol Pharm Bull* 2007; 30:922–7.
- 40 Yano S, Umeda D, Maeda N, Fujimura Y, Yamada K, Tachibana H. Dietary apigenin suppresses IgE and inflammatory cytokines production in C57BL/6N mice. *J Agric Food Chem* 2006; 54:5203–7.
- 41 Kanoh R, Hatano T, Ito H, Yoshida T, Akagi M. Effects of tannins and related polyphenols on superoxide-induced histamine release from rat peritoneal mast cells. *Phytomedicine* 2000; 7: 297–302.
- 42 Matsuo N, Yamada K, Shoji K, Mori M, Sugano M. Effect of tea polyphenols on histamine release from rat basophilic leukemia (RBL-2H3) cells: the structure-inhibitory activity relationship. *Allergy* 1997; 52:58–64.
- 43 Fujimura Y, Tachibana H, Yamada K. A tea catechin suppresses the expression of the high-affinity IgE receptor Fc epsilon RI in human basophilic KU812 cells. *J Agric Food Chem* 2001; 49:2527–31.
- 44 Fujimura Y, Tachibana H, Maeda-Yamamoto M, Miyase T, Sano M, Yamada K. Antiallergic tea catechin, (-)-epigallocatechin-3-O-(3-O-methyl)-gallate, suppresses Fc epsilon RI expression in human basophilic KU812 cells. *J Agric Food Chem* 2002; 50: 5729–34.
- 45 Tokura T, Nakano N, Ito T *et al*. Inhibitory effect of polyphenol-enriched apple extracts on mast cell degranulation in vitro targeting the binding between IgE and Fc epsilon RI. *Biosci Biotechnol Biochem* 2005; 69:1974–7.
- 46 Yano S, Tachibana H, Yamada K. Flavones suppress the expression of the high-affinity IgE receptor Fc epsilon RI in human basophilic KU812 cells. *J Agric Food Chem* 2005; 53:1812–7.
- 47 Camouse MM, Domingo DS, Swain FR *et al*. Topical application of green and white tea extracts provides protection from solar-simulated ultraviolet light in human skin. *Exp Dermatol* 2009; 18:522–6.
- 48 Katiyar SK, Elmets CA, Agarwal R, Mukhtar H. Protection against ultraviolet-B radiation-induced local and systemic suppression of contact hypersensitivity and edema responses in C3H/HeN mice by green tea polyphenols. *Photochem Photobiol* 1995; 62: 855–61.
- 49 Zhao JF, Zhang YJ, Jin XH *et al*. Green tea protects against psoralen plus ultraviolet A-induced photochemical damage to skin. *J Invest Dermatol* 1999; 113:1070–5.
- 50 Ichikawa D, Matsui A, Imai M, Sonoda Y, Kasahara T. Effect of various catechins on the IL-12p40 production by murine peritoneal macrophages and a macrophage cell line, J774.1. *Biol Pharm Bull* 2004; 27:1353–8.
- 51 Williamson MP, McCormick TG, Nance CL, Shearer WT. Epigallocatechin gallate, the main polyphenol in green tea, binds to the T-cell receptor, CD4: Potential for HIV-1 therapy. *J Allergy Clin Immunol* 2006; 118:1369–74.
- 52 Kawai K, Tsuno NH, Kitayama J *et al*. Epigallocatechin gallate attenuates adhesion and migration of CD8+T cells by binding to CD11b. *J Allergy Clin Immunol* 2004; 113:1211–7.
- 53 Ohmori Y, Ito M, Kishi M, Mizutani H, Katada T, Konishi H. Antiallergic constituents from oolong tea stem. *Biol Pharm Bull* 1995; 18:683–6.
- 54 Uehara M, Sugiura H, Sakurai K. A trial of oolong tea in the management of recalcitrant atopic dermatitis. *Arch Dermatol* 2001; 137:42–3.
- 55 Kojima T, Akiyama H, Sasai M *et al*. Anti-allergic effect of apple polyphenols on patients with atopic dermatitis: a pilot study. *Allergology International* 2000; 49:69–73.
