

REVIEW

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The anti-allergic potential of tea: a review of its components, mechanisms and risks

Qing-Sheng Li,^{†a,b} Ying-Qi Wang,^{†a} Yue-Rong Liang^a and Jian-Liang Lu^{id} ^{*a}

Allergy is an immune-mediated disease with increasing prevalence worldwide. Regular treatment with glucocorticoids and antihistamine drugs for allergy patients is palliative rather than permanent. Daily use of dietary anti-allergic natural products is a superior way to prevent allergy and alleviate the threat. Tea, as a health-promoting beverage, has multiple compounds with immunomodulatory ability. Persuasive evidence has shown the anti-allergic ability of tea against asthma, food allergy, atopic dermatitis and anaphylaxis. Recent advances in potential anti-allergic ability of tea and anti-allergic compounds in tea have been reviewed in this paper. Tea exerts its anti-allergic effect mainly by reducing IgE and histamine levels, decreasing FcεRI expression, regulating the balance of Th1/Th2/Th17/Treg cells and inhibiting related transcription factors. Further research perspectives are also discussed.

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1. Introduction

Allergy is an immune-mediated disease with high morbidity in the world and affects more than 20% of the population of western countries.¹ As one of the four types of hypersensitivity reactions, allergy is formally called type I (or immediate) hypersensitivity mainly mediated by the interaction of immunoglobulin E (IgE) with a sudden release of mast cell- and basophil-derived mediators into the circulatory system.² Based on allergen types, allergies can be classified into several types such as food allergies, drug allergies and insect allergies. In addition to ordinary allergies, a severe hypersensitivity named anaphylaxis is systemic and life threatening,³ causing respiratory symptoms, dizziness, unconsciousness, and gastrointestinal symptoms.⁴ The problem of anaphylaxis affects 1.21%–15.04% of the United States population with 1500 deaths per year, and calculated 0.3% of the population of Europe.^{5–7} Thus, allergy, as a worldwide public health problem, needs fundamental research studies (mechanism discovery and drug development), clinical therapeutics (proper diagnosis and immediate treatment) and preventive measures (immune regulation and functional edible product exploitation). Although allergic reactions can be clinically diagnosed and medicated effectively at present, people have misgivings about the side effects of allergy drugs and mounting medical expenses. There is also a demand for the development of functional foods to prevent allergies. Moreover, studies of certain

crops, fruits and herbals have shown the potential of natural products to prevent and inhibit allergies.

Tea, made from the tender shoots of the *Camellia sinensis*, is a worldwide-consumed herbal beverage with various pharmacological functions such as antioxidant,⁸ antidiabetic,⁹ anti-tumor,¹⁰ and anti-β-amyloid.¹¹ In addition, tea also has anti-allergic ability because of its multiple bioactive compounds such as polyphenols, polysaccharides and saponins. Recent evidence has shown that leaves harvested from special tea cultivars with high content of methylated catechins have better effects in alleviating allergic symptoms. However, more fundamental research is still needed to prove the effects of tea on the prevention and treatment against allergy, and the anti-allergic bioactive compounds of tea need further characterization. This review summarizes recent research on the anti-allergic effects of tea and tea components, including *in vivo* and *in vitro* studies, and offers directions for further study.

2. Phases of the allergic response modulated by tea

The words ‘allergy’ and ‘hypersensitivity’ are similar and inaccurately used occasionally. In 1960s, Gell and Coombs put forward the most recognized classification of hypersensitivity with four types based on the immunologic mechanisms related to the symptoms in organisms.¹² After entering the 21st century, a new hypersensitivity type was appended in the classification to represent the immune disorders when the body deals with a class of infectious agents.¹³ Regardless of the two classification methods, we generally recognize ‘allergy’ as type I hypersensitivity with the most clear-cut immuno-

^aTea Research Institute, Zhejiang University, China. E-mail: jllyu@zju.edu.cn;
Tel: +86 571 88982704

^bInstitute of Sericulture and Tea, Zhejiang Academy of Agricultural Sciences, China

[†]These authors contributed equally to this work.

pathological correlation, which is an IgE mediated allergic reaction. This allergic reaction comprises three phases: (1) inductive phase. An allergen enters the immune system and is taken up by antigen-presenting cells, the CD4 + T-cells differentiate into T-helper type 2 (Th2) cells and release cytokines. Due to the CD40L-CD40 interaction, allergen-specific IgE is secreted into the serum. Then, the Fc portion of the specific IgE binds to the high-affinity receptor FcεRI that is distributed on the surface of the mast cells and basophils. (2) Stimulation phase. Since the immune system re-exposes to the same allergen, the bound IgE will cross-link to the allergen. (3) Effector phase. Mast cells and basophils will be activated after the stimulation, and a robust secretion of inflammatory mediators into the serum triggers symptoms involving the skin, respiratory system or circulatory system.¹⁴ Modern therapeutic approaches towards allergy focus on modulating the sensitization in the inductive phase such as prevention, or the impact on allergic mediators released in the effector phase, thus alleviating allergy symptoms as treatment.^{15,16}

