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REVIEW



A review on polyphenols and their potential application to reduce food allergenicity

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ABSTRACT

This review summarized recent studies about the effects of polyphenols on the allergenicity of allergenic proteins, involving epigallocatechin gallate (EGCG), caffeic acid, chlorogenic acid, proanthocyanidins, quercetin, ferulic acid and rosmarinic acid, etc. Besides, the mechanism of polyphenols for reducing allergenicity was discussed and concluded. It was found that polyphenols could noncovalently (mainly hydrophobic interactions and hydrogen bonding) and covalently (mainly alkaline, free-radical grafting, and enzymatic method) react with allergens to induce the structural changes, resulting in the masking or/and destruction of epitopes and the reduction of allergenicity. Oral administration in murine models showed that the allergic reaction might be suppressed by regulating immune cell function, changing the levels of cytokines, suppressing of MAPK, NF- κ B and allergens-presentation pathway and improving intestine function, etc. The outcome of reduced allergenicity and suppressed allergic reaction was affected by many factors such as polyphenol types, polyphenol concentration, allergen types, pH, oral timing and dosage. Moreover, the physicochemical and functional properties of allergenic proteins were improved after treatment with polyphenols. Therefore, polyphenols have the potential to produce hypoallergenic food. Further studies should focus on active concentrations and bioavailability of polyphenols, confirming optimal intake and hypoallergenic of polyphenols based on clinical trials.

KEYWORDS

Polyphenols; allergenicity; allergens; allergic reaction

1. Introduction

Food allergies are an abnormal response of the immune system after exposure to certain foods (Wang, Pramod, et al. 2020), which are recognized by the World Health Organization as the sixth main disease affecting human health (Pu et al. 2021). It was reported that food allergies affected 5% of adults and 8% of children (Pi, Yang, Sun, Wang, et al. 2021), and the incidence continued to rise steadily due to modern environmental factors (Florsheim et al. 2021; Renz et al. 2018). Avoiding allergic foods is the most effective measure to prevent allergic reactions for allergic patients, but it may consequently affect the nutritional intake of the body and cause various nutritional deficiency syndromes, especially in children (Pi et al. 2019; Rahaman, Vasiljevic, and Ramchandran 2016; Wang, Pramod, et al. 2020). Thus, allergen avoidance is difficult and time-consuming, and it may be almost impossible in some instances (Renz et al. 2018). Moreover, medical treatments (e.g., antihistamines, adrenaline, steroid and non-steroid drugs) have various restrictions such as unsuitable for certain children under two years old, unaffordable for a poor person and some (steroids) may have adverse consequences in long term (Wang, Pramod, et al. 2020). Therefore, it

appears that food processing to reduce food allergenicity may contribute to preventing allergic reactions.

At present, numerous technologies have successfully been used to reduce food allergenicity, involving heat treatment, high-pressure treatment, enzyme catalysis, fermentation, glycosylation, irradiation, and binding of natural products, etc (Chizoba Ekezie, Cheng, and Sun 2018; Lv et al. 2021; Pi et al. 2019; Pi, Yang, Sun, Cui, et al. 2021; Pi, Yang, Sun, Wang, et al. 2021; Zhang, Cheng, et al. 2020). However, heat treatment, enzyme catalysis and fermentation may drastically change the organoleptic properties and nutrient compositions (Dong, Wang, and Raghavan 2021; Meinschmidt et al. 2016; Pu et al. 2021; Rahaman, Vasiljevic, and Ramchandran 2016). Glycosylation may produce advanced glycation end products to increase the allergenicity (Chung and Champagne 2001). The cost of high-pressure treatment is quite high and consumer acceptance of food irradiation remains controversial (Pi et al. 2019; Pi, Yang, Sun, Wang, et al. 2021). Binding with natural products may be a potentially safe technology to reduce allergenicity because of the direction and specificity of the protein modification (Pu et al. 2021).

Polyphenols are widely spread secondary metabolites in plants (e.g., fruit, tea, chestnut, coffee and vegetable, etc)

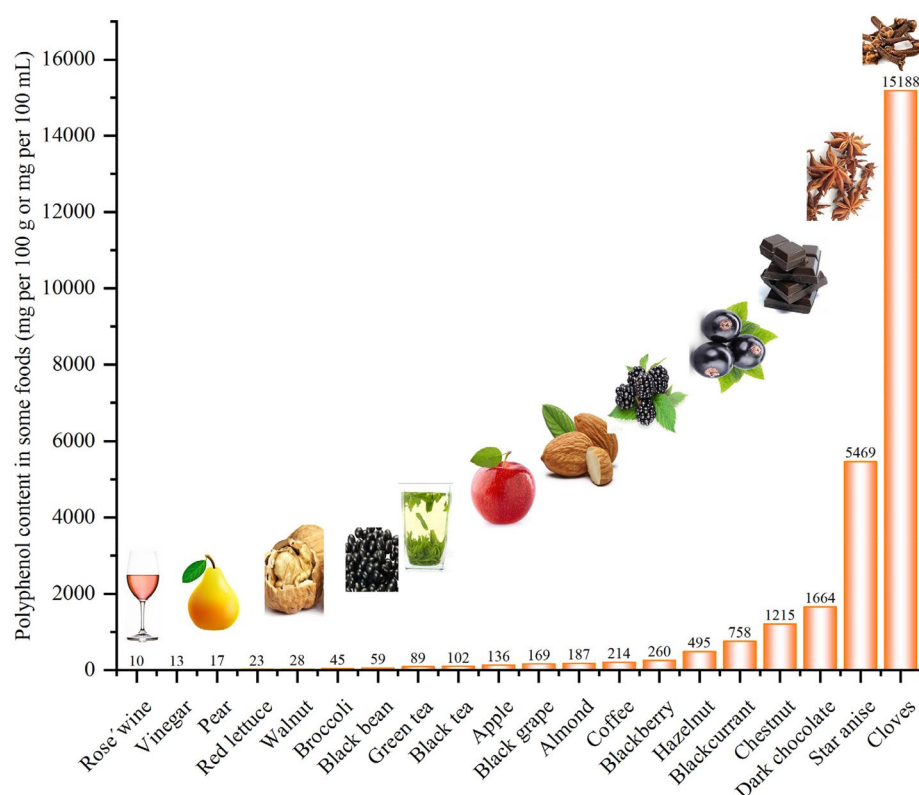


Figure 1. The content of total polyphenols in some foods (mg per 100 g or mg per 100 mL). The data was from (Perez-Jimenez et al. 2010).

(Figure 1) (Reis et al. 2020; Zhang, Cheng, et al. 2020), and are divided into three subgroups such as non-flavonoids, flavonoids and tannins (Reis et al. 2020) (Table 1), which are widely used in the foods, including oil, meat, jam, plant beverage, and seasoning products, etc. In vitro studies have suggested that the high content of polyphenols might correlate with reduced allergenicity of Mal d 1 in certain apple cultivars, and Ara h 1, 3, and 2/6 in germinated peanuts (Kschonsek et al. 2019a; Kschonsek et al. 2019b; Rao et al. 2018). Hamada et al. (2019) demonstrated that certain hydrolyzable tannins in walnuts decreased T-cell activation and growth in vitro and their supplementation in walnut-containing foods might ameliorate allergic reactions in susceptible individuals. Recently, isolated from apple, artichoke leaves, cranberries, green tea leaves, pomegranate juice, cranberry and blueberry, polyphenols have been successfully used to reduce the allergenicity of apple, wheat gliadins, cashew nut and peanut in vitro (Kschonsek et al. 2019a; Li and Mattison 2018; Perot et al. 2017; Plundrich et al. 2017). Moreover, oral administration in murine models has also shown that polyphenols can suppress allergic reactions (Bansode et al. 2018; Chu et al. 2016; Katayama et al. 2017; Mwakalukwa et al. 2019; Ognjenovic et al. 2014; Zhou et al. 2014). At present, there is no reviews about the effects of polyphenols on food allergies. Therefore, we provide a comprehensive and up-to-date overview for polyphenols alleviating food allergies, involving EGCG, caffeic acid, chlorogenic acid, proanthocyanidins, quercetin, ferulic acid and rosmarinic acid, etc.

2. Effects of various polyphenols on food allergies

As shown in Figure 2, polyphenols can noncovalently and covalently react with proteins, with the potential to result in the reduction of allergenicity induced by masking or/and destroying epitopes (He et al. 2020; Liu et al. 2018; Lv et al. 2021; Pessato et al. 2018). Noncovalent interactions are reversible and include hydrogen bond, hydrophobic interaction, ionic bond, electrostatic interaction and van der Waals forces of attraction (Figure 2A), in which hydrophobic interactions and hydrogen bonding are responsible for the noncovalent interactions (Pu et al. 2021; Sui, Zhang, and Jiang 2021). Covalent interactions are generally irreversible and can be achieved by alkaline (Figure 2B), free-radical grafting (Figure 2C), and enzymatic method (Figure 2D) (Li, Karboune, et al. 2021; Li et al. 2020; Quan et al. 2019). As shown in Figure 3, sandwich enzyme-linked immunosorbent assays had shown that the allergenicity of β -lactoglobulin was reduced by 72.6% after noncovalent interactions with EGCG, resulting from the structural changes induced by hydrogen bonding, van der Waals interactions and hydrophobic interaction (Pu et al. 2021). For covalent interactions, He et al. (2019) found that EGCG was conjugated with Cys74 in ovalbumin with the alkaline reaction to induce the protein-unfold and the reduction of α -helix, resulting in the reduction of allergenicity (Figure 4B). Similar results were shown in covalently EGCG-ovalbumin complexes through free-radical grafting, which showed the reduction of allergenicity in ovalbumin due to protein-unfold

