Journal of Ginseng Research 48 (2024) 354–365

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: www.sciencedirect.com/journal/journal-of-ginseng-research

Review Article

Effects of Panax species and their bioactive components on allergic airway diseases

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ARTICLE INFO

Keywords:
Allergic asthma
Allergic rhinitis
Ginsenoside
Immune response
Panax ginseng

ABSTRACT

Panax species include *Panax ginseng* Meyer, *Panax quinquefolium* L., *Panax notoginseng*, *Panax japonicum*, *Panax trifolium*, and *Panax pseudoginseng*, which contain bioactive components (BCs) such as ginsenosides and polysaccharides. Recently, growing evidence has revealed the pharmacological effects of *Panax* species and their BCs on allergic airway diseases (AADs), including allergic asthma (AA) and allergic rhinitis (AR). AADs are characterized by damaged epithelium, sustained acquired immune responses with enforced Th2 responses, allergen-specific IgE production, and enhanced production of histamine and leukotrienes by activated mast cells and basophils. In this review, we summarize how *Panax* species and their BCs modulate acquired immune responses involving interactions between dendritic cells and T cells, reduce the pro-inflammatory responses of epithelial cells, and reduce allergenic responses from basophils and mast cells *in vitro*. In addition, we highlight the current understanding of the alleviative effects of *Panax* species and their BCs against AA and AR *in vivo*. Moreover, we discuss the unmet needs of research and considerations for the treatment of patients to provide basic scientific knowledge for the treatment of AADs using *Panax* species and their BCs.

1. Introduction

Allergic airway diseases (AADs), including asthma, rhinitis, and sinusitis, are primarily characterized by a sustained acquired immune response that produces IgE antibodies owing to continuous exposure to inhaled antigens [1,2]. The inhaled antigens responsible for inducing AADs include pollen, animal dander, house dust mites (HDM; e.g., *Dermatophagoides pteronyssinus* and *Dermatophagoides farina*), and molds, which trigger epithelial cell damage during the initial stages of pathogenesis [3]. Following the inhalation of allergens, antigen presenting cells present and process allergens from the airways, leading to the activation of antigen-specific T and B cell responses [4,5]. The acquired immune responses associated with AADs are typified by Th2 responses and IgE production; however, recent research has revealed the involvement of various immune cells, such as Th17 cells, $CD8^+$ T cells, NK cells, eosinophils, and neutrophils, and their functions in pathogenesis [6–8]. Additionally, immune response mediators, including cytokines (e.g., IL-4, IL-5, IL-13, and TNF-α), histamine, and leukotrienes, are implicated in the immune response at the molecular levels [6,9].

Corticosteroids and biologicals have been used to modulate immune responses in patients with AADs [10–12]. Generally, the oral administration of corticosteroid tablets generates a variety of side effects that are risky in individuals with heart failure, hypertension, diabetes, and obesity [13]. In the case of allergic asthma (AA), long-acting bronchodilators are used to alleviate asthmatic symptoms [10]. Recently, a novel therapeutic approach using biologics, including antibodies against IL-4, IL-5, TSLP, or IgE, has been developed to reduce Th2 immune responses [11,12,14]. However, it has been reported that the effectiveness of corticosteroids, long-acting bronchodilators, and biologics is limited due to the heterogeneity of AADs [10]. Therefore, personalized treatment based on the patient's immune response related to disease

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https://doi.org/10.1016/j.jgr.2024.04.003
Received 28 December 2023; Received in revised form 17 April 2024; Accepted 17 April 2024
Available online 21 April 2024

characteristics and subtypes is challenging. Novel approaches, such as the use of functional foods, are required for the treatment of AADs.

Panax species consist of six different types, including *Panax ginseng* Meyer (*P. ginseng*; Korean ginseng), *Panax quinquefolium* L. (*P. quinquefolium*; American ginseng), *Panax notoginseng* (*P. notoginseng*), *Panax japonicum*, *Panax trifolium*, and *Panax pseudoginseng* [15]. Each species is known for its distinct geographical origin, root morphology, and composition of bioactive components (BCs) [16]. Dried roots of *P. ginseng* are termed white ginseng (WG), whereas those that have been steamed and dried are referred to as red ginseng (RG; also known as Korean Red Ginseng (KRG)) [17]. Traditionally, ginseng has been used as the main component of herbal medicines and functional foods and is

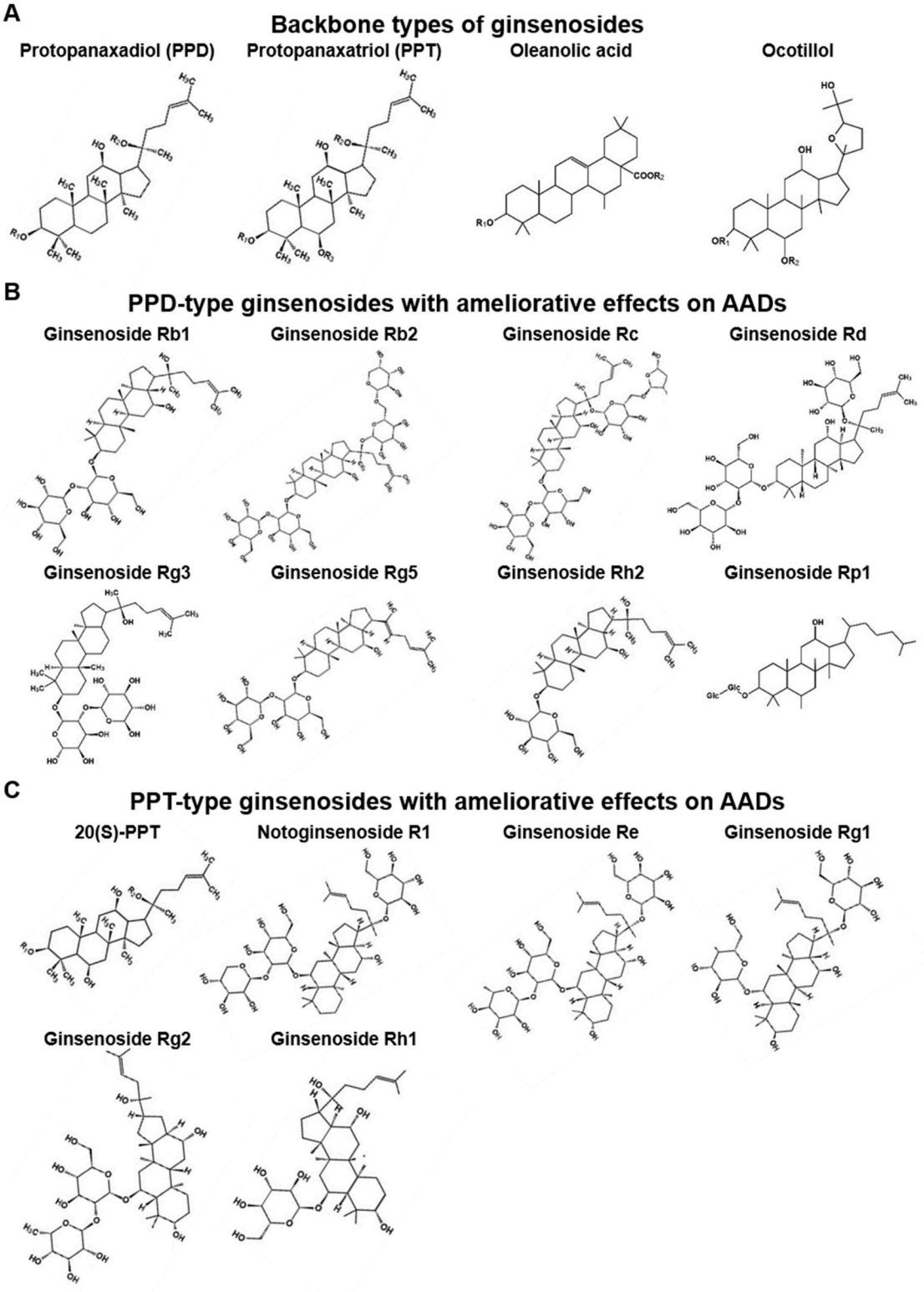

Fig. 1. Chemical structures of ginsenoside backbones and ginsenosides with alleviating effects on AADs.

known for its pharmacological effects, such as modulating immune responses, enhancing vitality, and inducing resistance to stress [18]. The BCs of *Panax* species include ginsenosides, polysaccharides, polyacetylenes, ginseng proteins, phenolic compounds, glycolipoproteins, phytosterols, polyacetylenic alcohols, and fatty acids [19]. Among the *Panax* species, *P. ginseng* is particularly rich in various ginsenosides [20].