Tea, as a natural herbal beverage, exerts anti-allergic effects not only in allergy prevention, but also in allergy treatment. It has been proved that tea has the anti-allergic ability against food allergy, respiratory allergy, atopic dermatitis and anaphylaxis. Generally, the down-regulated ratios of IgE and histamine are main indexes to evaluate the anti-allergic ability of certain compounds such as polyphenols, saponins and polysaccharides. The essential allergy phases interfered with by compounds in tea are postulated as follows (Fig. 1): (1) inhibiting allergen-IgE complex formation; (2) reducing FcεRI expression or allergen-IgE complex binding to FcεRI; (3) balan-

cing Th1/Th2/Th17/Treg systems; and (4) inhibiting cytokine release of Th2 cells.^{17–19} Among the four aspects, tea modulates the sensitization of the human body toward allergens through the former two ways, whilst the latter two means help the human body to alleviate allergy symptoms.

3. Anti-allergic compounds in tea

3.1. Polyphenols

Polyphenols in tea can mainly be classified into four types including catechins, flavone/flavonols, anthocyanidins/leucoanthocyanidin, and phenolic acids/depsides. The anti-allergic ability of tea is highly related with the compositions of catechins and flavonols, due to their predominant contents and physicochemical properties. Catechins are the most abundant polyphenols present in tea with four major components including (–)-epigallocatechingallate (EGCG), (–)-epicatechingallate (ECG), (–)-epigallocatechin (EGC), and (–)-epicatechin (EC).²⁰ Among the catechin derivatives, methylated catechins such as (–)-epigallocatechin-3-O-(3-O-methyl) gallate (EGCG3" Me) and (–)-epigallocatechin-3-O-(4-O-methyl) gallate (EGCG4" Me) should be emphasized for their superior anti-allergic ability. Meanwhile, quercetin and kaempferol are mainly discussed in this paper as main flavonols in tea. The chemical structures of the major polyphenols in tea are shown in Fig. 2.

3.1.1. Catechins. Catechins, particularly EGCG, have strong evidence to prove their anti-allergic ability in food allergy, allergic rhinitis and passive cutaneous anaphylaxis (PCA). In an ovalbumin (OVA) sensitized murine model of food allergy

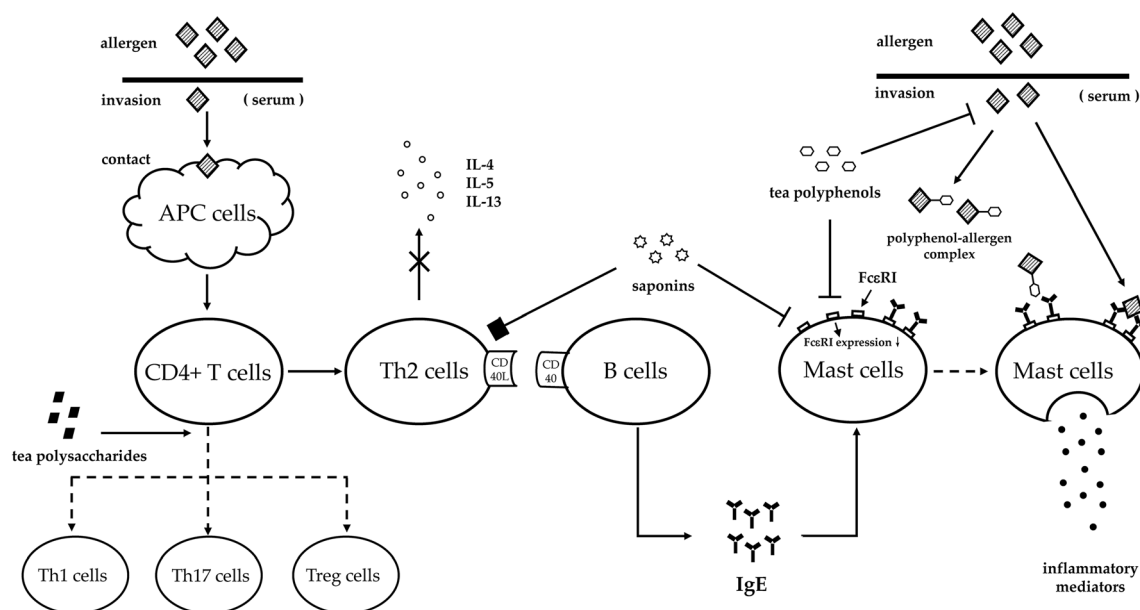


Fig. 1 The allergy phases interfered with by compounds in tea. Allergens invade the circulatory system of the human body and are captured by the APC cells. Then, CD4 + T cells differentiate into Th2 cells and release cytokines as IL-4, IL-5 and IL-13. Polysaccharides enhance CD4 + T cells differentiating into Th1/Th17/Treg cells to balance the T cell system. Saponins can inhibit Th2 cells from releasing cytokines (the mechanism needs further study). In addition, saponins and polyphenols can reduce the expression of FcεRI. Besides, polyphenols also can bind allergen directly to decrease its binding rate to mast cells, thus reducing the release of inflammatory mediators into the circulatory system eventually.