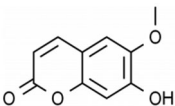
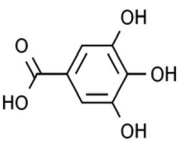
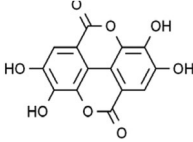
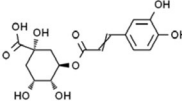
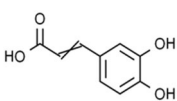
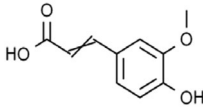
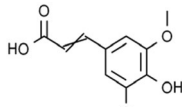
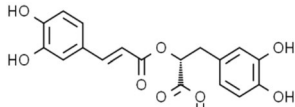
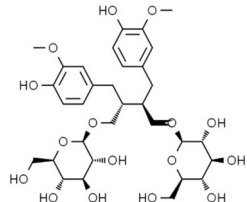
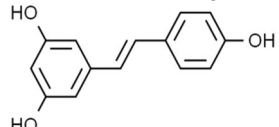
and the reduction of α -helix induced by conjugation with Cys74 and Glu347 (Figure 4B) (He et al. 2019). Tian et al. (2019) also found that the allergenicity of turbot parvalbumin was reduced by 34.94% after the enzymatic method (caffeic acid and tyrosinase) based on the indirect ELISA (enzyme-linked immunosorbent assay) analysis, resulting in the formation of o-quinones and changes of conformational structure. Similar results were shown in EGCG-lactoferrin complexes with laccase (Li, Karboune, et al. 2021). In conclusion, noncovalent and covalent conjugation can both reduce the allergenicity of food matrix, which was usually accompanied by structural changes (allergen specific therapies). In addition, food allergies are usually accompanied by an imbalance of Th1/Th2 response, low contents of IgA, intestinal flora diversity, Treg cells, and damaged epithelial

barrier and high levels of IgE, etc (Figure 5A) (Pi, Sun, et al. 2021; Pi, Yang, Sun, Cui, et al. 2021), which may be alleviated by the intake of polyphenols (Bansode et al. 2018; Chu et al. 2016; Katayama et al. 2017; Mwakalukwa et al. 2019; Ognjenovic et al. 2014; Zhou et al. 2014) (non-allergen specific therapies). Thus, food allergies can be alleviated by allergen and non-allergen specific therapies, involving EGCG, caffeic acid, chlorogenic acid, proanthocyanidins, quercetin, ferulic acid and rosmarinic acid, etc.

2.1. EGCG

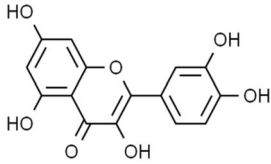
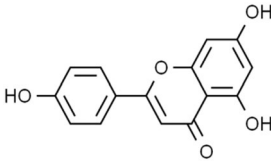
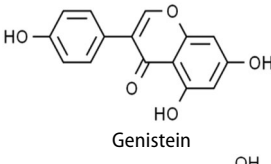
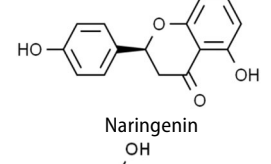
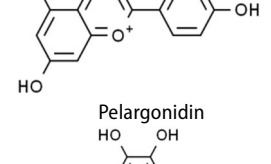
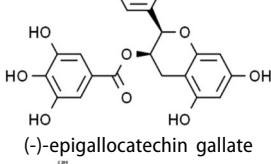
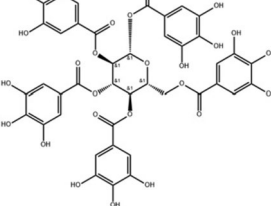
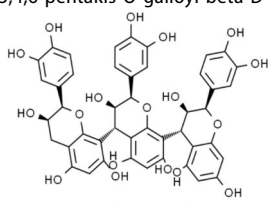
EGCG is a water-soluble catechin monomer and is a flavonoid derived from green tea (Pessato et al. 2018). Many studies have demonstrated that EGCG covalently and non-covalently

Table 1. Main classes of polyphenol compounds, representative chemical structures, and food source.

Main classes of polyphenol	Subgroup	Representative chemical structure	Food source (mg/100g)
Non-Flavonoids	Coumarins		Moringa fruit
	Phenolic acids		
	Hydroxybenzoic acids	 Gallic acid  Ellagic acid	Blackberry Coffee beans
	Hydroxycinnamic acids		
		 Chlorogenic acid  Caffeic acid	
		 Ferulic acid  Sinapic acid	
			
	Lignans		
			Linseed
	Stilbenes		
		 Resveratrol	Red grapes

(Continued)

Table 1. (Continued).

Main classes of polyphenol	Subgroup	Representative chemical structure	Food source (mg/100 g)
Flavonoids	Flavonols	 Quercetin	Capers (654.71) Saffron (509.99) Spinach (119.27)
	Flavones	 Apigenin	Celery seed (2094.00) Peppermint (1486.29)
	Isoflavones	 Genistein	Soy flour (466.99) Soy paste (264.40) Soy tempeh (147.72)
	Flavanones	 Naringenin	Dried Peppermint (8739.98) Dried Mexican oregano (1049.67)
	Anthocyanidins	 Pelargonidin	Black elderberry (1316.65) Black chokeberry (878.12)
	Flavanols	 (-)-epigallocatechin gallate	Cocoa powder (511.62) Chocolate dark (212.36)
Tannins	Hydrolyzable	 1,2,3,4,6-pentakis-O-galloyl-beta-D-glucose	Sumac fruit
	Condensed	 Proanthocyanidins	Apple

Note: The date was from (Mrduljaš, Krešić, and Bilušić 2017) and (Reis et al. 2020).

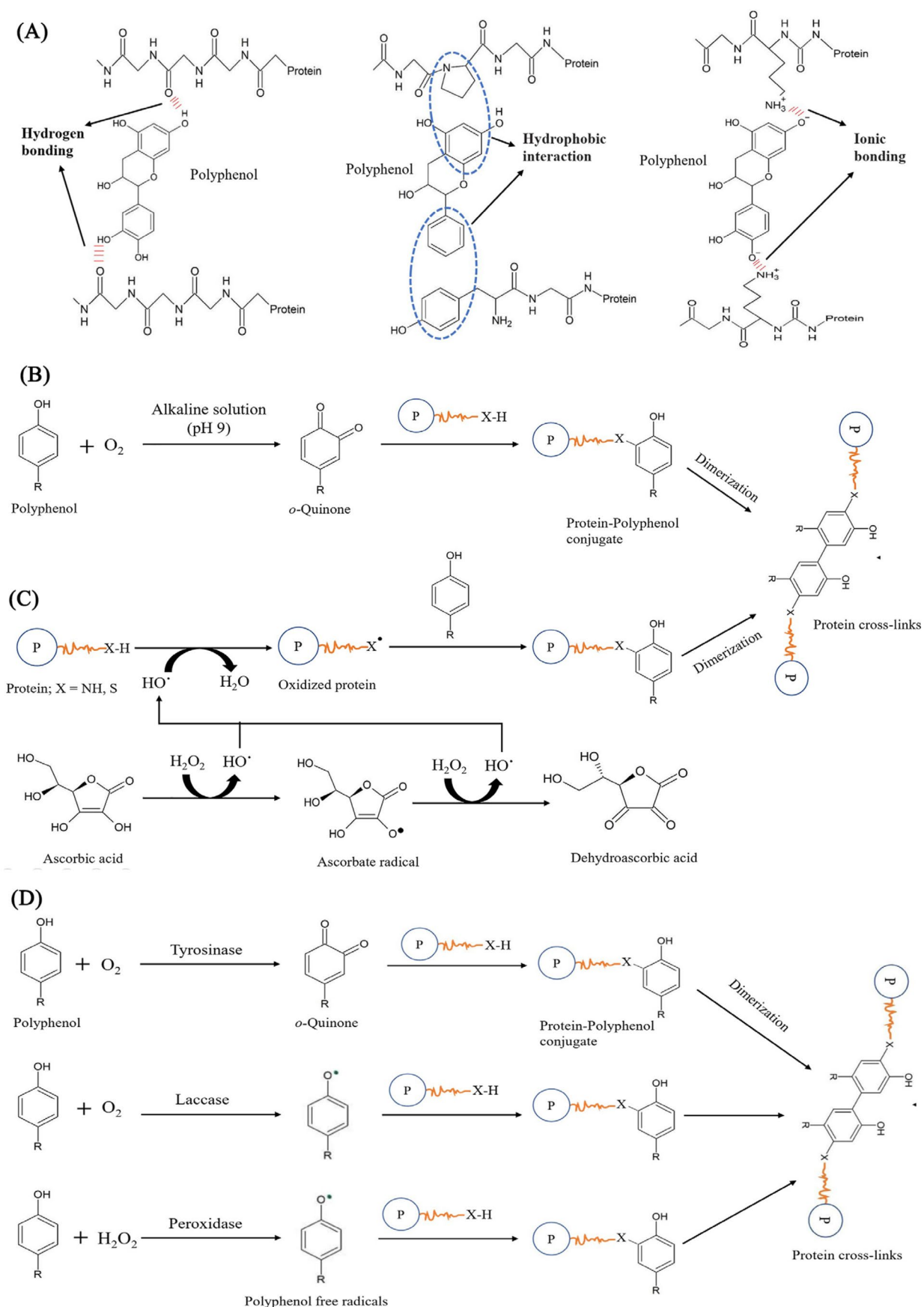


Figure 2. The reaction between polyphenols and protein. A. non-covalent reaction via hydrogen-bonding, hydrophobic interactions, and ionic bonds (Quan et al. 2019). B. Covalent interactions by alkaline treatment (pH 9.0). C. Covalent interactions by free-radical grafting method using ascorbic acid and H_2O_2 (C). D. covalent reaction by enzymatic method using polyphenols and enzymes (e.g., tyrosinase, laccase and peroxidase) (Li, Karboune, et al. 2021; Li et al. 2020; Quan et al. 2019).