Ginsenosides are a group of compounds classified as steroidal saponins with dammarane-type triterpene glycoside structures (Fig. 1) [21,22]. More than 150 ginsenosides have been identified and are typically labeled Rx, where x is determined by their polarity based on thin-layer chromatography, with Ra being the most polar and Rh the least polar [22]. Ginsenosides are further categorized based on their backbones into the protopanaxadiol type (PPD) with a dammarane backbone, protopanaxatriol type (PPT) with an additional hydroxyl group at C6 of the dammarane backbone, oleanolic acid type with a pentacyclic triterpenoid base, and ocotillol type with a five-membered epoxy ring at C20 [23]. PPD ginsenosides include ginsenoside Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Rc, Rd, F2, Rg3, Rg5, Rh2, and Rh3, and can undergo fermentation by gut microbiota in humans to produce secondary ginsenosides such as 20-*O*-β-D-glucopyranosyl-20(S)-protopanaxadiol (compound K) [24,25]. For PPD ginsenosides, M1, M2, M5, and M12 metabolites are generated *in vivo*, with M1 being the final metabolite [24,25]. PPT ginsenosides, including ginsenoside Re, Rg1, Rg2, Rg4, Rh1, Rh4, Rf, 20(S)-PPT, 20 (R)-PPT, and notoginsenoside R1, are further metabolized to M4 and M11, with M4 being the final metabolite [24,25]. Ocotillol-type ginsenosides include 24(R)-pseudoginsenoside-F11, 24(R)-pseudoginsenoside-RT5, Majonoside R1, and R2, whereas oleanolic acid-type ginsenosides include ginsenoside Ro [21,23]. In addition to ginsenosides, various polysaccharides have been identified in *Panax* species, and efforts have been made to develop products using these polysaccharides. For example, CVT-E002, is a water-soluble oligosaccharide or polysaccharide mixture extracted from *P. quinquefolium*, primarily composed of glucose, galacturonic acid, galactose, rhamnose, arabinose, and glucuronic acid [26,27].

To develop and/or improve the effectiveness of herbal medicines and functional foods for respiratory organs, numerous studies have investigated the pharmacological effects of *Panax* species extracts and individual or multiple components in the context of airway diseases, such as influenza A infection [28], acute lung injury [29,30], and chronic obstructive pulmonary disease [31]. In this review, we aim to highlight the protective effects of *Panax* species and their BCs against AADs *in vitro* and *in vivo*, with the goal of providing a scientific foundation for incorporating these BCs into herbal medicines or functional foods for the treatment of AADs.

2. *In vitro* and *in vivo* immunomodulatory roles of *Panax* species and their BCs on acquired immune responses

Panax species have been traditionally used in herbal medicine because they are believed to regulate immune responses. In the pathogenesis of AADs, cellular damage or death of the respiratory system can initiate immune responses, and tuning of the acquired immune system generates Th2-prone allergic microenvironments. Therefore, in this section, we have summarized the *in vitro* and *in vivo* immune regulatory function of *Panax* species and their BCs on the acquired immune responses through dendritic cells (DCs), T cells, and B cells (Table 1, Fig. 2).

2.1. Effects of polysaccharides on acquired immune responses

It has been demonstrated that the polysaccharide fraction CVT-E002 extracted from *P. quinquefolius* increases the induction of IL-2 and IFN-γ

Table 1
Immunomodulatory roles of *Panax* species and their BCs on acquired immune responses.

Component	Type and Origin	Level	Pro-/Anti-inflammation	Function	Ref
CVT-E002	Polysaccharides from *Panax quinquefolius*	Cellular (Human PBMCs)	Anti	Inducing Treg cell	[32]
CVT-E002	Polysaccharides from *Panax quinquefolius*	Cellular (Mouse splenocyte)	Pro	Increased productions of IL-2 and IFN-γ with concanavalin A stimulation	[27]
CVT-E002	Polysaccharides from *Panax quinquefolius*	Animal (BALB/c and C57BL/6)	Pro	Enhancing B cell proliferation Increased total IgG in serum	[26]
Ginsan	Acidic polysaccharides from *Panax ginseng*	Cellular (Mouse BMDC and T cell)	Pro	Enhanced Th1 and Th2 responses through increased activation of BMDC	[33]
NGP	Neutral ginseng polysaccharide from *Panax ginseng*	Cellular (Mouse BMDC and T cell)	Pro	Inducing maturation and activation of DC Increased production of IL-12p70 and TNF-α	[34]
Polysaccharides	Polysaccharides from Ginseng leaves	Animal (BALB/c)	Pro	Elevated the level of antigen-specific IgG2b Inducing the expression of IL-2, IFN-γ, and GM-CSF with increased T cell proliferation	[36]
Polysaccharides	Polysaccharides from *Panax notoginseng*	Cellular (Mouse BMDC and T cell)	Pro	Inducing maturation and activation of DC with enhanced NF-κB pathways Augmenting T cell proliferation with IFN-γ production	[35]
M1 and M4	Metabolites of ginsenosides	Cellular (Human PBMC)	Pro	Inducing activation, mobilization and Ca^{2+} uptake of moDC Increased Th1 cell and cytotoxic T cell responses	[24,25]
Ginsenoside Rd	Ginsenoside from the roots of *Panax notoginseng*	Animal (ICR)	Pro	Increased levels of antigen-specific IgG, IFN-γ, TNF-α, IL-2, IL-4, and IL-5 in blood	[41]
Ginsenoside Rg1	Ginsenoside	Animal (BALB/c)	Pro	Increased antigen-specific IgG, IgG1, IgG2a, IL-5, and IFN-γ production	[39,40]
Ginsenoside Rp1	Ginsenoside	Cellular (Mouse splenocyte) Animal (C57BL/6)	Anti	Augmenting memory T reg responses Reduced CD62L and increased TGF-β and CTLA-4 expression on T cell	[43]
PNS	Ginsenosides from *Panax notoginseng*	Animal (ICR)	Pro	Enhanced antigen-specific splenocyte proliferation Elevated levels of antigen-specific IgG	[38]
Ginsenoside fraction	Ginsenosides from dried root of *Panax ginseng*	Cellular (Human moDC)	Anti	Suppressive effects on moDC differentiation by reduced levels of CD80, CD86, CD40, and CD11c	[42]
GB	Ginseng berry extract	Cellular (Mouse BMDC) Animal (C57BL/6)	Pro	Inducing maturation and activation of DC Increased expression of IFN-γ, TNF-α, and T-bet in splenic T cells TLR4-MyD88 pathway dependently	[37]

BMDC, bone marrow-derived dendritic cell; CTLA-4, cytotoxic T lymphocyte antigen-4; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; moDC, monocyte-derived dendritic cell; PBMC, peripheral blood mononuclear cell; TGF, tumor growth factor; Th1, type 1 helper T cell; Th2, type 2 helper T cell; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell.