- 56 Meydani M. Potential health benefits of avenanthramides of oats. *Nutr Rev* 2009; 67:731–5.
- 57 Sur R, Nigam A, Grote D, Liebel F, Southall MD. Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity. *Arch Dermatol Res* 2008; 300:569–74.
- 58 Guo W, Wise ML, Collins FW, Meydani M. Avenanthramides, polyphenols from oats, inhibit IL-1beta-induced NF-kappaB activation in endothelial cells. *Free Radic Biol Med* 2008; 44:415–29.
- 59 Nie L, Wise ML, Peterson DM, Meydani M. Avenanthramide, a polyphenol from oats, inhibits vascular smooth muscle cell proliferation and enhances nitric oxide production. *Atherosclerosis* 2006; 186:260–6.
- 60 Papaliodis D, Boucher W, Kempuraj D, Theoharides TC. The flavonoid luteolin inhibits niacin-induced flush. *Br J Pharmacol* 2008; 153:1382–7.
- 61 Katsarou A, Davoy E, Xenos K, Armenaka M, Theoharides TC. Effect of an antioxidant (quercetin) on sodium-lauryl-sulfate-induced skin irritation. *Contact Dermatitis* 2000; 42:85–9.
- 62 Neukam K, Stahl W, Tronnier H, Sies H, Heinrich U. Consumption of flavanol-rich cocoa acutely increases microcirculation in human skin. *Eur J Nutr* 2007; 46:53–6.
- 63 Heaton T, Mallon D, Venaille T, Holt P. Staphylococcal enterotoxin induced IL-5 stimulation as a cofactor in the pathogenesis of atopic disease: the hygiene hypothesis in reverse? *Allergy* 2003; 58:252–6.
- 64 Patel GK, Wyatt H, Kubiak EM, Clark SM, Mills CM. *Staphylococcus aureus* colonization of children with atopic eczema and their parents. *Acta Derm Venereol* 2001; 81:366–7.
- 65 Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema. *Cochrane Database Syst Rev* 2008; CD003871.
- 66 Choi O, Yahiro K, Morinaga N, Miyazaki M, Noda M. Inhibitory effects of various plant polyphenols on the toxicity

- of Staphylococcal alpha-toxin. *Microb Pathog* 2007; 42:215–24.
- 67 Rasooly R, Do PM, Friedman M. Inhibition of biological activity of staphylococcal enterotoxin A (SEA) by apple juice and apple polyphenols. *J Agric Food Chem* 2010; 58:5421–6.
 - 68 Ganeshan K, Neilsen CV, Hadsaitong A, Schleimer RP, Luo X, Bryce PJ. Impairing oral tolerance promotes allergy and anaphylaxis: a new murine food allergy model. *J Allergy Clin Immunol* 2009; 123:231–8.
 - 69 Liu T, Wang BQ, Zheng PY, He SH, Yang PC. Rhinosinusitis derived Staphylococcal enterotoxin B plays a possible role in pathogenesis of food allergy. *BMC Gastroenterol* 2006; 6:24.
 - 70 Liu AH, Jaramillo R, Sicherer SH *et al.* National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2010; 126:798–806.
 - 71 Labuckas DO, Maestri DM, Milton P, Martinez ML, Lamarque AL. Phenolics from walnut (*Juglans regia* L.) kernels: antioxidant activity and interactions with proteins. *Food Chem* 2008; 107:607–12.
 - 72 Nozaki A, Hori M, Kimura T, Ito H, Hatano T. Interaction of polyphenols with proteins: binding of (–)-epigallocatechin gallate to serum albumin, estimated by induced circular dichroism. *Chem Pharm Bull (Tokyo)* 2009; 57:224–8.
 - 73 Anderson KC, Teuber SS. Ellagic acid and polyphenolics present in walnut kernels inhibit in vitro human peripheral blood mononuclear cell proliferation and alter cytokine production. *Ann N Y Acad Sci* 2010; 1190:86–96.
 - 74 Akiyama H, Sato Y, Watanabe T *et al.* Dietary unripe apple polyphenol inhibits the development of food allergies in murine models. *FEBS Lett* 2005; 579:4485–91.
