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Review Article

Panax ginseng: a candidate herbal medicine for autoimmune diseaseJoon-Il Lee¹, Kyoung Sun Park², Ik-Hyun Cho^{1,3,*}¹ Department of Science in Korean Medicine and Brain Korea 21 Plus Program, Graduate School, Kyung Hee University, Seoul, Republic of Korea² Department of Korean Medicine Obstetrics & Gynecology, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea³ Department of Convergence Medical Science and Institute of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

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ABSTRACT

Panax ginseng Meyer (*P. ginseng*; Korean ginseng) is well known for its medicinal properties. It can alleviate pathological symptoms, promote health, and prevent potential diseases via its anti-inflammatory, antioxidant, homeostatic, and other positive effects on biological metabolism. Although many studies have determined effects of *P. ginseng* on various diseases, such as cardiovascular, neurological, and immunological diseases, little is known about the effect of *P. ginseng* on autoimmune diseases. Here, we review a few reports about effects of *P. ginseng* on autoimmune diseases (e.g., multiple sclerosis, Crohn's disease, ulcerative colitis, atopic dermatitis, and rheumatoid arthritis) and suggest the possibility of *P. ginseng* as a candidate herbal medicine to prevent and treat autoimmune diseases as well as the need to study it.

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1. Introduction

Panax ginseng Meyer (*P. ginseng*; Korean ginseng) in the family of Araliaceae has been used as a traditional herbal medicine in East Asian countries such as Korea, China, and Japan for a long period of time. It has been used as a single herbal medicine or in combination with other herbal medicines to cure various diseases, such as cardiovascular, neurological, and immunological diseases [1–5]. *P. ginseng* consists of berries, leaves, stalk, and root [6]. The term 'ginseng' indicates the root of *P. ginseng*. Its root is mostly used as herbal medicine. Because fresh *P. ginseng* is easily degraded at room temperature, it is processed into red ginseng (Ginseng Radix Rubra) through a process of steaming and drying or processed into white ginseng (Ginseng Radix Alba) by a simple drying process [7]. According to general knowledge, red ginseng has higher biological effects and fewer adverse effects compared with fresh and white ginseng [7]. Active constituents of *P. ginseng* include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids [8–10]. Recently, scientists have introduced a new pharmacological activity of *P. ginseng* (extracts, fractions, and constituents) in various disease of human body and *in vivo/vitro* disease models related to its wide range of activity for immune regulation [11,12]. However, pharmacological effects of *P. ginseng* on autoimmune diseases

remain unclear. Therefore, further elucidating the accommodative function of *P. ginseng* may be highly attractive in the prevention and eradication of autoimmune diseases. In this review, we will summarize the current knowledge on effects of *P. ginseng* and its components on autoimmune diseases and suggest significance to study *P. ginseng* in autoimmune diseases in the future. Here, we focus on multiple sclerosis (MS), Crohn's disease (CD), ulcerative colitis (UC), atopic dermatitis, and rheumatoid arthritis (RA) among various autoimmune diseases (Tables 1–4).

2. Effects of *P. ginseng* on immune cells

P. ginseng is a well-known immune modulator. It may maintain immune homeostasis and enhance resistance to illness or microbial attacks by modulating the immune system [6,13–15]. The immune system is composed of diverse types of cells (macrophages, dendritic cells, microglia, lymphocytes, natural killer cells, and so on) with their own specialized functions [16,17]. Extracts, fractions, and constituents of *P. ginseng* can differentially regulate each type of immune cells [13]. For instance, Korean Red Ginseng extract (KRGE) can inhibit helper T cell 17 (Th17) differentiation and promote regulatory T (Treg) cell differentiation under Th17-polarizing condition [11]. Ginsenoside Rg3-fortified KRGE can suppress helper T

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Table 1
Effects of *Panax ginseng* on multiple sclerosis.