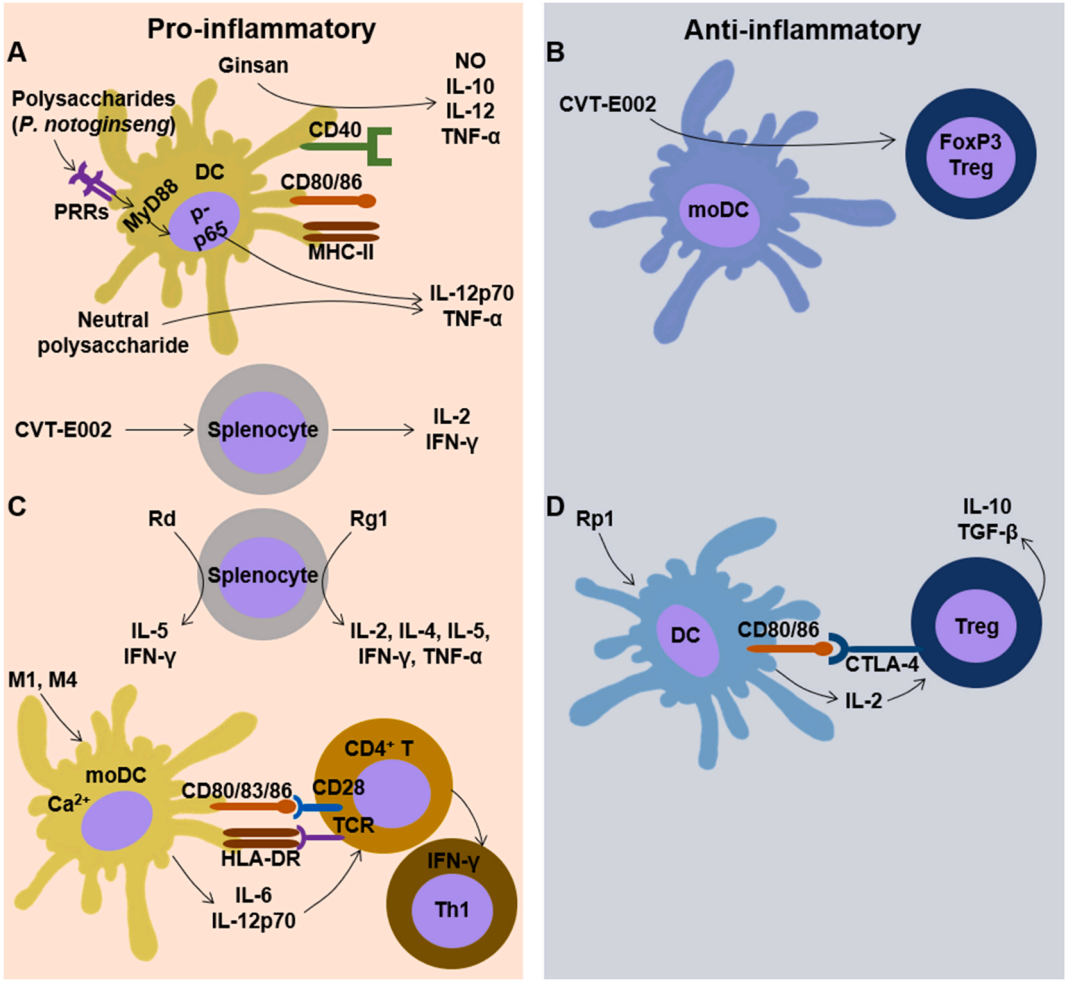

Fig. 2. Immunomodulatory effects of the BCs of *Panax* species.

in splenocytes cultured with concanavalin A (ConA) to stimulate T cells *in vitro* [27]. Without ConA treatment, the administration of CVT-E002 alone does not alter cytokine expression in murine splenocytes [27]. After oral administration of CVT-E002 to mice, enhanced B cell proliferation with elevated serum total IgG was observed, suggesting that pro-inflammatory responses was induced by CVT-E002 *in vivo* [26]. However, there is evidence of the anti-inflammatory roles for CVT-E002. After treatment with CVT-E002 for monocyte-derived DCs (moDCs) differentiation with GM-CSF and IL-4 from human peripheral blood mononuclear cells (PBMCs), the population of $FoxP3^+$ T cells increased [32]. Notably, co-culture of $FoxP3^+$ T cells with anti-CD3/CD28 antibody–stimulated T cells resulted in increased apoptosis and few proliferative features [32]. As the stimulation of anti-CD3/CD28 antibody mimics stimulation of T cells by antigen-presenting cells, this suggests that CVT-E002–treated human moDCs induced the differentiation of functional regulatory T cells (Tregs), which could in turn suppress the activity of antigen-specific T cells (Fig. 2A and B).

When mouse bone marrow-derived dendritic cells (BMDCs) were treated with ginsan, an acid polysaccharide extracted from *P. ginseng*, an increase in nitric oxide, IL-12, IL-10, and TNF-α production, as well as elevated MHC-II and CD86 levels was reported [33]. After co-culture with T cells, ginsan-treated BMDCs elicited enhanced $CD4^+$ T cell proliferation and increased production of both IFN-γ and IL-4 [33]. In addition to ginseng, neutral polysaccharides from *P. ginseng* can also lead to morphological changes in mouse BMDCs, resulting in a mature shape, such as long protrusions and cascading folds with decreased vacuoles and lysosomes [34]. These matured BMDCs show decreased acid phosphatase activity and phagocytosis with higher levels of MHC-II, CD40, CD80, CD83, CD86, IL-12p70, and TNF-α, inducing enhanced T cell proliferation [34]. Similarly, treatment with the polysaccharide fraction of *P. notoginseng* could elicit murine BMDCs maturation, generating increased T cell proliferation and IFN-γ production via stimulation of multiple pattern recognition receptors, including TLR4, TLR2, and MR in DCs, enhancing the NF-κB signaling pathway involving MyD88, *p*-IKKβ, and p-p65 levels [35] (Fig. 2A).

Growing evidence on the immunomodulatory roles of *Panax* species-derived polysaccharides in T cells has steered research efforts toward utilizing these polysaccharides as adjuvants. To verify this hypothesis, water extracts from *P. ginseng* leaves with high molecular weights were immunized with ovalbumin (OVA) combined with Freund's incomplete adjuvant via subcutaneous injection into BALB/c mice [36]. When ginseng polysaccharide was treated with Freund's incomplete adjuvant *in vivo*, augmentation of T cell responses such as increased IFN-γ and GM-CSF production, enhanced T cell proliferation, increased OVA-specific IgG2b in serum, and reduced IL-10 production were demonstrated [36]. Collectively, these polysaccharides from *Panax* species primarily regulate adaptive immune responses and modulate T cell and B cell responses. In addition to modulating adaptive immune responses, it is necessary to understand how these substances regulate innate immune responses in order to utilize polysaccharides from *Panax* species to develop herbal medicines and functional foods.

2.2. Effects of ginsenosides on acquired immune responses

Similar to the polysaccharides, it has been reported that ginsenosides have pro-inflammatory roles on acquired immune responses. In an *in vitro* experiment utilizing *P. ginseng* berry extract containing multiple ginsenosides, morphological changes in mouse BMDCs with increased expression of CD40, CD80, CD86, and MHC-II were reported [37]. Intraperitoneal or intravenous injection of *P. ginseng* berry extract *in vivo* resulted in elevated CD86 and MHC-II expression in murine splenic DCs with increased expression of IFN-γ, TNF-α, and T-bet in splenic $CD4^+$/$CD8^+$ T cells in a TLR4-MyD88 pathway-dependent manner [37]. Moreover, when *P. notoginseng* saponins were administered along with the OVA, there was an increase in OVA-specific IgG, IgG1, and IgG2b levels *in vivo*, leading to enhanced splenocyte proliferation upon ConA, lipopolysaccharide (LPS), and OVA stimulation [38].