 - 75 Jung M, Triebel S, Anke T, Richling E, Erkel G. Influence of apple polyphenols on inflammatory gene expression. *Mol Nutr Food Res* 2009; 53:1263–80.
 - 76 Kobayashi S, Watanabe J, Fukushi E, Kawabata J, Nakajima M, Watanabe M. Polyphenols from some foodstuffs as inhibitors of ovalbumin permeation through caco-2 cell monolayers. *Biosci Biotechnol Biochem* 2003; 67:1250–7.
 - 77 Sehm J, Linder Mayer H, Dummer C, Treutter D, Pfaffl MW. The influence of polyphenol rich apple pomace or red-wine pomace diet on the gut morphology in weaning piglets. *J Anim Physiol Anim Nutr (Berl)* 2007; 91:289–96.
 - 78 Penissi AB, Rudolph MI, Piezzi RS. Role of mast cells in gastrointestinal mucosal defense. *Biocell* 2003; 27:163–72.
 - 79 Szabo A, Boros M, Kaszaki J, Nagy S. The role of mast cells in mucosal permeability changes during ischemia-reperfusion injury of the small intestine. *Shock* 1997; 8:284–91.
 - 80 Park HH, Lee S, Son HY *et al.* Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells. *Arch Pharm Res* 2008; 31:1303–11.
 - 81 Kanda T, Akiyama H, Yanagida A *et al.* Inhibitory effects of apple polyphenol on induced histamine release from RBL-2H3 cells and rat mast cells. *Biosci Biotechnol Biochem* 1998; 62:1284–9.
 - 82 Kaneko M, Kanesaka M, Yoneyama M, Tominaga T, Jirillo E, Kumazawa Y. Inhibitory effects of fermented grape marc from *Vitis vinifera* Negroamaro on antigen-induced degranulation. *Immunopharmacol Immunotoxicol* 2010; 32:454–61.
 - 83 Rechner AR, Kuhnle G, Bremner P, Hubbard GP, Moore KP, Rice-Evans CA. The metabolic fate of dietary polyphenols in humans. *Free Radic Biol Med* 2002; 33:220–35.
 - 84 Scalbert A, Morand C, Manach C, Remesy C. Absorption and metabolism of polyphenols in the gut and impact on health. *Biomed Pharmacother* 2002; 56:276–82.
 - 85 van DJ, Vaughan EE, Jacobs M *et al.* Microbes and health Sackler colloquium: metabolic fate of polyphenols in the human superorganism. *Proc Natl Acad Sci USA* 2010; 108 (Suppl. 1): 4531–38.
 - 86 Williamson G, Clifford MN. Colonic metabolites of berry polyphenols: the missing link to biological activity? *Br J Nutr* 2010; 104 (Suppl. 3):S48–S66.
 - 87 Bialonska D, Ramnani P, Kasimsetty SG, Muntha KR, Gibson GR, Ferreira D. The influence of pomegranate by-product and punicalagins on selected groups of human intestinal microbiota. *Int J Food Microbiol* 2010; 140:175–82.
 - 88 Hervet-Hernandez D, Pintado C, Rotger R, Goni I. Stimulatory role of grape pomace polyphenols on *Lactobacillus acidophilus* growth. *Int J Food Microbiol* 2009; 136:119–22.
 - 89 Tominaga T, Kawaguchi K, Kanesaka M, Kawauchi H, Jirillo E, Kumazawa Y. Suppression of type-I allergic responses by oral administration of grape marc fermented with *Lactobacillus plantarum*. *Immunopharmacol Immunotoxicol* 2010; 32:593–9.
 - 90 Parkar SG, Stevenson DE, Skinner MA. The potential influence of fruit polyphenols on colonic microflora and human gut health. *Int J Food Microbiol* 2008; 124:295–8.
 - 91 Lee HC, Jenner AM, Low CS, Lee YK. Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Res Microbiol* 2006; 157:876–84.
 - 92 Monagas M, Khan N, Andres-Lacueva C *et al.* Dihydroxylated phenolic acids derived from microbial metabolism reduce lipopolysaccharide-stimulated cytokine secretion by human peripheral blood mononuclear cells. *Br J Nutr* 2009; 102:201–6.