Component	Experimental model	Results	References
Purified acidic polysaccharide	MOG-induced EAE	(↓) Th1 cytokines; (↓) splenic proinflammatory cytokines; (↑) regulatory T cells	[36]
	PLP-induced EAE	(↓) immune cell infiltration level in the spinal cord; (↓) splenic proinflammatory cytokines; (↓) spinal demyelination; (↓) neurological scores	[37]
KRGE	MBP-induced EAE and MOG-induced EAE	(↓) immune cell activation and infiltration in the spinal cord; (↓) BBB disruption; (↓) proinflammatory cytokine level; (↑) regulatory T cells; (↓) neurological scores	[33,34]
Rd	MOG-induced EAE	(↓) neurological scores; (↓) IFN- γ level in splenocytes and cerebral cortex; (↑) IL-4; (↑) NGF and BDNF in cerebral cortex and spinal cord	[35]

MOG, myelin oligodendrocyte glycoprotein; EAE, experimental autoimmune encephalomyelitis; Th1, helper T cell 1; PLP, proteolipid protein; KRGE, Korean Red Ginseng extract; MBP, myelin basic protein; BBB, blood-brain barrier; IFN- γ , interferon-gamma; NGF, neural growth factor; BDNF, brain-derived neurotrophic factor

cell 1 (Th1) differentiation and the expression of interferon gamma (IFN- γ) and T-bet in well-characterized T-cell *in vitro* differentiation systems [18]. Acidic polysaccharides derived from *P. ginseng* also exert anti-immunosenescent effect by suppressing thymic involution and modulating several types of immune cells (CD11c-positive B cells in the spleens and CD4- and CD8-positive T cells in the thymi) [12]. They also display antisepticaemic activity by stimulating macrophages for macrophage function [19]. Ginsenoside Rh2 can inhibit proliferation of MCF-7 breast cancer cells by regulating epigenetic methylation of the cell-mediated immune pathway [20]. Ginsenoside Rg3 can increase beta amyloid clearance by enhancing the phagocytotic activity of microglia (uptake, internalization, and digestion), a specialized population of macrophages found in the central nervous system [21]. As shown previously, *P. ginseng* and its components can modulate the immune system intricately linked to a lot of diseases.

3. Autoimmune diseases

An autoimmune disease is a condition arising from an abnormal immune response to a normal body part [22,23]. The cause of autoimmune disease is generally unknown. Stress, genetic factors, and environmental factors are suggested as factors that can trigger an autoimmune disease. However, correlation between these suggested factors and an autoimmune disease is very complex [22,23]. There are at least 80 types of autoimmune diseases. Nearly any body part can be involved [22]. Each classified disease has its own specific symptoms such as fatigue, joint pain and swelling, skin problems, abdominal pain or digestive issues, recurring fever, and swollen glands [24–27]. These symptoms can lower patients' quality of life. Unfortunately, incidence and prevalence of autoimmune diseases are gradually increasing in the world [28]. It has been reported that annual percent increases of rheumatic, endocrinological, gastrointestinal, and neurological autoimmune diseases are 7.1, 6.3, 6.2, and 3.7, respectively [28]. Additionally, while treatment such as nonsteroidal anti-inflammatory drugs, immunosuppressants, and intravenous immunoglobulin usually can improve symptoms, they typically cannot cure the disease. In

addition, they have some side effects [29]. Therefore, developing appropriate cures for patients with autoimmune diseases are very important.

As shown previously, *P. ginseng* is a possible alternative medicine and an immune modulator with preventive and therapeutic effects on various diseases via immune regulation. Here, we discuss the current knowledge on effects of *P. ginseng* on MS, CD, UC, atopic dermatitis, and RA and suggest significance of research and development using *P. ginseng* for autoimmune diseases.