Comparative studies of different types of ginsenosides, including PPD ginsenosides (ginsenoside Rg3, Rd, Rc, Rd1, and Rb2) and PPT ginsenosides (ginsenoside Rg1, Re, and Rg2), have been conducted to determine the type of ginsenoside that induces the most significant immune response when co-administered with antigens [39]. Ginsenoside Rg1 was found to have the most potent effect on inducing antigen-specific splenocyte proliferation, IFN-γ and IL-5 production, as well as antigen-specific IgG, IgG1, and IgG2a levels [39,40]. When ginsenoside Rd extracted from roots of *P. notoginseng* was administered with OVA to ICR mice, the levels of OVA-specific IgG, IgG1, IgG2b, IFN-γ, TNF-α, IL-2, IL-4, and IL-5 were increased, suggesting that both Th1 and Th2 immune responses were augmented [41]. Additionally, the expression of HLA-DR, CD1a, CD80, CD83, CD86, and the production of IL-6 and IL-12p70 in moDCs from PBMCs were increased by treatment with M1 and M4, leading to increased DCs mobilization, Ca^{2+} uptake, enhanced cytotoxic T lymphocyte responses, and the generation of IFN-γ-expressing Th1 cells [24,25], suggesting that various ginsenosides could elicit pro-inflammatory immune response via modulating DCs functions (Fig. 2C).

In addition to their pro-inflammatory effects, ginsenosides can modulate the function of DCs and generate anti-inflammatory responses [42,43]. In experiments with an 80 % ethanol extract of dried *P. ginseng* roots composed of ginsenosides Rb1, Rd, and Rg3, the expression of CD11c, CD40, CD80, and CD86 decreased during the differentiation of $CD14^+$ human monocytes into DCs [42]. In splenocyte cultures, the counts of $CD8^+$ T cells, DCs, and Tregs decrease as a result of treatment with ginsenoside Rp1 [43]. Ginsenoside Rp1 also induces memory Tregs with increased IL-10 expression and decreased CD62L expression on their surface *in vitro* [43]. In addition, when ginsenoside Rp1 and LPS were co-administrated, splenic DCs exhibited increased expression levels of CD80 and CD86 with increased expression levels of IL-2, TGF-β, and CTLA-4 compared to those seen with LPS only, leading to anti-inflammatory responses via induction of tolerance on T cells (Fig. 2D) [43]. Collectively, ginsenosides from *Panax* species play a dual role in regulating the function of DCs, generating both pro-inflammatory and anti-inflammatory T cell responses (Fig. 2C and D). Therefore, it is necessary to investigate the immunomodulatory functions of each ginsenoside from *Panax* species on acquired immune responses to prevent AADs.

3. *In vitro* anti-allergic effects of ginsenoside

3.1. Preventive effects of ginsenoside on the pro-inflammatory functions of epithelial cells

Epithelial cells are initially exposed to allergens and are capable of regulating the subsequent immune response [44,45]. To investigate the *in vitro* therapeutic efficacy of the novel substances against AADs, the inflammatory functions of bronchial epithelial cells exposed to allergens were evaluated. Epithelial cell lines, such as NCI–H292, 16HBE, HNEpC, A549, and Beas-2B, and airway epithelial tissue cultures have been utilized in these studies to assess the function of ginsenosides from *Panax* species (Table 2, Fig. 3A).

In NCI–H292 cells, treatment with saponin before stimulation with diesel exhaust particle reduced MUC5AC production, TLR4, IL-6, and IL-8 production, and NF-κB phosphorylation [46]. Treatment of NCI–H292 cells with compound K before stimulation with phorbol myristate acetate (PMA), a potent PKC activator for inducing NF-κB signaling pathways, has been shown to decrease TNF-α and MUC5AC secretion while inhibiting the phosphorylation of NF-κB, mTOR, JNK, ERK, EGR-1, and RSK [47]. In particular, treatment of NCI–H292 cells with Rg5 before PMA stimulation resulted in reduced MUC5AC production, accompanied by changes in lipid metabolism [48]. Microarray analysis has revealed increased expression of genes related to cholesterol metabolism, glycerolipid metabolism, TGF-β signaling pathway, and MAPK signaling pathway upon ginsenoside Rg5 treatment with decreased expression of genes related to TNF and NF-κB signaling pathway, TNF and NF-κB downstream targets, and MAPK signaling pathways [48]. These changes in gene expression were associated with increased cellular lipid droplets, decreased cellular reactive oxygen species (ROS), and decreased phosphorylation of ERK and p38 [48].

Table 2
Anti-allergic effects of ginsenosides on epithelial cells *in vitro*.

Component	Cell	Function	Ref
Compound K	NCI–H292 (Human)	Suppressed TNF-α and MUC5AC secretion Attenuated the activation of MAPK and NF-κB signaling	[47]
Notoginsenoside R1	16HBE (Human)	Decreased production of IL-13 and TNF-α Reduced activation of NF-κB signaling	[49]
Notoginsenoside R1	HNEpC (Human)	Inhibited mitochondrial fission via activation and translocation of Drp Reduced cellular and mitochondrial ROS production Increased phosphorylation of AMPKα Attenuated TXNIP/NLRP3 inflammasome activation	[50]
Ginsenoside Re	A549 (Human)	Reduced production of IL-1α, IL-8, IL-10, and RANTES	[51]
Ginsenoside Rg3	A549 (Human)	Decreased the ratio of phospho-p65/p65 and expression of COX-2	[53]
Ginsenoside Rg3	Beas-2B (Human)	Declined production of CCL24, CCL11, CCL5, MCP-1, IL-6, IL-8, MUC5AC, and MUC5B Reduced the levels of NF-κB and phospho–NF–κB Decreased level of ICAM-1 and less adherent to macrophages Attenuated ROS production	[54, 55]
Ginsenoside Rg3	Human asthmatic airway epithelial tissue culture	Reduced the ratio of phospho-p65/p65 and expression of COX-2 Declined the expression of IL-4, TNF-α and eotaxin	[53]
Ginsenoside Rg5	NCI–H292 (Human)	Increased lipid droplets and decreased cellular ROS Declined phosphorylation of ERK and p38	[48]
Ginsenoside Rh1	A549 (Human)	Reduced production of IL-1β, TNF-α, MCP-1, ICAM-1, MMP2, and MMP9 Abolished PMA-induced ERK1/2, JNK, p38, Akt, and NF-κB p65 activation	[52]

CCL, C–C motif chemokine ligand; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; RANTES, regulated upon activation of normal T cells expressed and secreted; TNF, tumor necrosis factor.