 - 93 Gross G, Jacobs DM, Peters S *et al.* In vitro bioconversion of polyphenols from black tea and red wine/grape juice by human intestinal microbiota displays strong interindividual variability. *J Agric Food Chem* 2010; 58:10236–46.
 - 94 Nauta AJ, Engels F, Knippels LM, Garsen J, Nijkamp FP, Redegeld FA. Mechanisms of allergy and asthma. *Eur J Pharmacol* 2008; 585:354–60.
 - 95 Jung WK, Choi I, Oh S *et al.* Anti-asthmatic effect of marine red alga (*Laurencia undulata*) polyphenolic extracts in a murine model of asthma. *Food Chem Toxicol* 2009; 47:293–7.
 - 96 Lee M, Kim S, Kwon OK, Oh SR, Lee HK, Ahn K. Anti-inflammatory and anti-asthmatic effects of resveratrol, a polyphenolic stilbene, in a mouse model of allergic asthma. *Int Immunopharmacol* 2009; 9:418–24.
 - 97 Noguchi Y, Fukuda K, Matsushima A *et al.* Inhibition of Df-protease associated with allergic diseases by polyphenol. *J Agric Food Chem* 1999; 47:2969–72.
 - 98 Garcia V, Arts IC, Sterne JA, Thompson RL, Shaheen SO. Dietary intake of flavonoids and asthma in adults. *Eur Respir J* 2005; 26:449–52.
 - 99 Seifried HE, Anderson DE, Fisher EI, Milner JA. A review of the interaction among dietary antioxidants and reac-

- tive oxygen species. *J Nutr Biochem* 2007; 18:567–79.
- 100 Kim HJ, Ryu JH, Kim CH *et al*. Epicatechin gallate suppresses oxidative stress-induced MUC5AC overexpression by interaction with epidermal growth factor receptor. *Am J Respir Cell Mol Biol* 2010; 43:349–57.
 - 101 Chang JH, Song KJ, Kim HJ, Kim JH, Kim NH, Kim KS. Dietary polyphenols affect MUC5AC expression and ciliary movement in respiratory cells and nasal mucosa. *Am J Rhinol Allergy* 2010; 24:e59–e62.
 - 102 Biswas S, Rahman I. Modulation of steroid activity in chronic inflammation: a novel anti-inflammatory role for curcumin. *Mol Nutr Food Res* 2008; 52:987–94.
 - 103 Franova S, Nosalova G, Pechanova O, Sutovska M. Red wine polyphenolic compounds inhibit tracheal smooth muscle contraction during allergen-induced hyperreactivity of the airways. *J Pharm Pharmacol* 2007; 59:727–32.
 - 104 Franova S, Joskova M, Novakova E, Adamcova K, Sutovska M, Nosal S. Effects of flavin7 on allergen induced hyperreactivity of airways. *Eur J Med Res* 2009; 14 (Suppl. 4):78–81.
 - 105 Oh SW, Cha JY, Jung JE *et al*. Curcumin attenuates allergic airway inflammation and hyper-responsiveness in mice through NF-kappaB inhibition. *J Ethnopharmacol* 2010; doi: 10.1016/j.jep.2010.07.026.
 - 106 Joskova M, Franova S, Nosalova G, Pechanova O, Prisenznakova L, Sutovska M. A beneficial influence of provinol on the reduction of allergen induced hyperreactivity in guinea pigs. *Bratisl Lek Listy* 2009; 110:454–8.
 - 107 Enomoto T, Nagasako-Akazome Y, Kanda T, Ikeda M, Dake Y. Clinical effects of apple polyphenols on persistent allergic rhinitis: a randomized double-blind placebo-controlled parallel arm study. *J Invest Allergol Clin Immunol* 2006; 16:283–9.
 - 108 Kishi K, Saito M, Saito T *et al*. Clinical efficacy of apple polyphenol for treating cedar pollinosis. *Biosci Biotechnol Biochem* 2005; 69:829–32.