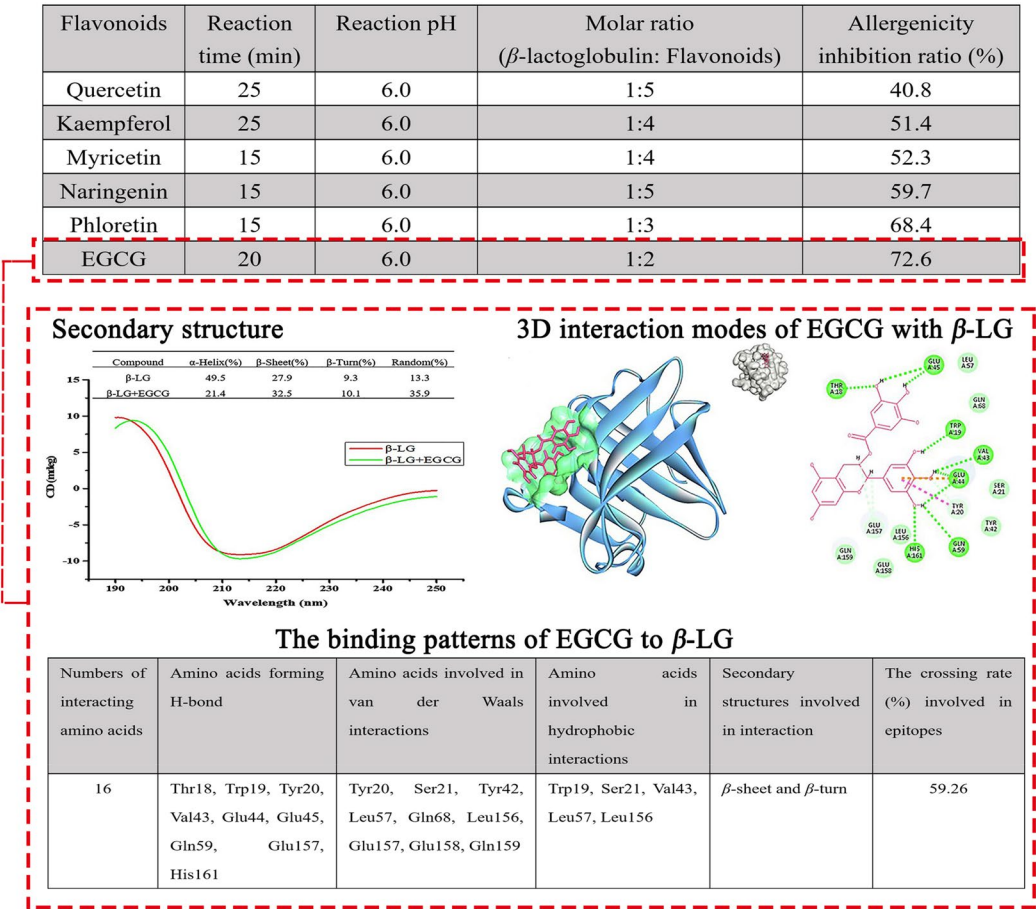


Figure 3. The non-covalent reaction between flavonoids EGCG and β -lactoglobulin (Pu et al. 2021).

conjugated with allergens to reduce the allergenicity, involving ovalbumin (He et al. 2019; Ognjenovic et al. 2014), whey proteins (Pessato et al. 2018), β -lactoglobulin (Pu et al. 2021; Wu et al. 2018), Ara h 1(He et al. 2020), soybean proteins (Zhou et al. 2020) and shrimp tropomyosin (Lv et al. 2021).

Recently, Pu et al. (2021) found that EGCG non-covalently conjugated with β -lactoglobulin to induce the highest reduction of allergenicity in β -lactoglobulin, compared to other flavonoids, which contributed to the highest crossing rate of 59.26% induced by the 16 amino acids (located in the β -sheet and β -turn of β -lactoglobulin) reacted with EGCG (Figure 3). In addition, structural changes such as the reduction of α -helix were observed in EGCG- β -lactoglobulin. However, contrast structural changes such as increase and no-changes of α -helix caused the masking or destruction of epitopes in whey protein, resulting in the reduction of allergenicity in noncovalent EGCG-whey protein complexes at pH 7.0 and pH 3.5 (Pessato et al. 2018). Therefore, pH plays an important role in noncovalent reactions. C3H/HeJ mice model furtherly showed that non-covalent EGCG-whey protein complexes reduced the contents of IgG2a and mMCP-1 in serum and suppressed allergic reaction by modulating Th1/Th2 response and increasing CD4⁺ Foxp3⁺ LAP⁺ T and IL-17A⁺CD4⁺ T cell populations (Pessato et al. 2019).

Similar to non-covalent conjugations, the structural changes such as the reduction of α -helix were responsible for the reduction of allergenicity in covalent conjugations, including

EGCG-Ara h 1, -ovalbumin, or -lactoferrin complexes prepared by alkali treatment (He et al. 2019; He et al. 2020; Li, Karboune, et al. 2021), EGCG-tropomyosin, -ovalbumin, -lactoferrin or - β -lactoglobulin complexes prepared by free radical grafting (He et al. 2019; He et al. 2020; Li, Karboune, et al. 2021; Lv et al. 2021), EGCG-lactoferrin complexes prepared by enzymatic method (Li, Karboune, et al. 2021). Recently, Lv et al. (2021) found that EGCG-tropomyosin complexes using free radical grafting showed the low allergenicity from indirect ELISA, a few inflammatory mediators from RBL-2H3 cell model, a low tropomyosin-specific antibody and T-cell cytokine and an increase of content in IFN- γ from BALB/c mice model. Similar results were shown in EGCG-tropomyosin and - soybean protein complexes using alkali treatment (He et al. 2020; Zhou et al. 2020). Moreover, in the simulated digestion process, the allergenicity was lower for digested conjugates (free radical grafting and alkali treatment) than digested unmodified ovalbumin (He et al. 2019). Besides, physicochemical and functional properties also changed after enzymatic treatment, similar to free radical grafting and alkali treatment (Li, Karboune, et al. 2021).

2.2. Caffeic acid

Caffeic acid is commonly present in coffee and citrus fruits (Pessato et al. 2018). It has been reported that caffeic acid covalently and non-covalently conjugates with allergens to

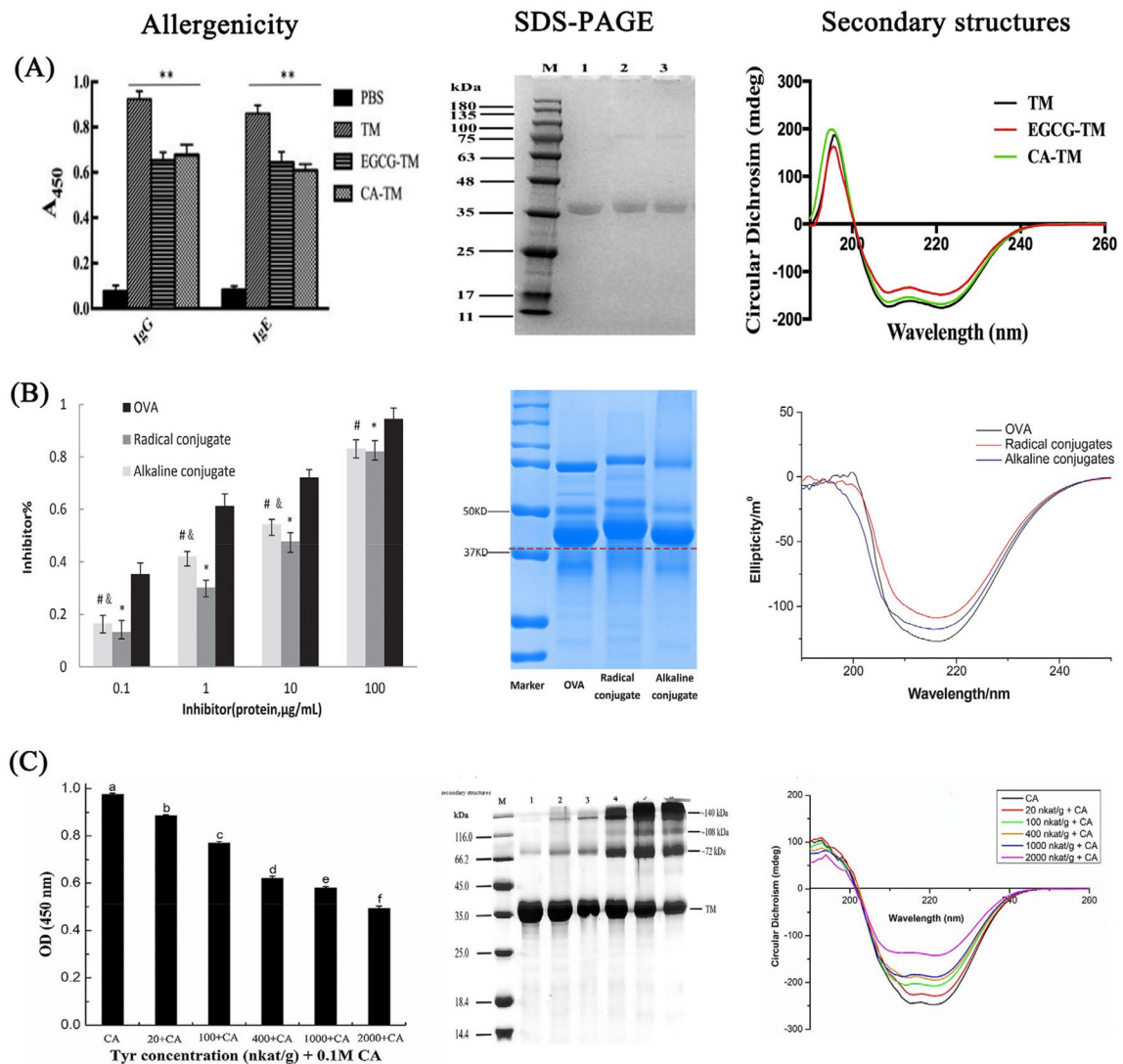


Figure 4. The covalent reaction between polyphenols and allergens for the reduction of allergenicity. A. The covalent reaction between polyphenols (EGCG and chlorogenic acid (CA)) and shrimp tropomyosin (TM) by radical method. For SDS-PAGE, lane M, 1, 2, and 3 represented protein marker, tropomyosin, tropomyosin-EGCG, and tropomyosin-CA, respectively (Lv et al. 2021). B. The covalent reaction between EGCG and ovalbumin (OVA) by radical and alkaline reaction (He et al. 2019). C. The covalent reaction between caffeic acid (CA) and tropomyosin by enzymatic method (tyrosinase, Tyr catalyzed). For SDS-PAGE, Lane 1-6 represented tropomyosin-caffeic acid complexes catalyzed by tyrosinase at 0, 20, 100, 400, 1000 and 2000 nkat/g (Ahmed et al. 2018).

reduce the allergenicity, including turbot parvalbumin (Ahmed et al. 2019; Tian et al. 2019), whey proteins (Pessato et al. 2018), ovalbumin (Liu et al. 2018; Tong et al. 2018), and peanut protein (Chung and Champagne 2009).