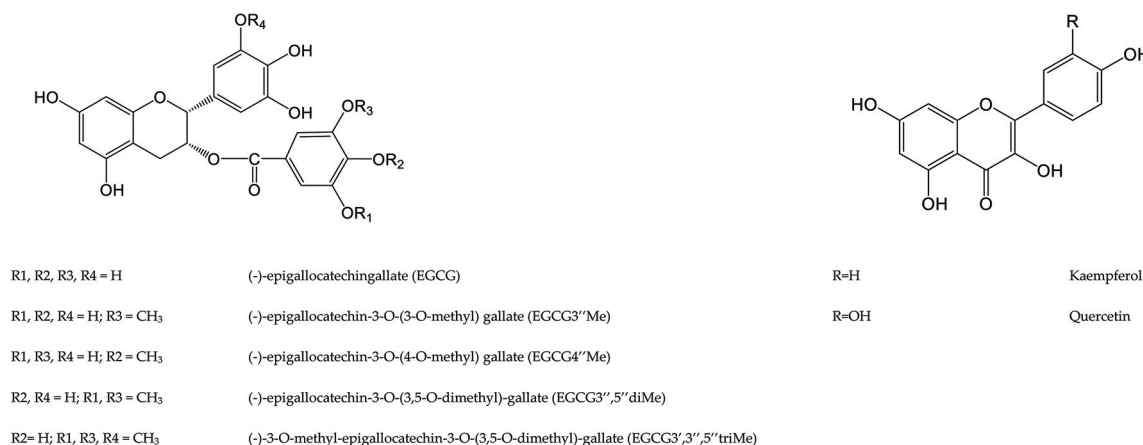


Fig. 2 The chemical structures of the major anti-allergic polyphenols in tea.

or allergic rhinitis, oral administration of catechins could modulate allergy symptoms by decreasing IgE and histamine contents in a dose-dependent manner.^{21,22} Meanwhile, the cytokine contents and transcriptional levels of interleukin (IL)-1 β , IL-4, and IL6 were reduced *in vivo*.^{22,23} With the abilities to modulate antibody and autacid contents in serum, EGCG could also combine with whey allergenic proteins to attenuate their oral sensitization, thus reducing whey allergy risks eventually.²⁴

Methylated catechins, a group of catechin derivatives, have drawn attention from researchers for their superior anti-allergic ability to regular catechins.^{25–27} Combined with the fact that methylated catechins can be detected as metabolites in human serum and urine after tea or catechin consumption, methylated catechins may contribute to the anti-allergic ability of tea more directly.^{28–30} Drinking tea with methylated catechins for a long term can significantly alleviate allergy symptoms, such as throat pain, nose-blowing and tears.³¹ Class I O-methyltransferase (CsOMT) isolated from tea cultivars can synthesize EGCG3'Me, EGCG4'Me, (–)-epigallocatechin-3-O-(3,5-O-dimethyl)-gallate (EGCG3'',5''diMe), and (–)-3-O-methyl-epigallocatechin-3-O-(3,5-O-dimethyl)-gallate (EGCG3',3'',5''triMe) from EGCG.^{32,33} Among these methylated catechins, EGCG3'Me and EGCG4'Me, which are the major methylated catechins, have been found in multiple tea cultivars from Japan and China.^{34,35} The average content of EGCG3'Me in regular tea cultivar is less than 0.45%, while it could reach 2.0% in specific cultivars such as 'Benifuuki'.^{35–37} However, EGCG3'Me can exhibit better anti-allergic effects even at low concentration because of its high bioavailability and bioactivity. The absolute quantity of EGCG3'Me is only one fifth of that of EGCG in 'Benifuuki', but the anti-allergic effect of EGCG3'Me is higher than that of EGCG.^{38–40} Because of the high bioavailability of the EGCG3'Me, it could significantly relieve allergy symptoms by inhibiting mast cell activation, histamine release and cytokine production.^{39,41} One of the underlying causes of high efficiency of methylated catechins may be that the methyl groups added onto regular catechins increase

their lipophilicity, thus enhancing the absorptivity of catechins.

3.1.2. Flavonols. The anti-allergic ability of flavonols has been well proved *in vivo* and *in vitro*.^{42,43} Among the common flavonols in plants, quercetin and kaempferol are the most abundant aglycones in tea and they usually exist in their glycoside forms.⁴⁴ Quercetin and kaempferol can not only reduce the release of IgE, β -hexosaminidase and histamine from basophils and mast cells, but also inhibit the Fc ϵ RI receptor *via* reducing the phosphorylation of different kinases such as spleen tyrosine kinase (Syk), protein kinase C (PKC), and p38 mitogen-activated protein kinase (MAPK).^{45,46}