 - 109 Yoshimura M, Enomoto T, Dake Y *et al*. An evaluation of the clinical efficacy of tomato extract for perennial allergic rhinitis. *Allergol Int* 2007; 56:225–30.
 - 110 Alvarez P, Alvarado C, Mathieu F, Jimenez L, De la Fuente M. Diet supplementation for 5 weeks with polyphenol-rich cereals improves several functions and the redox state of mouse leucocytes. *Eur J Nutr* 2006; 45:428–38.
 - 111 Aviram M, Rosenblat M, Gaitini D *et al*. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clin Nutr* 2004; 23:423–33.
 - 112 Borges G, Mullen W, Mullan A, Lean ME, Roberts SA, Crozier A. Bioavailability of multiple components following acute ingestion of a polyphenol-rich juice drink. *Mol Nutr Food Res* 2010; 54 (Suppl. 2):S268–S277.
 - 113 D'Archivio M, Filesi C, Vari R, Scazzocchio B, Masella R. Bioavailability of the polyphenols: status and controversies. *Int J Mol Sci* 2010; 11:1321–42.
 - 114 Scheepens A, Tan K, Paxton JW. Improving the oral bioavailability of beneficial polyphenols through designed synergies. *Genes Nutr* 2010; 5:75–87.
 - 115 Alonso-Salces RM, Ndjoko K, Queiroz EF *et al*. On-line characterisation of apple polyphenols by liquid chromatography coupled with mass spectrometry and ultraviolet absorbance detection. *J Chromatogr A* 2004; 1046:89–100.
 - 116 Biasutto L, Marotta E, Garbisa S, Zoratti M, Paradisi C. Determination of quercetin and resveratrol in whole blood—implications for bioavailability studies. *Molecules* 2010; 15:6570–9.
 - 117 Celik SE, Ozyurek M, Guclu K, Apak R. Determination of antioxidants by a novel on-line HPLC-cupric reducing antioxidant capacity (CUPRAC) assay with post-column detection. *Anal Chim Acta* 2010; 674:79–88.
 - 118 Medina-Remon A, Barrionuevo-Gonzalez A, Zamora-Ros R *et al*. Rapid Folin-Ciocalteu method using microtiter 96-well plate cartridges for solid phase extraction to assess urinary total phenolic compounds, as a biomarker of total polyphenols intake. *Anal Chim Acta* 2009; 634:54–60.
 - 119 Vrhovsek U, Rigo A, Tonon D, Mattivi F. Quantitation of polyphenols in different apple varieties. *J Agric Food Chem* 2004; 52:6532–8.
 - 120 Wojdylo A, Oszmianski J, Laskowski P. Polyphenolic compounds and antioxidant activity of new and old apple varieties. *J Agric Food Chem* 2008; 56:6520–30.
 - 121 Rogerio AP, Kanashiro A, Fontanari C *et al*. Anti-inflammatory activity of quercetin and isoquercitrin in experimental murine allergic asthma. *Inflamm Res* 2007; 56:402–8.
 - 122 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.
 - 123 Hirano T, Kawai M, Arimitsu J *et al*. Preventative effect of a flavonoid, enzymatically modified isoquercitrin on ocular symptoms of Japanese cedar pollinosis. *Allergol Int* 2009; 58:373–82.
 - 124 Kawai M, Hirano T, Arimitsu J *et al*. Effect of enzymatically modified isoquercitrin, a flavonoid, on symptoms of Japanese cedar pollinosis: a randomized double-blind placebo-controlled trial. *Int Arch Allergy Immunol* 2009; 149:359–68.
 - 125 Kim HR, Lee DM, Lee SH *et al*. Chlorogenic acid suppresses pulmonary eosinophilia, IgE production, and Th2-type cytokine production in an ovalbumin-induced allergic asthma: activation of STAT-6 and JNK is inhibited by chlorogenic acid. *Int Immunopharmacol* 2010; 10:1242–8.
 - 126 Jung WK, Lee DY, Choi YH *et al*. Caffeic acid phenethyl ester attenuates allergic airway inflammation and hyperresponsiveness in murine model of ovalbumin-induced asthma. *Life Sci* 2008; 82:797–805.