It was reported that non-covalent caffeic acid-parvalbumin complexes showed low allergenicity (7.23% reduction) due to structural changes (e.g., the loss of α -helix and the decrease of surface hydrophobicity) (Tian et al. 2019). However, the different structural changes such as increase or no-change of α -helix were responsible for the reduction in non-covalent caffeic acid-whey protein complexes at pH 7.0 or pH 3.5, respectively (Pessato et al. 2018). Thus, structural changes varied from pH and food matrix types. Whey protein-sensitized C3H/HeJ mice models furtherly showed that non-covalent caffeic acid-whey protein complexes relieved allergic reaction by reducing the levels of IgE, IgG1, IgG2a and mMCP-1, and activating CD4⁺LAP⁺Foxp3⁺ T and

Th17 cells (Pessato et al. 2019). Similar results were shown in Ahmed et al. (2019), who found that the allergenicity of non-covalent caffeic acid-parvalbumin was reduced by western blot and the reduction of β -hexosaminidase, histamine, tryptase, cysteinyl leukotrienes, prostaglandin D2, IL-4 and IL-13 after the complexes were exposed to RBL-2H3.

Similar to non-covalent conjugations, the structural changes (loss of α -helix, decrease of UV absorption spectrum and surface hydrophobicity) were responsible for the reduction of allergenicity in caffeic acid-ovalbumin complexes by enzymatic (polyphenol oxidase-catalyzed oxidation) (Liu et al. 2018). Compared to non-covalent complexes (allergenicity reduction, 7.23%), the bigger loss of α -helix (reduction rate, 38.3%) and decrease of surface hydrophobicity (59.95%) were observed in covalent caffeic acid-parvalbumin complexes by enzymatic (tyrosinase-catalyzed oxidation), which was responsible

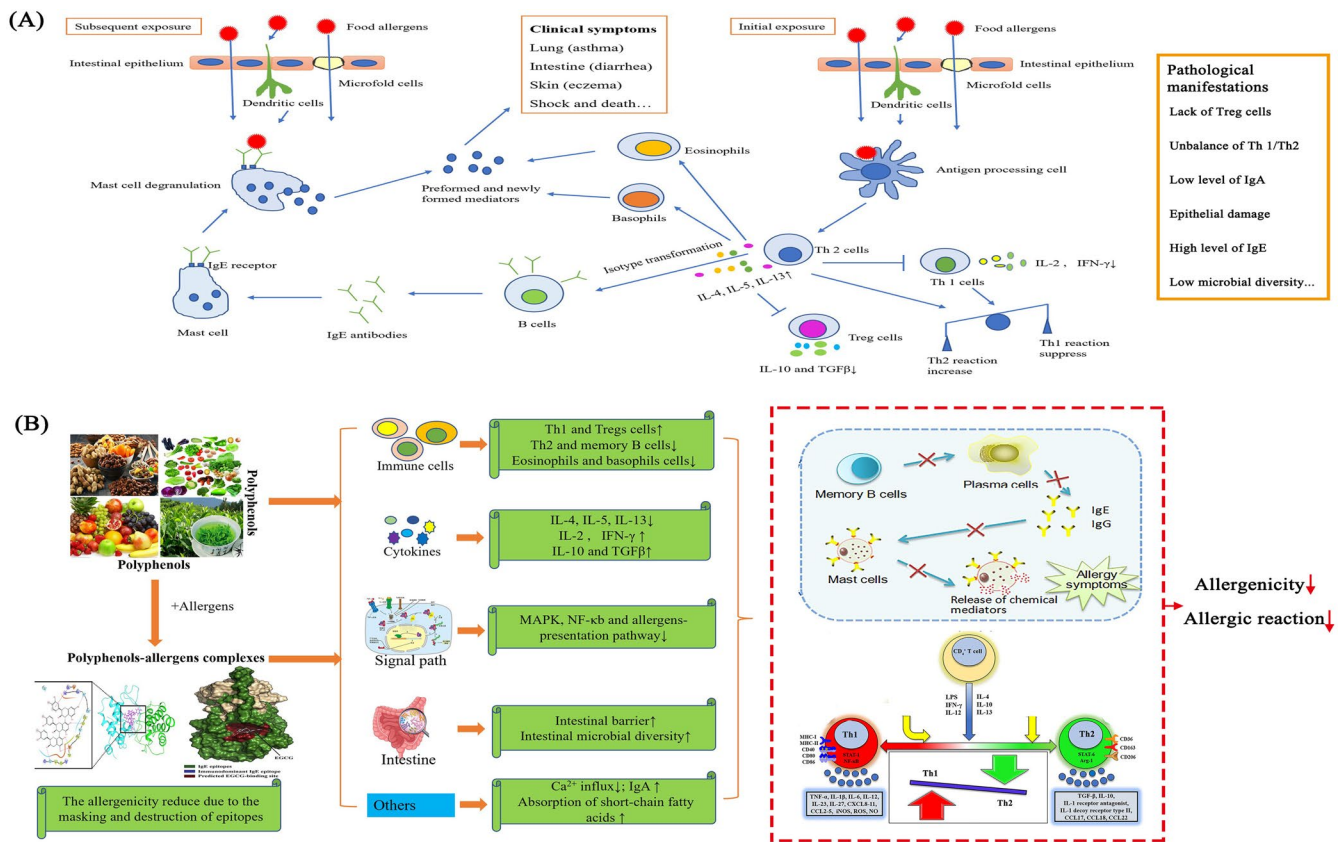


Figure 5. The mechanism of IgE-mediated food allergies and desensitization of polyphenols. A. The mechanism of IgE-mediated food allergies (Barni et al. 2020; Pi, Sun, et al. 2021; Pi, Yang, Sun, Cui, et al. 2021). Food allergens pass through the intestinal epithelium by two adjacent enterocytes (passive system), microfold cells, CD103+ dendritic cells (active system). Subsequently, the allergens are presented to Th2 cells by antigen processing cell, which helps regulate cellular immunity, promote isotype transformation and produce specific IgE antibodies from B cell. Then IgE antibodies bind to one allergen molecule, resulting in the release of mediators and the happen of clinical symptoms. B. The effect of polyphenols on the allergenicity and allergic reaction. Polyphenols-allergens complexes are from (Ognjenovic et al. 2014; Plundrich et al. 2019) and the figures in the red box are adapted from (Liang et al. 2019; Mohammadi et al. 2019).

for the reduction (34.94%) of allergenicity in covalent complexes (Tian et al. 2019). Similar results were shown in Ahmed et al. (2019), who found that there was a bigger reduction of β -hexosaminidase (reduction rate, 66.02%), histamine (35.01%), tryptase (29.25%), cysteinyl leukotrienes (29.72%), prostaglandin D2 (34.96%), IL-4 (43.99%) and IL-13 (38.93%) form RBL-2H3 models, compared to non-covalent complexes. In enzymatic (tyrosinase-catalyzed oxidation) treatment, the allergenicity of tropomyosin was reduced with the increase of tropomyosin concentration, resulting from the loss of α -helix (Ahmed et al. 2018). Similar results were shown in Kschonsek et al. (2019a), who found that the allergenicity in apple Mal d 1 might be reduced with the increase of caffeic acid content during enzymatic treatment (polyphenol oxidase). Tong et al. (2018) further found that caffeic acid-ovalbumin complexes by enzymatic (polyphenol oxidase-catalyzed oxidation) showed a low allergenicity from indirect ELISA, a strong inhibition of IL-4, IL-5, IL-13 and IFN- γ production in the stimulated spleen cell, a high reduction of allergen-specific IgE, IgG, IgG1 and IgG2a levels, as well as serum histamine and mMCP-1 concentration from BALB/c mice model. Unfortunately, there were reports about free radical grafting and alkaline treatment.

2.3. Chlorogenic acid

Chlorogenic acid is a depsilic acid produced by the reaction of caffeic acid and quinic acid, and it is one of the main antibacterial and antiviral pharmacological components of honeysuckle. It was observed that chlorogenic acid effectively reduced the allergenicity of foods covalently and noncovalently, involving peanut (Chung and Champagne 2009; He et al. 2020; Plundrich et al. 2019), tropomyosin (Lv et al. 2021), β -lactoglobulin (Wu et al. 2018; Xu, Hao, et al. 2019), whey protein (Xu, Hao, et al. 2019) and ovalbumin (Lu et al. 2018).

It was reported that chlorogenic acid noncovalently bound β -lactoglobulin to modify seven (Leu39, Val41, Val43, Leu58, Ile56, Phe105 and Met107) amino acid residues of β -lactoglobulin, resulting in 71.7% reduction of allergenicity in β -lactoglobulin (Xu, Hao, et al. 2019). In addition, the structure of β -lactoglobulin was changed after a non-covalent reaction with chlorogenic acid, resulting from the increase of UV absorption and α -helix, and reduction of hydrophobicity in β -lactoglobulin (Xu, Hao, et al. 2019). Similar results in chlorogenic acid-Ara h 2 complexes, which showed low allergenicity due to the decrease in α -helical and UV absorption induced by the modification of four amino acids (Arg25, Arg49, Ser54, and Gln56) and the formation of hydrogen bonds (Plundrich et al. 2019).