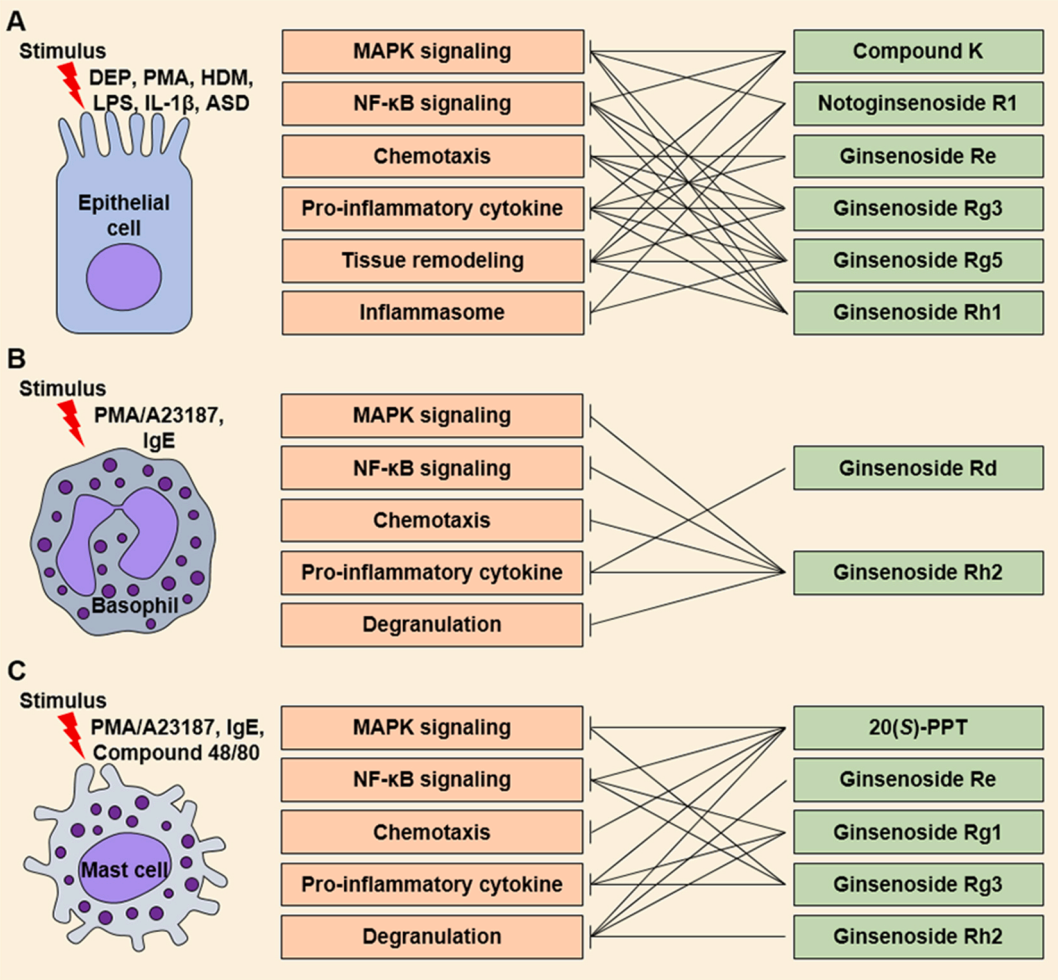

Fig. 3. Schematic illustration of the anti-allergic effect of ginsenosides *in vitro*.

It has also been reported that the production of IL-13 and TNF-α and the activation of the NF-κB signaling pathway were declined by notoginsenoside R1 treatment with HDM in 16HBE cells [49]. After treatment with notoginsenoside R1 on IL-13-stimulated HNEpCs, mitochondrial function was altered to increase production of ROS and AMPK phosphorylation while attenuating TXNIP/NLRP3 inflammasome activation [50]. In A549 cells, LPS-induced production of IL-1α, IL-8, IL-10, and RANTES was also inhibited by the treatment of ginsenoside Re [51]. Moreover, after treatment of ginsenoside Rh1 in A549 cells, PMA-induced IL-1β, TNF-α, MCP-1, ICAM-1, MMP2, and MMP9 gene expression and ERK1/2, JNK, p38, Akt, and NF-κB p65 activation were also suppressed [52]. Treatment of IL-1β-stimulated A549 cells with ginsenoside Rg3 reduced COX-2 expression and the ratio of phospho-p65/p65 [53]. After treatment with ginsenoside Rg3 in Beas-2B cells, elevated CCL24, CCL11, CCL5, MCP-1, IL-6, IL-8, ICAM-1, and ROS production by IL-4 and TNF-α stimulation was attenuated, resulting in less adherent THP-1 macrophages [54]. Additionally, pre-treatment of Beas-2B cells with ginsenoside Rg3 before Asian sand dust exposure decreased MUC5AC and MUC5B production and reduced total and phosphorylated NF-κB levels [55]. Of note, the anti-inflammatory effect of ginsenoside Rg3 was also reported in human asthmatic airway epithelial tissue culture, resulting in decreased expression of IL-4, TNF-α, and eotaxin [53]. In conclusion, ginsenosides are believed to inhibit the pro-inflammatory stimuli in epithelial cells *in vitro* (Table 2, Fig. 3A).

3.2. *Anti-allergenic effects of ginsenosides on basophils and mast cells*

During the pathogenesis of AADs, both basophils and mast cells possess Fcε receptors (FcεR) with high-affinity on their surfaces to evoking allergen-specific detrimental functions. When allergens cross-link with these receptors, they release inflammatory mediators, leading to pro-allergenic responses. In general, IgE-dependent acute allergic responses and chronic allergic inflammation are mediated by mast cells and basophils, respectively [56]. Basophils and mast cells were chosen to evaluate the therapeutic effects of ginsenosides by comparing their ability to produce inflammatory mediators and their degranulation activities (Table 3, Fig. 3B and C). For assessment of the function of ginsenosides from *Panax* species on basophils and mast cells, RBL-2H3 cells (rat basophil cell line), HMC-1 cells (human mast cell line), mouse bone marrow–derived mast cells (BMMCs), and primary mast cells from guinea pigs (guinea pig mast cells; GPMCs) and rats (rat peritoneal mast cells; RPMCs) were utilized (Table 3).

With the stimulation of A23187, a calcium ionophore for non-FcεR-specific stimulation, IL-4 production was increased in RBL-2H3 cells and restored by treatment with *P. ginseng* [57]. Ginsenoside Rd also inhibited IL-4 secretion in PMA/A23187-stimulated RBL-2H3 cells [58]. In addition to non-FcεR-specific stimulation, anti-dinitrophenyl IgE (anti-DNP IgE)-sensitization with DNP-HSA activation was induced on RBL-2H3 cells in order to mimic antigen-specific IgE stimulation on FcεR [59, 60]. After stimulation of FcεR by anti-DNP IgE with DNP-HSA, ginsenoside Rh2 inhibited the secretion of histamine, β-hexosaminidase, IL-1β, IL-4, IL-8, and TNF-α in RBL-2H3 cells and the phosphorylation

Table 3
Anti-allergic effects of ginsenosides on basophils and mast cells *in vitro*.

Component	Cell	Function	Ref
20(*S*)-PPT	GPMC (Guinea pig, mast cell)	Inhibited histamine and leukotriene release Inhibited intracellular Ca^{2+} influx Declined level of PLA_2	[61]
20(*S*)-PPT	BMMC (Mouse, mast cell)	Reduced production of IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, TNF-α, IFN-γ, histamine and leukotriene Declined level of PLA_2, Syk, and COX-2 Lower PKC activity and Ca^{2+} influx Reduced phosphorylation of PKCs and MAPKs Reduced activity of NF-κB and AP-1	[61]
Ginsenoside Rd	RBL-2H3 (Rat, basophil)	Decreased secretion of IL-4	[58]
Ginsenoside Re	HMC-1 (Human, mast cell)	Reduced secretion of histamine Prevented degranulation	[51]
Ginsenoside Rg1	HMC-1 (Human, mast cell)	Reduced mRNA and protein levels of TSLP and IL-1β Reduced the NF-κB/Rel A levels in the nucleus Inhibited IκB-α degradation and expressions of RIP2 and IKK-β	[62]
Ginsenoside Rg1	RPMC (Rat, mast cell)	Reduced the release of histamine	[62]
Ginsenoside Rg3	HMC-1 (Human, mast cell)	Decreased histamine release Blocking Ca^{2+} influx and enhancing intracellular cAMP level Reduced productions of IL-1β, IL-6, and TNF-α Decreased the activation of MAPK and NF-κB signaling Suppressed RIP2 activation and cleavage of caspase-1	[63]
Ginsenoside Rh2	RPMC (Rat, mast cell)	Restored morphology of cell surface and decreased granularity Reduced Ca^{2+} uptake	[59]
Ginsenoside Rh2	RBL-2H3 (Rat, basophil)	Inhibited degranulation of histamine and β-hexosaminidase Reduced secretion of IL-1β, IL-4, IL-8 and TNF-α Reduced phosphorylation of Lyn, Syk, LAT, PLCr2, PI3K, and ERK1/2 Decreased PI3K activity and Raf-1 expression Reduced levels of *p*-AKT and p-p38, increased expression of Keap1 Increased nuclear translocation of Nrf2 Decreased level of NF-κBp65 in nucleus and Ca^{2+} influx	[59, 60]

IFN: interferon, IL: interleukin, TNF: tumor necrosis factor, TSLP: thymic stromal lymphopoietin.

levels of Lyn, Syk, LAT, PLCr2, PI3K, and ERK1/2 decreased due to the reduction in PI3K activity and NF-κB p65 levels [59]. Moreover, intracellular Ca^{2+} influx was increased by ginsenoside Rh2 treatment on FcεR-stimulated RBL-2H3 cells with increased Nrf2 nuclear translocation [59,60], suggesting that Rh2 has anti-allergic effects induced by allergen-IgE-FcεR signaling by reducing NF-κB pathway (Fig. 3B).