Quercetin has anti-allergic abilities in inhibiting mast cell activation, histamine release, and eosinophilic inflammation. Quercetin can stabilize the membrane of mast cell, inhibit the release of histamine, leukotrienes (LTs), prostaglandin D2 (PGD2), and granulocyte macrophage-colony stimulating factor (GM-CSF).⁴⁷ Meanwhile, quercetin can down-regulate the gene expression and decrease the production of the relevant cytokines such as tumor necrosis factor (TNF)- α , IL-1 β , IL-6, and IL-8 *in vitro* directly or collaboratively.⁴⁸ Moreover, quercetin has better function than the typical mast cell stabilizer named cromolyn in inhibiting IL-8 and TNF- α release, which offers a strong evidence for preventing allergy by a natural product.⁴⁹ Essential mechanisms of the action may be related to the fact that quercetin can decrease the cytosolic calcium level, inhibit the NF- κ B activation and the MAPK activity.^{50,51} Besides, quercetin can also inhibit the synthesis of downstream enzymes such as tryptase, histidine decarboxylase, phospholipase A₂ and eosinophil peroxidase.^{52–54} Briefly, quercetin is an inhibitor of human mast cell activation *via* the inhibition of Ca²⁺ influx and the prevention of histamine, LTs and PGs release.

Orally administration with kaempferol is effective to alleviate symptoms of OVA-induced murine model of food allergy and allergic asthma. As far as food allergy prevention, kaempferol can reduce diarrhea rate and anaphylaxis risk with decreased levels of IL-4, IL-5, and IL-13.⁵⁵ In respiratory allergy, kaempferol can alleviate the infiltration of eosinophils

and mast cells through inhibiting the anti- α -smooth muscle actin expression in the airways and blocking their degranulation in the lung tissue, as well as reducing IgE, histamine and IL-4 levels, and increasing interferon- γ (IFN- γ) content.^{56,57} A cytokine named IL-32 has been observed above normal level in the nasal mucosa of AR patients, and it significantly elevates the downstream thymic stromal lymphopoietin (TSLP) production in monocytes. Treating with kaempferol to murine model decreases the IL-32 and TSLP levels, thus inhibiting the TSLP-driven Th2 inflammatory cell infiltration, cytokine secretion, and IgE production.⁵⁸ Hemeoxygenase (HO)-1 is generally known as a rate-limiting enzyme in degradation of heme, while it also has the ability to transfect mast cells to decrease degranulation.⁵⁹ Kaempferol can improve HO-1 expression to inhibit histamine and β -hexosaminidase release.⁶⁰ Those evidences suggest kaempferol has anti-allergic abilities in relaxing airway muscles and inhibiting histamine release.

3.1.3. Theaflavins. Theaflavins, enzymatically oxidized catechins during the fermentation process, are important compounds in black tea.⁶¹ Theaflavins exhibit preventive effects against type IV hypersensitivity when they are percutaneously or orally administered to male ICR mice.⁶² Feeding theaflavins to ICR mice can inhibit the increase of IL-12 and TNF- α in macrophages, which implied that the anti-allergic mechanisms of theaflavins might involve reducing cytokine release in allergic mice. Studies of theanine and theaflavins in preventing and treating allergy are few, yet the existing results of histology, gene/protein expression and symptom differentiations *in vivo* can prove their anti-allergic ability theoretically.

3.2. Saponins

Tea saponins are natural non-ionic surfactants that are present in tea leaves, stem, flowers, and mostly in seeds.^{63–65} The content of saponins reaches more than 10%, up to 19.57%, of the dry weight in tea seeds.^{66,67} Saponins are widely recognized as constituents of cleaning products and are used in soil remediation.^{68,69} Besides, saponins have been also proved to show anti-allergic potential against asthma, PCA, atopic dermatitis and systemic anaphylactic shock.^{70–72} Saponins extracted from tea leaves can inhibit bronchospasm in a Guinea pig model and PCA reaction in a rat model in a dose-dependent manner, along with the inhibition of LT D₄ release.⁷⁰ Oral administration of saponins to mice sensitized with 2,4-dinitrochlorobenzene can reduce the thickness of the epidermis/dermis and dermal infiltration of inflammatory cells and mast cells in the ears.⁷¹ In addition, saponins can inhibit the β -hexosaminidase activity and histamine release, and block the production of TNF- α , IFN- γ , IL-4, IL-5, IL-6 and IL-13 *in vivo/in vitro*.^{71,73–75}

3.3. Polysaccharides

Polysaccharides, important bioactive components of tea, are nonstarch protein-bound acidic polysaccharides.^{76,77} Tea polysaccharides can improve immunity by enhancing the activity of splenocytes or by decreasing the level of pro-inflammatory cytokines.^{78,79} Though little definite evidence can prove polysac-