Recently, He et al. (2020) found that chlorogenic acid conjugated with His494 in Ara h 1 in alkaline treatment to decrease UV fluorescence and the α -helix, resulting in the reduction of allergenicity from ELISA and histamine release from human basophil KU812 cells. The structural changes such as the decrease of α -helix were also responsible for the reduction of allergenicity for the radical method, including chlorogenic acid-tropomyosin (Lv et al. 2021), -whey protein (Xu, Hao, et al. 2019), β -lactoglobulin (Wu et al. 2018) and -ovalbumin complexes (Lu et al. 2018). It was observed that chlorogenic acid conjugated with Lys20 and Lys17 in ovalbumin to decrease α -helix and unfolding ovalbumin, resulting in the reduction of allergenicity from ELISA and decrease of histamine release from histamine from cells moles (Lu et al. 2018). Similar results were shown in Lv et al. (2021), who found that the allergic reaction was reduced by chlorogenic acid-tropomyosin complexes under the radical method, resulting from the reduction ($25.1 \pm 0.6\%$) of allergenicity from ELIAS, the reduction (34.8% and 36.7%) of histamine and β -hexosaminidase release from RBL-2H3 cells, and the reduction of IgE, IgG1, serum histamine, mMCP-1, IL-4 and IL-13 and the increase of IFN- γ levels. In general, chlorogenic acid induces the increase of digestibility of Ara h 1 and whey protein by radical method, in turn, digestion complexes didn't generate allergic peptides and showed lower allergenicity than the control (He et al. 2020; Xu, Hao, et al. 2019). Besides, similar to caffeic acid, the allergenicity of apple Mal d 1 was reduced by 54.6% with the increase of chlorogenic acid using enzymatic treatment (polyphenol oxidase) (Kschonsek et al. 2019a).

2.4. Proanthocyanidins

Proanthocyanidins can produce anthocyanins under heating in an acidic medium, and it is multimers composed of different amounts of catechins or epicatechins, in which oligomers (two to pentamers) are the most widely distributed. It was reported that procyanidin C1 in vaccinium fruit significantly bound to Ara h 2 to reduce the allergenicity of Ara h 2 by 37%, resulting from the structural change of Ara h 2 induced by the formation of Ara h 2-procyanidin C1 complexes (Plundrich et al. 2019). For the suppression of allergic reactions, the research focus is mainly on proanthocyanidins rather than their complexes. Ovalbumin-sensitized BALB/c mice showed that intaking of oligomeric proanthocyanidins suppressed allergic reactions, resulting from the inhibition of dendritic cells maturation and reduction of inflammatory cells, ovalbumin-specific serum IgE and Th2 cytokines (IL-4, IL-5 and IL-13) (Li et al. 2017). For proanthocyanidin from grape seed, RAW264.7 cell experiments showed that proanthocyanidins reduced inflammatory reactions by inhibiting MAPK and NF- κ B signal pathways extract, resulting from the reduction of TNF- α , IL-1 β and COX-2 and the increase of IL-10 (Chu et al. 2016). Ovalbumin-sensitized BALB/c mice further observed that it reduced inflammatory response by downregulating the expression of inducible nitric oxide synthase, resulting in the enhancement of IFN- γ level and decrease of total IgE, IL-4, IL-13, the

total inflammatory cell and eosinophil (Zhou et al. 2011). Similar results were shown in sensitization BALB/c mice induced by 2,4-dinitrofluorobenzene, which showed the inhibition of T cell proliferation, the blocking of activation in mitogen-activated protein kinases (MAPK) and NF- κ B signaling pathways, resulting in ameliorating contact-hypersensitivity (Tang et al. 2012). For proanthocyanidin from other plants or food, Chen et al. (2015) observed that proanthocyanidins in the bark of *Metasequoia glyptostroboides* ameliorated allergic contact dermatitis by suppressing T cells activation and Th1/Th17 responses, which due to the reduction of CD69/CD25 of T cells and specific cytokines of Th1/Th17 (IL-2, IFN- γ and IL-17). Katayama et al. (2013) evaluated that apple-derived procyanidins also upregulated IL-12 and TNF- α , and suppressed the antigen presentation, resulting in the reduction of allergic reaction. Therefore, different sources of anthocyanins have slightly different ways to reduce allergic responses.

2.5. Quercetin

Quercetin, also known as quercetin, quercetin, is almost insoluble in water and tastes very bitter, which is widely existed in rutin, quercetin and hyperoside through the major forms of aglycon or glycoside. It was reported that quercetin was successfully used to reduce the allergenicity covalently and noncovalently, including ovalbumin and β -lactoglobulin (Pu et al. 2021; Zhang, Cheng, et al. 2020). Cell assays also evaluated that quercetin reduced allergic responses due to the reduction of Ca^{2+} influx, β -hexosaminidase, histamine, TNF- α , IL-1 β , and IL-4 (Yun et al. 2010).

It was assessed that quercetin noncovalently reacted with β -lactoglobulin at pH 6.0 to result in the formation of 4 hydrogen bonds, the loss of α -helical, and the increase of UV fluorescence in β -lactoglobulin, which induced 40.8% reduction of allergenicity in β -lactoglobulin (Pu et al. 2021). However, the increase of α -helix was responsible for the reduction of allergenicity in noncovalent quercetin-wheat gliadin complexes at pH 5.0 (Wang, Pramod, et al. 2020).

Recently, Zhang, Cheng, et al. (2020) found that covalent quercetin-ovalbumin complexes with alkaline treatment showed the loss of α -helical structures, unfolding of protein structure, resulting in the reduction of allergenicity from ELISA, the decrease of histamine and IL-6 from human basophilic KU812 cells, and the reduction of IgE, IgG, IgG1, histamine, mMCP-1, Th2-related cytokines (IL-13, IL-4 and IL-5), damaged intestines, Fc ϵ RI + and c-kit + expression, and a slight increase in IFN- γ level from BALB/c mice. Similar results were shown in radical quercetin-ovalbumin complexes (Zhang, Cheng, et al. 2020). Besides, the thermal stability of ovalbumin was decreased, with being lower in alkaline quercetin-ovalbumin complexes than radical complexes. By contrast, the antioxidant was increased (Zhang, Cheng, et al. 2020). For example, the DPPH scavenging activity was increased, with being higher in radical quercetin-ovalbumin complexes than alkaline complexes, and ABTS + scavenging activity was increased, with being higher in alkaline quercetin-ovalbumin complexes than radical complexes (Zhang, Cheng, et al. 2020).

2.6. Ferulic acids

Ferulic acid is a kind of phenolic acid widely found in plants such as Asafetida, Angelica, Chuanxiong, Cimicifuga and Jujube Seed, etc, and it is the skeleton of the cell wall by combining with polysaccharides and proteins in the cell wall. It was reported that ferulic acids covalently and non-covalently reduced the allergenicity of peanut (Chung and Champagne 2009) and egg white proteins (Li, Karboune, et al. 2021). Chung and Champagne (2009) treated peanut protein extracts and liquid peanut butter with ferulic acids to result in the reduction of allergenicity due to the reduction of the level of soluble major peanut allergens induced by the formation of insoluble complexes. Li, Karboune, et al. (2021) also found that the allergenicity of lysozyme and ovalbumin were reduced, after covalent reaction with ferulic acid under laccase-catalyzation, and emulsifying and foaming properties were also increased. Ovalbumin-sensitized BALB/c mice furtherly observed that ferulic acid suppressed Th2 immune reaction to reduce the allergic response, resulting in the reduction of OVA-specific IgE, lung chemokine (CCL20, CCL11 and CCL5) and lung cytokine (L-4, IL-5, IL-13, TSLP, IL-25 and IL-33) (Sin Singer Brugiolo et al. 2017). Besides, the reduction of Th2 cytokine (L-4, IL-5, IL-13) reduced with the increase in ferulic acid intake (Sin Singer Brugiolo et al. 2017). (Katayama et al. 2017) also found that ferulic acid and its rutinoides attenuates allergic response in ovalbumin-sensitized BALB/c mice, resulting from the reduction of TGF- β 1, systemic anaphylactic scores, histamine, total IgE and OVA-specific IgE and the increase of TGF- β and total IgA. Besides, ferulic acid rutinoides increased Treg cells (Katayama et al. 2017).

2.7. Rosmarinic acid

Rosmarinic acid is a water-soluble natural phenolic acid compound isolated from lamiaceae, and is an ester of caffeic acid, which is considered as a cumulative defense compound in plants. Although the interaction between rosmarinic acid and allergens has not been reported recently, many mice experiments have proved the function of rosmarinic acid for preventing and treating allergic responses. Costa et al. (2012) found that oral administration of 200 mg/kg rosmarinic acid resulted in the significant reduction of leukocytes/eosinophils, eosinophil peroxidase activity, IL-4 and histopathological changes in *Blomia tropicalis* mite-sensitized A/J mice. Oh et al. (2011) evaluated that rosmarinic acid alleviated immune response in ovalbumin-sensitized mice because of the blockade of inflammatory cell infiltration in the nasal mucosa and of caspase-1 activation in mast cells, which was reflected by the reduction of antigen-specific IgE, histamine, IL-1 β , IL-6, tumor necrosis factor- α , NF- κ B/Rel A and caspase-1 activation. Similar studies also evaluated that the allergic reaction was suppressed due to the inhibition of inflammatory cells and Th2 cytokines (Liang, Xu, et al. 2016), and inhibition of the MAPK and NF- κ B signaling pathways in BALB/c mice (Liang, Nie, et al. 2016).