Growing evidence shows that ginsenosides could also adjust the immunological function of mast cells to prevent allergic responses (Table 3, Fig. 3C) [51,59,61–63]. It has been reported that treatment with the ginsenoside 20(S)-PPT results in decreased histamine and leukotriene release and inhibited intracellular Ca^{2+} influx in mast cells with antigen-specific antibody responses, which were GPMCs stimulated by anti-OVA antibody with OVA challenge and mouse BMMCs stimulated by anti-DNP IgE with DNP-HSA on FcεR [61]. With the treatment of ginsenoside 20(S)-PPT, the expression of IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, TNF-α, and IFN-γ decreased in FcεR-stimulated BMMCs along with decreased levels of Syk, COX-2, and inhibited PKC activity [61]. This phenomenon was accompanied by a decrease in PKCs and MAPK phosphorylation, which was confirmed to be due to the inhibition of NF-κB and AP-1 activity in FcεR-stimulated BMMCs treated with 20 (S)-PPT [61]. Furthermore, ginsenoside Rh2 treatment has been reported to alter the morphology of FcεR-stimulated rat peritoneal mast cells (RPMCs) and reduce granularity [59]. Ginsenoside Rg1 lowers histamine release from RPMCs stimulated with compound 48/80, as a non-IgE dependent stimulator of mast cells [62], suggesting that *Panax* species and their BCs could elicit immunomodulatory roles on mast cells for both FcεR-specific and non-FcεR-specific stimulations.

In human mast cell line (HMC-1) culture stimulated by PMA/A23187, ginsenoside Rg1 could suppress TSLP and IL-1β expression and inhibit IκB-α degradation, resulting in decreased nuclear translocation of NF-κB/Rel A [62]. When stimulated with compound 48/80, HMC-1 cells treated with ginsenoside Re showed inhibition of histamine secretion and prevention of degranulation [51]. Ginsenoside Rg3 inhibited histamine release in HMC-1 cells stimulated with PMA/A23187, decreased intracellular Ca^{2+}, the phosphorylation of ERK, JNK, and p38, and reduced NF-κB signaling pathway activity. Furthermore, ginsenoside Rg3 increased intracellular cAMP levels, suppressed the production of IL-1β, IL-6, and TNF-α, and inhibited RIP2 activity and caspase-1 cleavage [63]. These immunomodulatory roles of ginsenoside Rg3 were also observed in FcεR-stimulated RBL-2H3 cells manifested as reduced histamine release with a suppressed NF-κB pathway [63]. Collectively, ginsenosides are believed to play a role in suppressing pro-inflammatory responses in epithelial cells, basophils, and mast cells to mitigate their detrimental effects on AADs (Tables 2–3, Fig. 3).

4. Alleviation of AADs by extracts of *Panax* species or their BCs

4.1. AA

Various studies have validated the therapeutic effects of *Panax* species and their BCs on AADs, revealing their molecular mechanisms *in vivo* (Table 4). Oral administration of ginseng (Gerimax, Denmark) to OVA-induced AA mice resulted in a reduction in the basement membrane, epithelium, and subepithelial smooth muscle layer, with a lower number of goblet cells and mast cells [64]. Intraperitoneal injection of *P. ginseng* hot water extract in OVA-induced AA mice led to a decrease in inflammatory cell infiltration, goblet cell count, MUC5AC production, eosinophil secondary granules, $CD40^{-}CD40L$, expression of IL-1β, IL-4, IL-5, and TNF-α, as well as inhibited phosphorylation of ERK, JNK, and p38 in the lungs [65].

To evaluate the therapeutic efficacy of WG and RG against AADs, extracts were prepared using 80 % ethanol and administered to OVA-induced AA mice [66]. In this study, RG exhibited a greater effect than WG, leading to decreased immune cell counts in bronchoalveolar lavage fluid (BALF), reduced Penh values, lowered serum IgE levels, and restoration of peribronchial cytokine profiles (IL-4, IL-5, IL-6, and IL-13) [66]. Another study confirmed that oral administration of KRG water extract to OVA-induced AA mice led to a decrease in Penh value and serum OVA-specific IgE levels, which was associated with a decrease in immune cell counts in BALF, ROS production, and levels of Th2-related cytokines [67]. The anti-asthmatic effects of KRG were accompanied by a reduction in HO-1, iNOS, and phosphorylated p65 levels and the inhibition of NRF2 nuclear translocation [67]. To verify whether fermentation could enhance the therapeutic effects of ginseng, different forms of RG extract, including whole RG, 50 % ethanol extract, and fermented RG extract, were orally administered to OVA-induced AA mice [58]. Ginseng extracts could reduce allergic symptoms, and the fermented RG extract exhibited the highest efficacy with restored intestinal microbes (Firmicutes, Actinobacteria, and Bacteroidetes), decreased IL-4, IL-5, IL-13, and TNF-α levels in the colon, and reduced the myeloperoxidase activity [58].

The different pharmacological effects observed in AA upon

Table 4
Defined molecular mechanisms of *Panax* species and their BCs on AADs *in vivo*.

Material	Allergic diseases	Effects	Ref
Panax ginseng water extract	Asthma	Reduced phosphorylation of ERK, JNK, and p38	[65]
Water extract from Korean Red Ginseng	Asthma	Reduced HO-1, iNOS and p-p65 levels in lung Decreased nuclear translocation of NRF2	[67]
Notoginsenoside R1	Asthma	Reduced activation of pIKK–NF–κB pathways in lung	[49]
Notoginsenoside R1	Rhinitis	Reduced apoptosis with decreased cleavage of caspase-3 and caspase-9 Reduced expression of Bax, Cytochrome *c*, and Apaf-1 Increased level of Bcl-2 Reduced ROS production	[50]
Compound K	Asthma	Decreased ER stress, ferroptosis, apoptosis and NF-κB signaling	[69]
Ginsenoside Rd	Asthma	Restore intestinal microbe	[58]
Ginsenoside Rg1	Rhinitis	Decreased the level of MIP-2, ICAM-1, COX-2, active form of caspase-1, and caspase-1 activity in nasal mucosa	[62]
Ginsenoside Rg3	Asthma	Increased GSH, SOD, and HO-1 levels, increased nuclear translocation of Nrf2 and lower level of MDA in lung	[54]
Ginsenoside Rg3	Rhinitis	Increased SOD and decreased MDA level in serum Modulation of metabolic pathways modulating immune responses	[75]
Ginsenoside Rh2	Asthma	Blocking MAPK–NF–κB signaling Reduced levels of *p*-Lyn and *p*-Syk	[59, 73]

processing or altering the extraction methods of ginseng may be attributed to the varying efficacies of the BCs of *P. ginseng*. Therefore, studies have been conducted to dissect the roles of the individual components or fractions of *Panax* species in animal models of AA. When CVT-E002 extracted from *P. quinquefolium* was orally administered to OVA-induced AA mice, Penh was reduced, the number of immune cells and lymphocytes in BALF decreased, and eosinophil counts decreased while $CD3^+FoxP3^+$ cell numbers within lungs increased [32]. Intraperitoneal injection of ethanol-insoluble ginsan from *P. ginseng* extract into OVA-induced AA mice also led to reduced Penh values, immune cell infiltration, and restored airway remodeling, with increased levels of COX-1/2 in the lungs and increased PGE_2 levels in BALF [68]. In addition to the polysaccharide fractions, intravascular injection of saponins suppressed immune cell infiltration and reduced mucin hypersecretion and MUC5AC overproduction in an AA model of OVA with diesel exhaust particles [46].