charides from tea have the ability to prevent allergy, polysaccharides from other species show the anti-allergic ability as circumstantial evidence to imply their functions in tea. The current studies have shown that polysaccharides have the ability to alleviate the symptoms of allergic rhinitis, food allergy and atopic dermatitis directly or collaboratively. Oral administration of 180 mg of cassis polysaccharides twice a day to Japanese cedar pollinosis patients, suffering from a type of allergic rhinitis, can moderate their symptoms of sneezing, itchy nose, itchy eye and watery eye.⁸⁰ Treatment of OVA induced rats with allergic rhinitis with 3, 9 and 27 mg kg⁻¹ *Cryptoporus* polysaccharides decreased the sneezing rate of 27.4%, 38.4%, and 44.3%, and nasal rubbing rate of 27.5%, 34.9%, and 47.7% compared with the model group, respectively.⁸¹ Meanwhile, polysaccharides show their anti-food allergic ability in a mouse model. A daily dose of 5 mg/mouse of polysaccharides from *Gracilaria lemaneiformis* can decrease the anaphylactic response and diarrhea rates moderately, and diminish the increase of histamine and mast cell proteinase concentrations.⁸² In addition, polysaccharides can alleviate intestinal villi injury in a food-allergy mouse model by decreasing B cell and mast cell populations, IgE, histamine, mast cell protease-1, IL-4, and increased IFN- γ level in serum.⁸³ However, polysaccharides alleviate atopic dermatitis symptoms with diverse causes. Polysaccharides can significantly increase the water content of the stratum corneum and decrease the epidermal thickness of skin besides Th2 system regulation.^{84,85} Oral treatments with polysaccharides can suppress allergy symptoms through the induction of galectin-9 *in vivo*, which can recognize β -galactoside and prevent IgE binding to mast cells.⁸⁶

3.4. Other potential anti-allergic components

Besides polyphenols, polysaccharides and saponins, another bioactive compound in tea named theanine also has anti-allergic potential. Intragastric administration of L-theanine to OVA induced murine models of asthma will inhibit mucus production and inflammatory cell infiltration with significant decrease of IgE, monocyte chemoattractant protein-1 (MCP-1), IL-4, IL-5, IL-13 and TNF- α .⁸⁷ Similar to the inhibition results of L-theanine to asthma, theanine can inhibit systemic anaphylactic shock and ear swelling responses of ICR mice by oral administration or injection. Theanine inhibits not only histamine release from mast cells, but also TNF- α , IL-1 β , IL-6, and IL-8 secretions by blocking the activation of NF- κ B and receptor interacting protein-2/caspase-1.⁸⁸

4. Anti-allergic mechanisms of tea

4.1. General

The basic indexes to evaluate the anti-allergic properties of tea or natural products are the release content of IgE, histamine and β -hexosaminidase in serum. However, these indexes are the results of anti-allergic activity through different mechanisms such as inhibition of Fc ϵ RI expression, protein kinases and transcription factor activities, control of mediators and

balance of Th1/Th2/Th17/Treg cells. Consequently, tea and the compounds in tea have a deep impact on several immune cells and immune mechanisms which are important in the allergic processes (Table 1).

4.2. Inhibiting IgE receptor FcεRI

The mechanisms underlying alleviation of allergy symptoms, particularly inhibition of histamine release by catechins, are blocking the production of protein tyrosine kinases (PTK) and reduction of FcεRI expression. FcεRI is an IgE high-affinity receptor which is distributed on the surface of mast cells and basophils with a tetrameric structure comprising one α-chain, one β-chain, and two γ-chains.⁸⁹ The γ chains of FcεRI are critical for both membrane orientations of the whole receptor and signal transduction, while β chain can amplify the γ subunit-generated signals by associating constitutively with PTK and stabilize the receptor. The down-regulated expression of FcεRI can reduce histamine release from mast cells and basophils. EGCG3''Me administration can reduce the transcript levels of FcεRI α and γ.¹⁸ EGCG and methylated EGCG can regulate basophils or mast cells through a cell-surface receptor named 67 kDa laminin receptor (67LR). Down-regulated FcεRI expression by EGCG3''Me is due to the 67LR-mediated inhibition of myosin II regulatory light chain (MRLC) and extracellular signal-regulated kinase1/2 (ERK1/2) phosphorylation.⁹⁰ It has been proved that EGCG can bind to plasma membrane microdomains as lipid rafts, and inhibit the phosphorylation of ERK1/2, and consequently suppress the expression of FcεRI,^{91–93} whilst EGCG3''Me and EGCG4''Me can inhibit PTK resulting in the decrease of histamine release.⁹⁴ Moreover, a derivative from gallic acid (GA), which is a part of EGCG, is able to directly bind to the α-chain of FcεRI, thus reducing the possibility of IgE binding to FcεRI.⁹⁵ These results indicate that catechins and methylated catechins reduce histamine release through two phases, but all relate to FcεRI.