2.8. Other polyphenols

It was reported that other polyphenols such as theaflavin, delphinidin-3-O-glucoside, phloretin, naringenin, myricetin, kaempferol and tannic acid were also used to reduce the allergenicity, involving β -lactoglobulin and peanut (Chung and Reed 2012; Pu et al. 2021; Xu, Hao, et al. 2019). Xu, Hao, et al. (2019) found that theaflavin and delphinidin-3-O-glucoside noncovalently reacted with β -lactoglobulin to induce 70.5% and 60.8% reduction of allergenicity in β -lactoglobulin, resulting from the masking or destruction of epitopes induced by the structural changes. Many cell and mice assays have also evaluated that the immune response was relieved by oral intaking of polyphenols such as gallic acid (Hamada et al. 2019), ellagic acid (Hamada et al. 2019), curcumin (Liang et al. 2019), and resveratrol (Zhang et al. 2019). Ovalbumin-sensitized mice experiments assessed that curcumin-loaded ovalbumin nanoparticles alleviated immune response, resulting from the reduction of antigen-specific IgG1 and IgE, CD4⁺ T activity, and ovalbumin-sensitized memory B cells (Liang et al. 2019),

3. The mechanism of polyphenols for preventing food allergies

Food allergies are due to the lack of immunologic and clinical tolerance to food allergens (Barni et al. 2020; Renz et al. 2018), and are divided into IgE-mediated and non-IgE-mediated reaction types (Renz et al. 2018; Wang, Pramod, et al. 2020). As shown in Figure 5A, IgE-mediated reactions are approximately responsible for 90% of food allergies (Nie 2011) and cause clinical symptoms within 2 hours after exposure to allergens (Manuyakorn and Tanpowpong 2019). As shown in Figure 5B, polyphenols can react with allergens to form polyphenol-allergen complexes, resulting in the reduction of allergenicity (allergen specific therapies). The structures of allergens are usually changed, especially the loss of α -helix in covalent reactions. Moreover, oral administration of polyphenol-allergen complexes or polyphenols can regulate immune cell function, change the levels of cytokines, suppressing of MAPK, NF- κ B and allergens-presentation pathway and improving intestine function, etc, resulting in the alleviation of allergic reaction (non-allergen specific therapies). For allergen specific therapies, the efficiency of reducing the allergenicity is affected by the reaction condition between allergen and polyphenols (Figure 6). For non-allergen specific therapies, the efficiency of reducing the allergenicity is affected by the polyphenol types, oral time and oral dose (Figure 6).

3.1. Factors influencing the efficiency in allergen specific therapies

3.1.1. Crosslinking types

As shown in Figure 2, the formation of polyphenol-allergens complexes is induced by non-covalent and covalent reactions (alkaline treatment, free-radical grafting and enzymatic method). Many studies showed that the enzymatic method might induce lower allergenicity than alkaline, free-radical

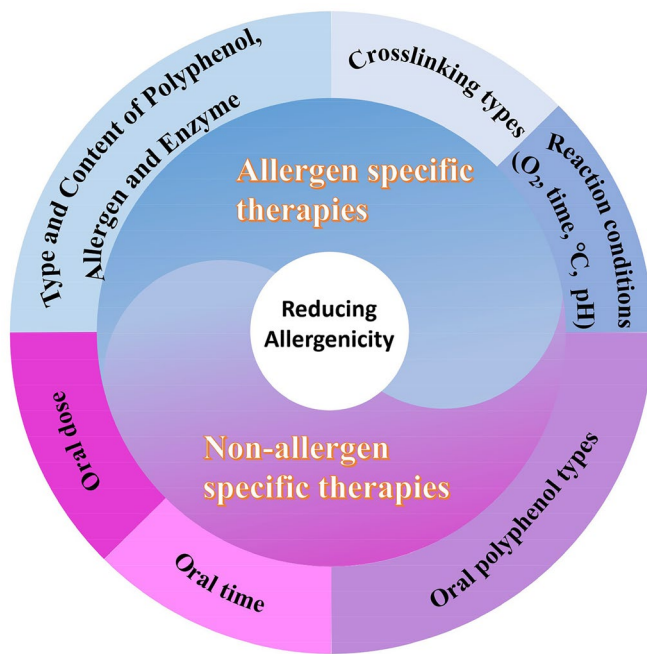


Figure 6. Factors influencing the efficiency of allergen and non-allergen specific therapies for reducing the allergenicity.

grafting and nonvalent reaction (Ahmed et al. 2019; Li, Karboune, et al. 2021; Tian et al. 2019). Enzyme-linked immunosorbent assay (ELISA) and a western blot assay showed that there was lower allergenicity in lactoferrin-EGCG complexes using the enzymatic method (laccase-catalyzed oxidation), followed by alkaline treatment and free-radical grafting (Li, Karboune, et al. 2021). Similar results were shown by He et al. (2019), who found that there was lower allergenicity in radical ovalbumin-EGCG complexes than in alkaline ovalbumin-EGCG complexes, resulting from the greater loss of α -helix induced by the modification of Cys74 and Glu347 in ovalbumin for radical conjugates (Figure 4B). Thus, different crosslinking types induce different efficiency in reducing the allergenicity, which is affected by allergen types. In addition, Plundrich et al. (2017) found that quercetin in the form of aglycon or glycoside bound to peanut protein covalently, while multimeric and monomeric proanthocyanins bound to peanut protein noncovalently in the complexes comprised of peanut proteins and cranberry (*Vaccinium macrocarpon* Ait.) or lowbush blueberry (*Vaccinium angustifolium* Ait.). Therefore, crosslinking types are affected by polyphenol types.

3.1.2. Polyphenol, allergen and enzyme types and their concentration

Recently, Pu et al. (2021) found that the allergenicity of β -lactoglobulin was reduced by 72.6%, 68.4%, 59.7%, 52.3%, 51.4% and 40.8% after noncovalent treatment with EGCG, phloretin, naringenin, myricetin, kaempferol and quercetin, respectively (Figure 3). There was lower allergenicity in radical EGCG- β -lactoglobulin and alkaline EGCG-Ara h 1 complexes than in their corresponding chlorogenic acid complexes, respectively (He et al. 2020; Wu et al. 2018). The efficiency of reducing the allergenicity varies from

polyphenol types, which is due to different degrees of antigenic epitope structural modification induced by different binding sites (He et al. 2020; Pu et al. 2021).

It was reported that the allergenicity of β -lactoglobulin and bovine serum albumin was reduced by 30% and 40% after whey protein non-covalently reacted with caffeic acid, in turn, after the same treatment with EGCG, the allergenicity was reduced by 35% and 60% (Pessato et al. 2018). Similar results were shown by Chung and Champagne (2009), who found that liquid peanut butter showed lower allergenicity than roasted peanut extracts after treatment with caffeic acid, chlorogenic acid and ferulic acid, respectively. Thus, the efficiency of reducing the allergenicity varies from the allergen type. The reason might be the different locations of the epitope varied by different food matrix and allergens (Pi, Sun, et al. 2021; Pi et al. 2019; Pu et al. 2021; Wu et al. 2018), resulting in different modification of epitopes.

As shown in Figure 2D, the different enzyme causes different modification of proteins in the enzymatic method, which may induce different modification of epitopes and reduction of allergenicity. It was proved that there was lower allergenicity in laccase-catalyzed lactoferrin-EGCG complexes than in tyrosinase-catalyzed complexes (Li, Karboune, et al. 2021).

It was reported that the allergenicity of peanut butter extracts was reduced with the increase of tannic acid concentration under pH 7.2 (Chung and Reed 2012). Similar results were shown in EGCG-soybean protein complexes using the alkaline treatment and caffeic acid-tropomyosin complexes using the enzymatic (tyrosinase-catalyzed oxidation) method, which showed the low allergenicity with the increase of EGCG and caffeic acid, respectively (Ahmed et al. 2018; Zhou et al. 2020). Of note, the high additional concentration of polyphenol doesn't suggest low allergenicity in polyphenol-protein complexes (Plundrich et al. 2019). Ahmed et al. (2018) also found that the allergenicity of tropomyosin was reduced with the increase of tyrosinase in the presence of 0.1 M caffeic acid (Figure 4C). Therefore, in the reaction between polyphenols and allergens, the concentration of polyphenol, allergen and enzyme has the optimal addition.

3.1.3. Reaction conditions

Reaction conditions, including oxygen, processing time, temperature and pH, also affect the effects of polyphenols on allergenicity. As shown in Figure 2, the existence of oxygen plays an important role in covalent reactions, which may induce the different modifications of proteins. The increase of processing time may induce more formation of complexes, resulting in the different modifications of proteins. It was proved by Liu et al. (2018), who found that the caffeic acid-ovalbumin (polyphenol oxidase-catalyzed oxidation) complexes increased with the increasing time at the ranges of 1–8 h, and then kept for 12 h and 24 h. The prolonged processing time also may cause different degrees of polyphenols' oxidation and formations of intermediates (Li, Karboune, et al. 2021). pH might induce a different

crosslinking way, which was proved that pH 3, 5, and 7 induced the formation of non-covalent wheat gliadin-quercetin complexes, whereas pH 9.0 caused the formation of covalent complexes (Wang, Pramod, et al. 2020). Moreover, the structural changes and complexes' stability varies from pH (Chung and Reed 2012; Pessato et al. 2018). In addition, pH and temperature also affect enzyme activity to influence the formation of complexes (Liu et al. 2018).