Various studies have investigated the therapeutic effects of individual ginsenoside components in mouse models of AA. The intravascular injection of notoginsenoside R1 reduced airway hyperresponsiveness (AHR), immune cell infiltration, mucus production, and IgE production in OVA-induced asthma by inhibiting the pIKK–NF–κB signaling pathway, leading to reduced levels of IL-4, IL-5, IL-8, IL-13 and TNF-α [49]. Similarly, oral administration of compound K reduced AHR, immune cell infiltration, mucus production, and IgE production in AA mice associated with inhibited NF-κB signaling and reduced levels of Ca^{2+}, ROS, MDA, and apoptosis markers (cleaved caspase-3 and BAX/Bcl2 ratio), as well as reduced $TUNEL^+$ apoptotic cells and iron-positive cells. These effects are accompanied by a decrease in ER stress-related proteins, such as PERK, eIL2a, ATF4, and CHOP, and the restoration of ferroptosis-related markers SLC7A11, GPX4, and 4-HNE [69].

Oral administration of ginsenoside Rb1 in OVA-induced AA mice could reduce airway resistance and decrease immune cell infiltration in BALF, as well as lower IL-4 levels and OVA-specific IgE levels associated with suppressed GATA-3 expression, while increasing T-bet expression and IFN-γ levels in BALF, indicating a tendency to induce Th1 responses and suppress Th2 responses [70]. Similarly, the inhibition of GATA-3 expression in lung tissue increases T-bet expression following intraperitoneal injection of ginsenoside Rg2 from the hot water extract of *P. ginseng* [71]. Moreover, injecting ginsenoside Rg3 into OVA-induced asthma mice also led to an increase in IFN-γ levels in lung tissue and BALF with reduced AHR, immune cell infiltration, and lowered BALF levels of CCL11, CCL24, TNF-α, IL-4, IL-5, IL-6, and IL-13. Additionally, reduced eosinophilia, goblet cell hyperplasia, and collagen production in the lungs were observed [54]. It has been suggested that the anti-asthmatic effects of ginsenoside Rg3 are associated with a decrease in COX-2 production and MDA levels within the lung tissue, an increase in GSH, SOD, HO-1 levels, and nuclear translocation of Nrf2 [54].

Additionally, oral administration of ginsenoside Rd in an OVA-induced AA model reduced Th2 immune responses and suppressed allergic symptoms by restoring intestinal Bacteroidetes [58]. In the treatment with ginsenoside Rh1 to OVA-induced AA mice, the AHR, inflammatory cell infiltration, and OVA-specific IgE levels were reduced. There was also a decrease in eotaxin, IL-4, IL-5, IL-13, and IL-33 levels in BALF and serum, while IL-12 and IFN-γ levels were elevated [72]. Ginsenoside Rh1 also restored the number of neutrophils, eosinophils, and macrophages in BALF and lowered serum OVA-specific IgE and IL-4 levels in BALF in an AA model against OVA with intratracheal LPS injection [52]. Oral administration of ginsenoside Rh2 to OVA-induced AA mice reduced inflammatory cell infiltration, goblet cell proliferation, mucus secretion, Penh values, and IL-1β, IL-4, IL-5, IL-8, TNF-α, IL-13, and β-hexosaminidase levels, while IFN-γ level was restored [59,73]. Ginsenoside Rh2 has been reported to display anti-asthmatic effects through the inhibition of NF-κB signaling [73] and the decrease in tryptase, *p*-Lyn, and *p*-Syk levels *in vivo* (Table 4) [59].

4.2. Allergic rhinitis (AR)

In addition to AA, the therapeutic effects of *Panax* species and their BCs on AR were evaluated *in vivo* (Table 4). In OVA-induced AR mice, alleviation of AR resulted in decreased serum IgE levels, reduced IL-4 and IL-5 production, and decreased eosinophil and $MUC5AC^+$ cell counts following the administration of KRG [74]. A comparative study of RG and fermented RG reported a decrease in the levels of IL-4, OVA-specific IgE, eosinophil count, basophil count, and thickness of the nasal epithelium, with fermented RG displaying a stronger effect than RG [57].

Furthermore, the therapeutic effects of single components of *Panax* species have been evaluated using AR [50,62,75]. When notoginsenoside R1 was intraperitoneally injected into OVA-induced AR mice, it alleviated rhinitis symptoms, such as sneezing and nasal rubbing, lowered the levels of OVA-specific IgE, IL-4, IL-6, IL-8, IL-13, and TNF-α, and eosinophilia in nasal submucosa [50]. The alleviation of AR by notoginsenoside R1 is hypothesized to be mediated by the suppression of BAX, Cytochrome *c*, and Apaf-1, a decrease in ROS production, and caspase-3/9 cleavage, resulting in a reduction in apoptotic cells in the nasal mucosa [50]. Oral administration of ginsenoside Rg1 in OVA-induced AR mice resulted in a reduction in rub score and nasal/ear weight, with inhibited TSLP, IL-1β, histamine, OVA-specific IgE, and IgG_1 production, accompanied by a reduction in mast cells, eosinophils, and IL-1β-producing cells in the nasal mucosa. These improvements facilitated by ginsenoside Rg1 were attributed to decreased MIP-2, ICAM-1, COX-2, and caspase-1 activities [62].

Recently, attempts have been made to analyze the effect of ginsenoside Rg3 on AR through transcriptome and metabolome analyses of the nasal mucosa [75]. Administration of ginsenoside Rg3 to OVA-induced AR mice alleviated symptoms such as sneezing and rubbing, with decreased production of IL-4, IL-5, IL-13, and IgE, accompanied by decreased inflammatory cell infiltration in the nasal mucosa. Transcriptome and metabolome analysis of the nasal mucosa revealed

that treatment with ginsenoside Rg3 led to an increase in the expression of Cyp26b1, a gene related to retinol metabolism, and an increase in β-retinol ($C_{20}H_{30}O$), suggesting that increased retinol metabolism by ginsenoside Rg3 could potentially suppress Th2 cytokines in AADs, regulate goblet cell hyperplasia, mucus hypersecretion, and histamine release, thus alleviating allergic responses [75]. Collectively, the therapeutic effects of *Panax* species and their BCs in AADs were confirmed *in vivo*, and various attempts have been made to elucidate the detailed mechanisms underlying the development of another therapeutic approach (Fig. 4).

5. Discussion

5.1. Unmet needs in the research

There is a need to investigate the roles of *Panax* species and their BCs in AADs. Various studies have investigated the immunomodulatory roles of *Panax* species and their BCs on the functions of DCs. It has been reported that TLR4, not TLR2 or MR, is the major surface receptor on DCs affected by Ginseng berry extract and the polysaccharide fraction from *P. notoginseng* [35,37]. It has been postulated that TLR4 activation results in a reduction in Th2 immune responses, in line with the hygiene hypothesis [76]. Since airway instillation of LPS, a major ligand of TLR4, can generate pro-allergic responses and TLR4 signaling is required to induce airway hypersensitivity, the role of TLR4 in AADs remains controversial [77]. Therefore, it is necessary to identify other receptors of *Panax* species and their BCs to develop reliable treatment strategies for AADs. Second, there is also the possibility that *Panax* species and their BCs might be also have detrimental effects on AADs. It has been reported that treatment with ginsenoside Rg1 led to increased T cell proliferation, elevated CD69 expression, decreased IFN-γ expression, and increased Th2 dominance in BALB/c-derived $CD4^+$ T cells [28]. Since the Th2 immune response plays a crucial role in the initiation and progression of AADs, these findings suggest that ginsenoside Rg1 may exacerbate AADs. Finally, investigations have been conducted using single components *in vitro*, mostly limited to ginsenosides. Since total extracts from *Panax* species and the polysaccharide fractions have ameliorative effects on AADs *in vivo*, it is necessary to understand the