4.3. Balancing Th1/Th2/Th17/Treg systems

T-cells play crucial roles in the balance of adaptive immunity. Active T-cells differentiated from naïve T-cells can be classified into four main types namely Th1, Th2, Th17 and Treg cells.⁹⁶ While T-cell response will be a Th2-dominated immune response in allergic patients, the chain reaction is that cytokine IL-4 induces the differentiation of naïve T-cells into Th2 cells, which produce more IL-4, IL-5 and IL-13, and eventually IgE production and eosinophil activation are stimulated.² Balancing the T-cell model by decreasing Th2 cells is an appropriate way for alleviating allergy symptoms. The up-regulation of Th1, Th17 and Treg are immune responses to the reduction of CD4+ T-cell differentiation into Th2 cells. EGCG can increase Th1, Th17 and Treg cell population, along with their released cytokines.^{24,97} Quercetin can alter Th1/Th2 polarization *via* suppression of GATA-3 and increase of *T-bet* expression, and then reduce the increased levels of IL-4 and elevate the IFN-γ level in serum, thus inducing the CD4+ T-cell differentiation into Th1 cells.⁹⁸ Polysaccharides are able to suppress Th2 cell polarization, and reduce IgE, histamine and

Th2 cytokines including IL-2, IL-4, IL-5 and IL-13 levels in serum.^{82,85,99} In the meantime, polysaccharides can amplify IL-12 production to enhance antigen-primed naïve T cell transformation into Th1 cells with an increase of IFN-γ levels, and eventually modulate the imbalance of the Th1/Th2 immune response.^{100–102} Explaining that polysaccharides regulate allergy only according to the Th1/Th2 model is simplistic; it can also enhance the levels of IL-10, FOXP3, and transforming growth factor-β, which leads to the suppression of Th2 responses by the Treg cells.⁸³

4.4 Activity inhibition of protein kinases and transcription factors

Protein kinases are involved in signal transduction during cell activation in allergic reaction. Compounds in tea can modulate protein kinases by the inhibition of transcription factors, such as NF-κB and T-bet. NF-κB is translocated from the cytoplasm to the nucleus where it induces the expression of multiple immune related genes. In addition, NF-κB and STAT-1 are thought to play pivotal roles in the regulation of inflammatory responses as TNF-α and IFN-γ.^{103,104} Saponins can inhibit TNF-α, IFN-γ and IL-4 production by attenuating the activation of NF-κB and STAT-1.^{71,74} Moreover, saponins can inhibit tyrosine phosphorylation of Syk resulting in the decrease of the expression of FcεRI.^{74,75}

Flavonoids can regulate master regulatory transcription factors for Th2 cytokines such as GATA-3, and signal transducer and activator of transcription 6 (STAT-6).^{105,106} Quercetin can reduce the eosinophil peroxidase activity and alter Th1/Th2 polarization *via* suppression of GATA-3 and increasing *T-bet* expression, and then decrease the IL-4 level and increase the IFN-γ level.⁹⁸ Kaempferol can suppress LPS-induced *eotaxin-1* protein expression, which might be mediated likely *via* JAK2 signaling, and it can also attenuate the TNF-α induced expression of epithelial ICAM-1 and eosinophil integrin b2, and MCP-1 transcription encumbering eosinophil-epithelial cell interactions.⁵⁶ Moreover, polysaccharides can suppress basophil cells *via* suppression of MAPK and decreasing eotaxin expression.^{81,82}

5. Allergy caused by tea

In the previous sections of this paper, we totally focused on the ability of tea on attenuating the immune system and anti-allergies. However, some people might be allergic to tea in several medical cases. People who worked in tea manufacturing factories might have the possibility to develop green tea-induced asthma, particularly the workers who had a long term exposure history to tea powders.^{107,108} However, allergic respiratory symptoms caused by tea powders or its extract powders are rarely reported. Interestingly, Otera *et al.* reported a case of hypersensitivity pneumonitis caused by inhalation of catechin powders.¹⁰⁹ The essential allergens of those cases may be dust, fluff or specks. Besides, a young woman had oropharyngeal and respiratory symptoms after drinking green tea, who could

Table 1 Summarization of compounds in tea and their anti-allergic effects with mechanisms