3.2. Factors influencing the efficiency in non-allergen specific therapies

3.2.1. Polyphenol types

Oral administration of different polyphenols can induce different degrees of suppression in allergic reactions by different ways (Table 3) (Lv et al. 2021) found that the release of β -hexosaminidase decreased by 60.4% and 36.7%, the release of histamine reduced by 56.0% and 34.8%, the release of IL-4 reduced by 48.6% and 29.2%, and the release of IL-13 reduced by 49.6% and 26.9% after RBL-2H3 cells were exposed to EGCG-tropomyosin and chlorogenic acid-tropomyosin complexes, respectively. Similar results were shown in the tropomyosin-sensitized BALB/c mice model, which showed that EGCG-tropomyosin complexes induced lower levels of IgE and IgG1 and lower release of histamine, mast-cell protease-1 (mMCP-1), IL-4, and IL-13, and higher production of IFN- γ than EGCG-chlorogenic acid complexes (Lv et al. 2021). These results suggest that oral administration of EGCG suppress more allergic reaction than chlorogenic acid. Moreover, oral administration of different polyphenol types suppresses allergic reactions in different ways, which was proved by Pessato et al. (2019) found that oral application of EGCG-whey protein complexes attenuated allergic response by regulating Th1/Th2 response and increasing populations of CD4⁺ Foxp3⁺ LAP⁻ T and IL-17A⁺CD4⁺ T (Th17), whereas caffeic acid-whey protein complexes reduced allergic response by activating CD4⁺LAP⁺Foxp3⁺ T and IL-17A⁺CD4⁺ T (Th17) cells through whey protein-sensitized C3H/HeJ mice model experiments

3.2.2. Oral time and dose

Recently, Liang, Xu, et al. (2016) found that ovalbumin-sensitized female BALB/c mice with pretreatment of rosmarinic acid showed airway inflammation and hyper-responsiveness, resulting from the inhibition of inflammatory cells and Th2 cytokines, the total IgE and ovalbumin-specific IgE. However, challenging BALB/c mice with ovalbumin and then with rosmarinic acid, Liang, Nie, et al. (2016) found the suppression of allergic reaction due to inhibition of the MAPK and NF- κ B signaling pathways induced by the reduction of inflammatory cells, Th2 cytokines (e.g., IL-4, IL-5 and IL-13), total IgE, ovalbumin-specific IgE and NF- κ B etc. Therefore, regardless of the treatment order, polyphenols may still prevent and treat allergic responses. However, health statue of mice is different, indicating the different bioavailability and biological activity in polyphenols. Costa et al. (2012) further found that oral admiration of 200 mg/

kg rosmarinic acid resulted in the significant reduction of leukocytes/eosinophils, eosinophil peroxidase activity, IL-4 and histopathological changes in blomia tropicalis mite-sensitized A/J mice, compared to oral admiration of 20 mg/kg rosmarinic acid. Thus, oral time and dose play an important role in suppressing allergic reactions. However, the oral dose should be worth noting based on human health and national regulations (Mrduljaš, Krešić, and Bilušić 2017).

4. Discussion

Allergen and non-allergen specific therapies are both successfully used to reduce the allergenicity of foods. For allergen specific therapies, the interaction between polyphenols and proteins induced the structural changes to mask or destroy epitopes, resulting in a reduction in the allergenicity of foods. For non-allergen specific therapies, oral administration of polyphenols suppressed the allergic reaction to reduce the allergenicity of foods by regulating immune cell function (e.g., activation of Th1 and Treg cells and suppression of Th2, eosinophils and basophils cells), changing the levels of cytokines (e.g., reduction of Th2 mediated and increase of Th1 and Treg mediated), suppressing of MAPK, NF- κ B and allergens-presentation pathway and improving intestine function (e.g., increase of diversity of intestinal flora and epithelial barrier), etc.

For allergen specific therapies, the main basis for selecting polyphenols to inhibit allergies is that conjugation of polyphenols can induce structural changes in allergic proteins. Epitopes play important roles in food allergies and are divided into linear and conformational epitopes (He et al. 2019). Linear epitopes are contiguous sequences of amino acid residues determined by the primary structure of the protein, and conformational epitopes are discontinuous sequences, which are contingent in the tertiary or quaternary structure of the protein (Pu et al. 2021). Therefore, to achieve the purpose of reducing the allergenicity (masking and destroying epitopes), structural changes are required in allergic proteins after conjugation with polyphenols. Polyphenols exhibit high conformational flexibility and a high number of hydroxyl groups to make them an interesting molecule for interactions with proteins (Pessato et al. 2018), probably resulting in a great reduction of allergenicity in allergic proteins. It was proved that EGCG may have more phenolic hydroxyl groups than chlorogenic acid, resulting in a greater degree of antigenic epitope structural modification in Ara h 1, which was responsible for the lower allergenicity in Ara h 1-EGCG conjugates prepared by alkali method (He et al. 2020). Additionally, the same polyphenol could have different binding affinities to different proteins depending on the three-dimensional structure of each protein (Pessato et al. 2018). It was reported that β -lactoglobulin and bovine serum albumin are larger and more hydrophobic than α -lactalbumin, which may favor interactions of polyphenol with these two proteins instead of α -lactalbumin (Tássia B. Pessato et al. 2018). Of note, high binding affinity does not mean a high reduction of

Table 2. Effects of polyphenol on the allergenicity, physicochemical and functional properties of food allergens.

Polyphenols type	Treatment type	Allergens	Condition	Allergenicity	Allergic reaction	Physicochemical and functional properties	References
EGCG	Non-covalent conjugation	Whey proteins	pH 3.5 and 7.0, 25 °C, 60 min, molar ratios (1:1) of whey proteins: EGCG	Reduced	–	Thermal stability (especially pH 3.5) ↑	(Pessato et al. 2018)
		Whey proteins	pH 3.5, 25 °C, 60 min, molar ratios (1:1) of whey proteins: EGCG	–	C3H/HeJ mice: IgG2a and mMCP-1L, Populations of CD4 ⁺ Foxp3 ⁺ LAP ⁺ T and IL-17A ⁺ CD4 ⁺ T (Th17)↑, Modulation of Th1/Th2 response	–	(Pessato et al. 2019)
	Covalent conjugation	β-lactoglobulin	pH 6.0, 25 °C, 20 min, molar ratios (1:2) of β-lactoglobulin: EGCG	Reduced by 72.6%	–	–	(Pu et al. 2021)
		Tropomyosin	Radical method: addition of ascorbic acid and H ₂ O ₂ , 4 °C for 48 h	Reduced by 22.1%	RBL-2H3 cells: Release of β-hexosaminidase, histamine, cysteinyl leukotriene, prostaglandin D ₂ , IL-4 and IL-13↓ BALB/c mice: levels of IgE and IgG1↓; release of histamine, mast-cell protease-1 (mMCP-1), IL-4, and IL-13↓; production of IFN-γ↑	–	(Lv et al. 2021)
Caffeic acid	Noncovalent conjugation	Ara h 1	Alkaline method: pH 9.0, 25 °C for 40 h with free exposure	Reduced	KU812 cells: Histamine release↓	Antioxidant activity and digestibility↑, Thermal stability↓	(He et al. 2020)
		β-lactoglobulin	Radical method: addition of ascorbic acid and H ₂ O ₂ , 25 °C for 24 h	Reduced	–	Antioxidant activity and thermal stability↑	(Wu et al. 2018)
		Ovalbumin	Alkaline method: pH 9.0, under atmospheric air, 25 °C for 24 h	Reduced	–	Digestibility, antioxidant activity, emulsifying and foaming properties↑, Thermal stability↓	(He et al. 2019)
		Ovalbumin	Radical method: addition of ascorbic acid and H ₂ O ₂ , 25 °C for 24 h	Reduced	–	Digestibility, antioxidant activity, emulsifying and foaming properties↑, Thermal stability↓	(He et al. 2019)
		Soybean protein	pH 9.0, 25 °C, 24 h, 1, 2, 5 mM EGCG/g soybean protein	Reduced up to 58.48%–81.84% with the increase of EGCG concentrations	–	–	(Zhou et al. 2020)
		Lactoferrin	Enzymatic methods: laccase (60 U/g) was added and reacted for 16 h, pH 4.5	Reduced	–	Antioxidant activities and emulsifying properties↑	(Li, Karboune, et al. 2021)
		Parvalbumin	pH 6.5, 12 h, 37 °C, 0.1 mg/mg parvalbumin	Reduced	RBL-2H3 cells: IgE, IgG1, IgG2a and mMCP-1L, CD4 ⁺ LAP ⁺ Foxp3 ⁺ T and Th17 cell activation↑	Digestibility↓	(Ahmed et al. 2019)
		Parvalbumin	pH 6.5, 12 h, 37 °C, 0.1 mg/mg parvalbumin	Reduced by 7.23%	–	–	(Tian et al. 2019)
		Whey proteins	pH 3.5 and 7.0, 25 °C, 60 min, molar ratios (1:1) of whey proteins: caffeic acid	Reduced	–	Thermal stability (especially pH3.5) ↑	(Pessato et al. 2018)
		Whey proteins	pH 3.5, 25 °C, 60 min, molar ratios (1:1) of whey proteins: caffeic acid	–	C3H/HeJ mice: IgE, IgG1, IgG2a and mMCP-1L, CD4 ⁺ LAP ⁺ Foxp3 ⁺ T and Th17 cell activation↑	–	(Pessato et al. 2019)

(Continued)

Table 2. (Continued)