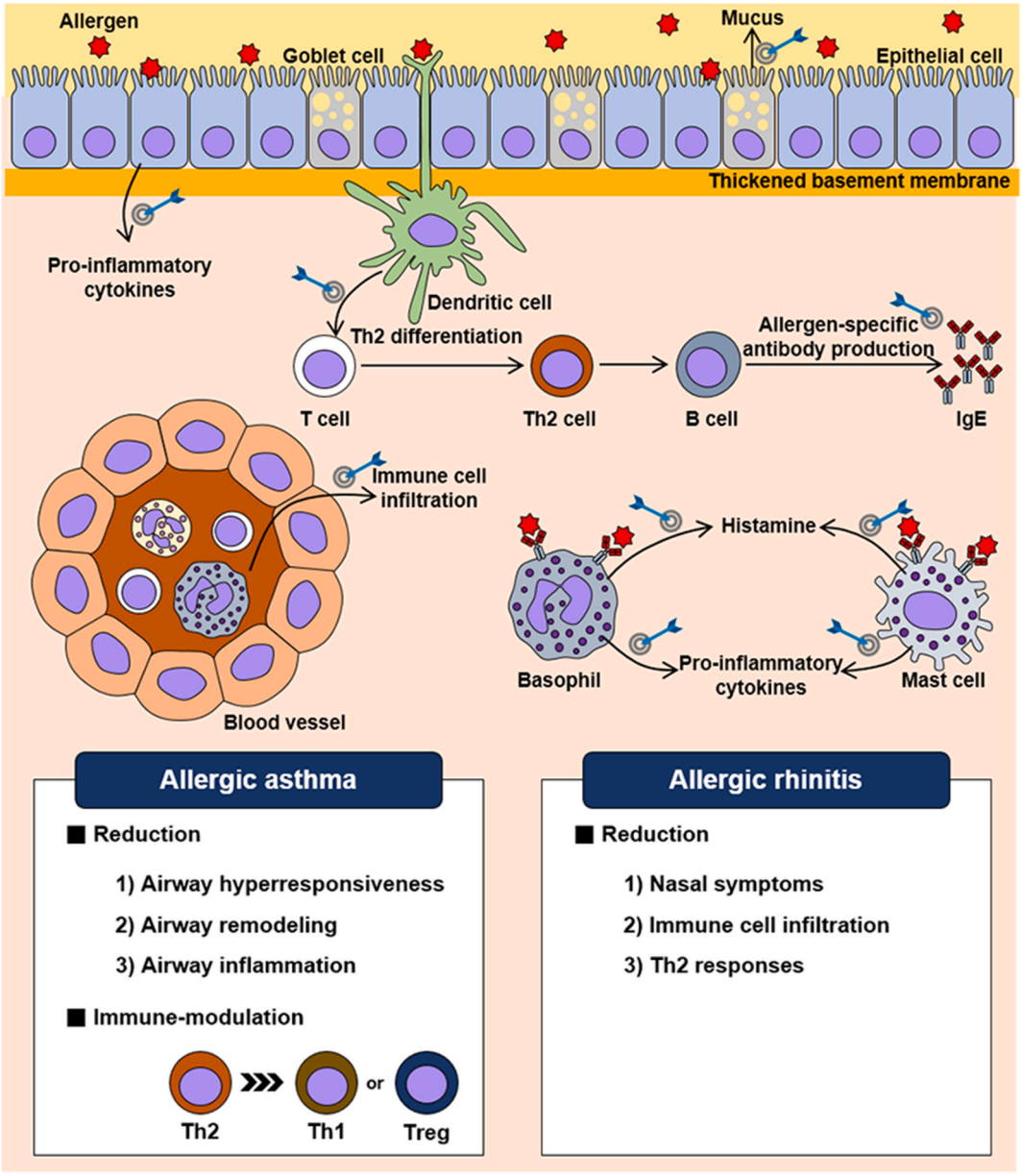

Fig. 4. Schematic illustration of the targets for the anti-allergic effects of *Panax* species and their BCs against AADs.

roles of every single component, not only ginsenosides but also other BCs on AADs.

5.2. Considerations for the use of Panax species for treating patients with AADs

In this review, we summarize both *in vitro* and *in vivo* studies that provide evidence for the therapeutic efficacy of *Panax* species in ameliorating AADs. In addition, extracts from KRG alone were used to examine its therapeutic efficacy in patients with AADs [78,79]. After 4 weeks of treatment with KRG extract, sneezing and nasal itching were ameliorated, and the levels of total IgE and IL-4 decreased in patients with AR (n = 60) [78]. Moreover, these patients had increased IL-10 levels and decreased eosinophil counts in nasal smears, suggesting an improvement in symptoms by modulating allergenic immune responses [78]. Patients with AA (n = 100) who consumed a modified Mai-Men-Dong-Tang containing American ginseng for four months showed positive therapeutic effects, including reduced FEV_1 and symptom scores [79]. Another study on patients with persistent perennial AR (n = 59) reported that treatment with fermented red ginseng could improve nasal congestion and emotional state when utilized in early stages [80]. Given these potential benefits, further in-depth analysis is necessary to understand the various effects of *Panax* species on AADs and to develop other therapeutic options for patients with AADs.

Panax species have been used for herbal medicine or functional food because of their pharmacological actions; however, some reports suggest that the administration of *P. ginseng* has several side effects [81,82]. A two-year follow-up study of 133 ginseng users found that more than half of the patients experienced a feeling of well-being, but various side effects, including morning diarrhea, skin eruptions, throat demulcent effects, nervousness, sleeplessness, hypertension, euphoria, and edema were reported [81]. Furthermore, the consumption of ginseng or ginseng-based products has been associated with side effects, such as allergic disorders, affective disorders, cardiovascular issues, gynecomastia, genital organ bleeding, hepatotoxicity, hypertension, reproductive toxicity, and even anaphylaxis in some cases [82].

Notably, there have been a few case reports of worsening asthma symptoms following ginseng exposure [83–85]. When exposed to Korean ginseng extract, a 34-year-old female who had suffered from AR for 9 years experienced a decrease in FEV_1 and an increase in IgE levels, with a strong positive response to the skin prick test [83]. After inhalation of ginseng dust, a 29-year-old female with no familial history of allergic disease had an FEV_1 decrease of 20 % with an early asthmatic response without anti-ginseng IgE [84]. In a 44-year-old male patient with seasonal AR, a 54 % decrease in FEV_1 was observed along with typical allergic responses, with positive skin prick results without ginseng-specific IgE [85]. Collectively, when using *Panax* species for treating patients with AADs, it is important to consider the potential side effects of ginseng consumption and the possibility of an allergenic response against ginseng.

6. Conclusion

Collectively, most studies have demonstrated the therapeutic effects of *Panax* species and their BCs on AADs, owing to their anti-inflammatory effects on epithelial cells, mast cells, and basophils and their immunomodulatory effects on DCs, boosting Treg or Th1 responses. However, further investigations are needed to identify the underlying mechanisms for each component of *Panax* species for developing safe and reliable treatments. Furthermore, a minority of individuals may exhibit allergic responses to ginseng extract, necessitating further investigations.

Conflict of interest statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or nonfinancial interest in the subject matter or materials discussed in this manuscript. Please specify the nature of the conflict on a separate sheet of paper if the space below is inadequate.

Authorship contributions

Conception and design of study: D. Shim, S.C. Park; acquisition of data: D. Shim, Y. Bak, H-G. Choi, S.C. Park; analysis and/or interpretation of data: D. Shim, Y. Bak, S. Lee, S.C. Park.

Drafting the manuscript: D. Shim; revising the manuscript critically for important intellectual content: D. Shim, Y. Bak, H-G. Choi, S. Lee, S. C. Park.

Approval of the version of the manuscript to be published (the names of all authors must be listed).

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (2020R1I1A3067369). This research was supported by Hallym University Research Fund and Korean Society of Ginseng in 2023.

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