Compounds		Methods	Models	Effects	Mechanisms	Ref.
Polyphenols (18%–36%)	Catechins (12%–24%)	<i>In vivo</i>	BALB/c mice	Inhibit IgE, IgG1 and mMCP-1 release; reduce IL-13 and IL-12a expressions	Reduce T-bet and GATA-3 expressions	21
			ddY mice	Inhibit IgE, histamine, IL-1 β , IL-4, and IL-6 release	Inhibit the mRNA and protein expressions of COX-2	22
				Inhibit the release of IL-4 from APC and Th2 cells; inhibit the release of IgE from B cells		23
			C3H/HeJ mice	Reduce IgG2a and mMCP-1 levels	Balance the Th1/Th2 system; increase Th17 cell populations	24
			ICR mice	Reduce histamine and IL-4 levels	Bind to Fc ϵ RI	94
		<i>In vitro</i>	KU812 cells		Reduce the expressions of α -chain and γ -chains of Fc ϵ RI	17
			RBL-2H3 cells	Reduce mast cell degranulation	Inhibit the phosphorylation of Lyn, Syk, Akt and NF- κ B	94
	Methylated catechins (0.45%–2%)	Epidemiology		Alleviate symptoms of throat pain, nose blowing, itchy eyes and tears		27, 31 and 39
		<i>In vivo</i>	ddY mice	Inhibit IgE, IL-4 and IL-10 release		23
				Inhibit histamine and LT release; inhibit cytokine production and secretion	Inhibit Lyn, Syk, and Bruton's tyrosine kinase	93
		<i>In vitro</i>	KU812 cells		Reduce the expressions of α -chain and γ -chains of Fc ϵ RI	18
				Associate lipid rafts to reduce Fc ϵ RI expression	Inhibit MRLC and ERK1/2 phosphorylation	89–92
		<i>in vivo</i>	BALB/c mice	Reduce IL-4 production; increase IFN- γ secretion	Reduce T-bet and GATA-3 expressions	97
				Inhibit histamine, PLA2, and EPO productions; inhibit the recruitment of leukocytes		52 and 53
		<i>In vitro</i>	HMC-1 cells	Reduces TNF- α , IL-1 β , IL-6, and IL-8 levels	Inhibits NF- κ B and MAPK activation	51
			LAD2 cells	Reduces histamine, LT, PGD2, IL-6, IL-8 and TNF levels	Inhibits cytosolic calcium increase and NF- κ B activation	49
			HCM cells	Inhibits histamine, LT, PGD2, and granulocyte release	Inhibits Ca ²⁺ influx and PKC activation	47
			Caco-2 cells	Suppresses TNF- α production and IL-8 expression; reduce β -hexosaminidase level		48
	Kaempferol (0.16%–0.35%)	<i>In vivo</i>	BALB/c mice	Reduces IgE, histamine, IL-4, IL-32 and TSLP levels	Reduces MIP-2, ICAM-1 and COX-2 levels	58
				Blunt eosinophil deposition and degranulation	Disturbs the NF- κ B signaling pathway	56
				Reduces IL-4, IL-5, and IL-13 levels		55
				Reduces IL-32, IL-8 and caspase-1 levels		56
		<i>In vitro</i>	RBL-2H3 cells	Reduces anti- α -smooth muscle actin expression; reduce PGD2 and PGF2 α levels		57
				Reduces histamine and β -hexosaminidase release	Increases HO-1 expression	60
				Inhibits LT C ₄ release		68
				Reduces IgE and TARC levels; reduce TARC, TNF- α , IFN- γ , IL-4, IL-5, and IL-13 expressions	Suppresses NF- κ B and STAT-1; induce HO-1 expression	69
Saponins (10%–19.57%)		<i>In vivo</i>	Guinea pigs Nc/Nga mice	Inhibit β -hexosaminidase release		61 and 71
				Inhibit β -hexosaminidase and histamine release; inhibit IL-4 and IL-6 expressions	Reduce the intracellular Ca ²⁺ level; reduce the expression of α -chain of Fc ϵ RI	73
		<i>In vitro</i>	RBL-2H3 cells	Reduce β -hexosaminidase and histamine release; reduce IL-4 and IFN- γ levels	Suppress Syk, Akt and MAP phosphorylation	72

Table 1 (Contd.)

Compounds	Methods	Models	Effects	Mechanisms	Ref.
Polysaccharides (0.4%–2.63%)	Epidemiology		Alleviate symptoms of sneezing, itchy nose, itchy eyes and watery eyes		78
	<i>In vivo</i>	Sprague-Dawley rats	Decrease the sneezing and nasal rubbing rate; decrease the eotaxin expression		79
		BALB/c mice	Reduce IL-4 and IL-13 levels; increase the TGF- β level	Suppress Th2 cell polarization; promote Treg cells; decrease GATA-3 expression; increase FOXP3 expression	80
			Reduce IgE, histamine, mast cell protease-1 and IL-4 levels; increase IFN- γ , IL-10 and TGF- β levels	Promote Treg cells	81
			Reduce histamine and IgE levels; reduce IL-4, IL-5 and IL-13 expressions; increase IFN- γ and IL-10 expressions	Inhibit the JNK and JAK2 signaling pathways	99
			Reduce IgE level; decrease IL-4 and IL-17A expressions		83
			Increase galectin-9 expression		84
		ICR mice	Reduce histamine, IgE and TNF- α levels		98
	<i>In vitro</i>	KU812 cells	Inhibit cell activation	Suppress the MAPK signaling pathway	80
		RBL-2H3 cells	Inhibit cell degranulation; reduce histamine, IL-4 and TNF- α levels		80
		Cells from BALB/c mice	Increase IFN- γ production; enhance Th1 cell differentiation; reduce IL-4 and IgE levels		100 and 101

Note: The percentages in the brackets are the concentration ranges of selected compounds in dry tea leaves or seeds.

tolerate tea beverage before.¹¹⁰ In 2014, a 43-year-old firefighter had sudden flushing and slight facial itching followed by dry mouth and progressive dizziness after drinking a green tea infusion. Moreover, he experienced the same symptoms, as well as syncope and loss of vesical sphincter control after eating a green tea ice cream the next year.¹¹¹ According to the SDS-PAGE and Western-blot results, the authors considered that an IgE-mediated hypersensitivity reaction to a 70 kDa protein from green tea extract might have caused the firefighter to suffer from such anaphylaxis. Nevertheless, the patient had positive test result of a specific black tea rather than regular black tea. The possibility of cross-reactivity dominates this case. Based on above rare cases, we cannot guarantee that tea is not a food allergen, but its risk is minimal.