Polyphenols type	Treatment type	Allergens	Condition	Allergenicity	Allergic reaction	Physicochemical and functional properties	References
Chlorogenic acid	Noncovalent conjugation	Ara h 2 β -lactoglobulin	Molar ratios (1:10) of Ara h 2: Chlorogenic acids Chlorogenic acids solution (5×10^{-3} M) mixed with β -lactoglobulin solution (1×10^{-4} M, pH6.6) Radical method: addition of ascorbic acid and H_2O_2 , 4°C for 48	Reduced by 50% Reduced by 71.7%		– Particle size $\uparrow$	(Plundrich et al. 2019) (Xu, Hao, et al. 2019)
	Covalent conjugation	Tropomyosin		Reduced by 25.1%	RBL-2H3 cells: β -hexosaminidase, histamine, cysteinyl leukotriene, prostaglandin D_2 , IL-4 and IL-13 $\downarrow$ BALB/c mice: IgE and IgG1 $\downarrow$, histamine, mMCP-1, IL-4, and IL-13 $\downarrow$, IFN- γ $\uparrow$	–	(Lv et al. 2021)
		β -lactoglobulin	Radical method: addition of ascorbic acid and H_2O_2 , 25°C for 24h	Reduced		Antioxidant activity and thermal stability $\uparrow$	(Wu et al. 2018)
Quercetin		Ara h 1	pH 9.0, 25°C for 40h with free exposure	Reduced	KU812 cells: Histamine $\downarrow$	Antioxidant activity and digestibility $\uparrow$ Thermal stability $\downarrow$	(He et al. 2020)
		Whey protein	Radical method: addition of ascorbic acid and H_2O_2 , 25°C for 24h	Reduced		Digestibility, solubility, emulsifying, foaming and antioxidant capacity $\downarrow$ Thermal stability $\downarrow$	(Xu, Hao, et al. 2019)
		Ovalbumin	Radical method: addition of ascorbic acid and H_2O_2 , 25°C for 24h	Reduced		Antioxidant activity $\uparrow$ Thermal stability $\downarrow$	(Lu et al. 2018)
		Mal d 1	enzymatic treatment: tyrosinase (10 μ L, 1 mg/mL, 44.78 kat/mg) for 60 min at room temperature pH6.0, 25°C, 25 min, molar ratios (1:5) of β -lactoglobulin: Quercetin	Reduced	–	–	(Kschonsek et al. 2019a)
	Noncovalent conjugation	β -lactoglobulin	pH6.0, 25°C, 25 min, molar ratios (1:5) of β -lactoglobulin: Quercetin	Reduced by 40.8%	–	–	(Pu et al. 2021)
	Covalent conjugation	Ovalbumin	Alkaline method: pH9.0, under atmospheric air, 25°C for 24h	Reduced	KU812 cells: histamine and IL-6 $\downarrow$ BALB/c mice: Anaphylactic shock symptoms $\downarrow$, IgE, IgG, IgG1, histamine and mMCP-1 $\downarrow$, Th2-related cytokines (IL-13, IL-4 and IL-5) $\downarrow$, Th1-related cytokines (IFN- γ) $\uparrow$, Expression of c-kit $^+$	Antioxidant activity $\uparrow$ Thermal stability $\downarrow$	(Zhang, Cheng, et al. 2020)
		Ovalbumin	Radical method: addition of ascorbic acid and H_2O_2 , 25°C for 24h	Reduced			

Table 3. Oral intaking of polyphenols for alleviating allergic reaction based on BALB/c mice model.

Polyphenols	Oral dose (mg/kg)	Results	References
Proanthocyanidin	20, 40 and 60	Airway hyperresponsiveness inflammatory cell and antigen-induced mucus↓ IL-4 and IL-13 (reduced with the increase of dose) ↓ IFN- γ (increased with the increase of dose) ↑ Expression of inducible nitric oxide synthase (iNOS)↓	(Zhou et al. 2011)
	30, 100 and 300	Histopathological changes (reduced with the increase of dose) ↓ Activation and proliferation of T cell in the draining lymph nodes↓ Activation of MAPK and NF- κ B signaling pathways↓	(Tang et al. 2012)
	7.5, 15 and 30	Asthma ↓ Eosinophils, macrophages and lymphocytes ↓ Ovalbumin-specific IgE, IL-4, IL-5 and IL-13 ↓ Expression of CD86, CD40, and MHC-II, proliferation of CD4 ⁺ T cells ↓ These results reduced with the increase of dose	(Li et al. 2017)
Ferulic acid	25, 50 and 100	Inflammatory cell infiltrate, the mucus production and number of eosinophils↓ Number of total cells, eosinophils, lymphocytes, neutrophils and macrophages↓ Levels of ovalbumin-specific IgE. and chemokine (CCL20, CCL11 and CCL5) ↓ Levels of cytokines (thymic stromal lymphopoietin (TSLP), IL-25, IL-33, IL-4, IL-5, and IL-13) ↓	(Sin Singer Brugiolo et al. 2017)
Rosmarinic acid	4	Ovalbumin-specific IgE, histamine, (IL)-1 β , IL-6, tumor necrosis factor- α (TNF- α)↓, Mast cell and eosinophil infiltration↓, NF- κ B/Rel A and caspase-1 activation↓, NF- κ B activation↓	(Oh et al. 2011)
	5, 10 and 20	Numbers of total cells, neutrophil, eosinophil, and lymphocyte (reduced with the increase of dose)↓, Secretion of total IgE, and eotaxin and ovalbumin -specific IgE↓, Th2 cytokine (IL-4, IL-5, IL-13)↓, Histopathological Changes in lungs↓, MAPK and NF- κ B pathway↓, Inflammatory gene (amcase, CCL11, CCR3, Ym2 and E-selectin) expression ↓	(Liang, Xu, et al. 2016)

allergenicity. Although caffeic acid has a higher binding affinity to whey proteins than EGCG in the non-covalent reaction, EGCG showed higher effectiveness than caffeic acid in reducing the allergenicity of β -lactoglobulin and bovine serum albumin because EGCG structure is larger than caffeic acid structure, masking more epitopes of whey proteins (Pessato et al. 2018). Therefore, for allergen specific therapies, the main basis for selecting polyphenols to inhibit allergies is that conjugation of polyphenols can induce structural changes to mask or destroy epitopes. However, the main basis of non-allergen specific therapies is only animal tests or clinical trials, showing the suppression of allergic reactions, although some polyphenols responsible for the regulation of immune cell function can be selected in advance based on previous reports.

For allergen specific therapies, the reaction between polyphenols and allergens involves covalent and non-covalent reactions, and it is affected by temperature, time, pH, types and contents of polyphenol, allergen and enzyme, etc. The reduction of allergenicity varies from these factors. Generally, the non-covalent complexes are unstable for food processing because they are easily affected by temperature, pH, and salt concentration et (Wu et al. 2018). Covalent allergen-polyphenol complexes are more stable than non-covalent complexes because covalent bonds are stronger and more resistant to the factors (e.g., pH) than non-covalent bonds (He et al. 2020; Li, Karboune, et al. 2021), which implies covalent allergen-polyphenol complexes may pass through the gut without being absorbed or causing an allergic response (Chung and Reed 2012). Besides, covalent interactions are irreversible with high affinity, which suggests that it is desirable for reducing the allergenicity in food processing (Li, Karboune, et al. 2021; Zhang, Cheng, et al. 2020). Therefore, covalent interactions (alkaline, free-radical grafting, and enzymatic method) are desirable for reducing the allergenicity in food processing. The covalent complexes using alkaline treatment

may be suitable for food processing because it is stable for temperature and pH and not use too many additives or expensive enzymes. However, the allergenicity might be not completely removed through covalent interactions (Li, Karboune, et al. 2021), probably because the linear epitopes present or the epitopes retain allergenicity (Xu, Hao, et al. 2019). To get a great reduction of allergenicity, the factors (e.g., reaction conditions, types and contents of polyphenol, allergen and enzyme) must be optimized. Of note, due to the different structural characteristics of various polyphenols and allergens, a certain polyphenol may just be the best option to reduce the allergenicity of single allergen, which may vary from crosslinking types in allergen specific therapies.

Although the reduction of allergenicity is evaluated by Western-bolt and ELISA in allergen specific therapies, animal experiments must be required to confirm the hypo-allergenic characteristics, therefore laying the foundation for clinical trials. In contrast, the reduction of allergenicity is assessed by animal experiments in non-allergen specific therapies, directly laying the foundation for clinical trials. Although different sensitized mice experiments are used to evaluate the reduction of allergenicity in non-allergen specific therapies, oral administration of polyphenols may alleviate the allergic reaction induced by multiple food allergens because food allergies are usually IgE-mediated reactions. Therefore, for patients allergic to multiple food allergens, non-allergen specific therapies may be more promising than allergen specific therapies for preventing food allergies.

As shown in Table 2, covalent and non-covalent conjugation of polyphenols reduced the allergenicity of food allergens, while improving functional properties (e.g., digestibility and antioxidant capacity) and physicochemical characteristics (e.g., solubility, emulsifying activity and foaming properties) to ameliorate the acceptability of food matrix. Moreover, for allergen specific therapies, polyphenols can control the

generation of AGE (advanced glycation end products in glycosylation) responsible for the increase of allergenicity in roasted foods (Chung and Champagne 2001; Khalifa et al. 2019; Maleki et al. 2000; Silvan et al. 2011), probably resulting in the reduction of allergenicity of heat-processed foods. In addition, the by-products harmful to human health (e.g., acrylamide) might be reduced by polyphenols during thermal treatment and Maillard reaction (Mildner-Szkudlarz et al. 2019). In contrast to allergen specific therapies, non-allergen specific therapies did not change the quality of the food matrix. As shown in Table 3, oral administration of polyphenols suppressed the allergic reaction, while contributing to the absorption of short-chain fatty acids responsible for the activation of Treg cells (Hirata and Kunisawa 2017; Pi, Yang, Sun, Cui, et al. 2021; Wang et al. 2021), therefore resulting in the reduction of allergenicity of foods. In addition, oral administration of polyphenols also presents great health effects such as anti-obesity, anti-diabetic, and anti-carcinogenic (Aravind et al. 2021; Reis et al. 2020; Zhang, Cheng, et al. 2020). Therefore, allergen and non-allergen specific therapies both have their advantages in the reduction of allergenicity.

5. Conclusion

Polyphenols may have the potential to reduce the allergenicity of foods, while improving food qualities in allergen specific therapies and presenting other great health effects in non-allergen specific therapies. The crosslinking and oral conditions should be furtherly investigated, laying the foundation for producing hypoallergenic foods. More clinical trials should be carried out to explore the feasibility of the related products from various aspects such as hypoallergenic, safety, maximum intake and bioavailability.

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Disclosure statement

Authors declare no conflict of interest.

Authors' contributions

Xiaowen Pi designed the manuscript, performed preliminary data analysis, and wrote the initial review. Professor Yuxue Sun discussed with "Xiaowen Pi" and helped "Xiaowen Pi" to modify manuscripts. Professor Guiming Fu suggested some amendments to the initial review. Professor Jianjun Cheng and Mingruo Guo supervised the project and edited the final version of the manuscript.

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