6. Further suggestions

6.1 Systematic epidemiological investigation

The current epidemiological studies of tea in preventing allergy and alleviating allergy symptoms are insufficiency with small sample scale. Most of them were performed in Japan to measure the anti-allergic ability of tea in reducing the symptoms of Japanese cedar pollinosis which is a regional respiratory allergy. Systematic epidemiological investigation in mul-

tle regions on various types of allergy, particularly in high incidence areas, should be comprehensively performed to offer a preference for tea in anti-allergy.

6.2 Binding sites and interaction effects of compounds

Recent research studies of natural products in preventing allergies usually focused on comparison and summarization of the anti-allergic functions of different products or their components. Thus, we have found plenty of products and compounds with anti-allergic potential. However, the AUCs and metabolites of such components in the circulatory system have been rarely investigated, let alone the interaction sites and transcriptional regulatory sites in cells. EGCG and methylated EGCG could regulate basophils or mast cells through a cell-surface receptor 67LR. Analyzing the structure of 67LR and figuring out the binding efficiency difference between EGCG and methylated EGCG would explain the mechanism of catechins in regulating the inductive phase of allergy. Moreover, we need to elucidate the interaction effects and synergistic functions of multiple compounds *in vivo*.

6.3 The veracity of anti-allergy by polysaccharides

Polysaccharides have been proved to have several bioactive functions. The anti-allergic ability of polysaccharides extracted from multiple herbal species also has been confirmed *in vivo*

and *in vitro*. Polysaccharides are mostly glycoconjugates in which a protein carries one or more carbohydrate chain(s) covalently attached to a polypeptide backbone. Most crude polysaccharides extracted from tea were usually contaminated with catechins and strictinin which might promote the formation of a catechin–polysaccharide complex. Thus, the immunomodulatory activity of polysaccharides might be the effects of the polysaccharide complexes rather than itself.¹¹² Pinpointing the most effective polysaccharide monomer could help illustrate the action mechanism and direct the industrial production of allergy prevention natural products.

6.4 Dietary mode development

As a traditional beverage, tea is usually drunk directly or mixed. Nowadays, tea is also produced as packaged beverage or food additives. With the popularity of tea drinks, it is easy to introduce tea into a lifestyle. Although the complete anti-allergic mechanism of tea is still unclear, its function of preventing allergy has been basically proved *in vivo* and *in vitro*. Studying and developing a dietary mode with tea products will offer the allergy patients with mild symptoms a supplementary option to ease the suffering and a preventive measure.

7. Conclusions

Allergy is an immune response of the human body in a chain reaction manner. Though it is not a severe epidemic disease with clustering paroxysm, it is lethal occasionally with increasing prevalence. The functional components of tea and the effects and partial mechanisms of tea against allergy have been explored and verified. Although the epidemiological investigations on such points are insufficient, evidence supporting that tea has anti-allergic functions *in vivo/in vitro* is obvious. Knowledge of more precise and deeper mechanisms of tea against allergy is required. Overall, tea plays a potential role in preventing allergy.

Abbreviations

IgE	Immunoglobulin E
Th1	T-helper type 1 cells
Th2	T-helper type 2 cells
Th17	T-helper type cells which produce IL-17A and IL-17F
Treg	Regulatory T cells
FcεRI	A receptor with Fc portion
EGCG	Epigallocatechingallate
ECG	Epicatechingallate
EGC	Epigallocatechin
EC	Epicatechin
EGCG3"Me	Epigallocatechin-3-O-(3-O-methyl) gallate
EGCG4"Me	Epigallocatechin-3-O-(4-O-methyl) gallate
OVA	Ovalbumin
IL	Interleukin

AUC	Area under the drug concentration time curves
Syk	Spleen tyrosine kinase
PKC	Protein kinase C
MAPK	p38 mitogen-activated protein kinase
PG	Prostaglandin
TNF	Tumor necrosis factor
IFN	Interferon
TSLP	Thymic stromal lymphopoietin
HO	Hemeoxygenase
LT	Leukotriene
MCP	Chemoattractant protein
ICR	Institute of cancer research
PTK	Protein tyrosine kinases
67LR	A cell-surface receptor named 67 kDa laminin receptor
ERK1/2	Extracellular signal-regulated kinase1/2
GA	Gallic acid
FOXP3	A member of forkhead/winged-helix
STAT-1	Signal transducer and activator of transcription 1
JNK	Jun N-terminal kinase
JAK2	Janus kinase 2
ICAM-1	Intercellular cell adhesion molecule 1
MRLC	Myosin II regulatory light chain.

Author contributions

Q.-S.L.: Section 1: Introduction; Section 3: Anti-allergic compounds in tea; Modification of the manuscript; Table 1; Y.-Q. W.: Fig. 1; Section 2: Phases of the allergic response modulated by tea; Fig. 2; Y.-R.L.: Section 4: Anti-allergic mechanisms of tea; Section 5: Allergy caused by tea; J.-L.L.: Section 6: Further suggestions; Section 7: Conclusions; Modification of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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