4. Effects of *P. ginseng* on autoimmune diseases

4.1. Effects of *P. ginseng* on MS

MS is a representative autoimmune disease in the central nervous system characterized by inflammatory demyelination. It affects more than 2.5 million people globally. Myelin is attacked by host immune cells, resulting in loss of motor functions, mood disorders, cognitive disorders, and other neurological symptoms [30]. MS is classified into four types depending on the course of the disease: relapsing-remitting MS (RRMS), primary progressive MS, secondary progressive MS, and progressive-relapsing MS [30]. RRMS is the general form of MS. It occurs predominantly in individuals aged 20 to 45 years and women [30,31]. Currently, drug cannot fully cure MS, although a few Food and Drug Administration-approved drugs (beta interferons, glatiramer acetate, fingolimod, and so on) can ameliorate symptoms of MS [30]. These drugs generally target inflammatory and immunological components (e.g., T-cell differentiation and migration) of MS [32]. Nevertheless, working mechanisms of these drugs are not clearly identified yet. Some of them also have side effects such as increasing risks for liver function abnormalities, leukopenia, thyroid disease, depression, and flu-like symptoms [30]. Therefore, efficient and safe drugs that can forestall the outbreak or delay the onset and progression of MS need to be developed.

P. ginseng and its compounds such as ginsenosides and polysaccharides have shown preventive and therapeutic effects on an experimental autoimmune encephalomyelitis (EAE) mouse

Table 2
Effects of *Panax ginseng* on Crohn's disease and ulcerative colitis.

Component	Experimental model	Results	References
Fermented <i>P. ginseng</i> powder	DSS-induced colitis	(↓) ZO-1 loss; (↓) proinflammatory response; (↓) NF- κ B signaling	[47]
	LPS-induced inflammation in RAW 264.7 cell	(↓) TNF- α , IL-12p40 expression; (↓) NF- κ B translocation levels	[47]
Rf	LPS-induced inflammation in peritoneal macrophages	(↓) TNF- α , IL-12p40, IL-1 β , IL-6, IFN- γ expression	[47]
	LPS-induced inflammation in RAW 264.7 cell	(↓) NO level; (↓) ROS level; (↓) proinflammatory cytokine and enzyme; (↓) NF- κ B translocation levels	[48]
	TNF- α -induced inflammation in HT-29 cell	(↓) IL-1 β , IL-6, iNOS expression; (↓) NF- κ B translocation levels	[48]

DSS, dextran sodium sulfate; ZO-1, zonula occludens-1; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated b cells; LPS, lipopolysaccharide; TNF- α , tumor necrosis factor alpha; IL-12p40, interleukin-12 subunit p40; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IFN- γ , interferon-gamma; NO, nitric oxide; ROS, reactive oxygen species; iNOS, induced nitric oxide synthase

Table 3
Effects of Panax ginseng on atopic dermatitis (AD).

Component	Experimental model	Results	References
KRGE	TNCB-challenged NC/Nga mouse	(↓) serum IgE level; (↓) epidermal hyperplasia; (↓) eosinophil, monocyte infiltration; (↓) cytokine levels of TNF- α , IFN- γ	[51,52]
	Early AD model of TNCB-challenged NC/Nga mouse	(↓) ear thickness; (↓) transepidermal water loss; (↓) serum IgE level; (↓) lymphocyte infiltration;	[53]
	DNCB-challenged Balb/C mouse	(↓) TSLP, TNF- α expression (↓) scratching behavior; (↑) skin condition; (↓) serum IgE levels; (↓) IL-4, IL-10 expression level;	[54]
	DNFB-challenged Balb/C mouse	(↓) MAPK pathway & Ikaros translocation level	[55]
	TNF- α +IFN- γ -induced inflammation HaCaT cell	(↓) serum IgE level; (↓) IL-6, IL-8, TARC, MDC level; (↓) MAPK & NF- κ B signaling	[55]
MCGE	PMA+A23187-induced inflammation HMC-1 cell	(↓) MIP-1 α , MIP-1 β , RANTES MCP-1, IL-1 β , IL-6, IL-8, TNF- α level; (↓) MAPK & NF- κ B signaling	[55]
	DNCB-challenged NC/Nga mouse	(↑) skin lesion; (↓) serum IgE level; (↓) pro-inflammatory cytokine level;	[56]
CFE	TNF- α +IFN- γ -induced inflammation HaCaT cell	(↓) TARC level	[56]
	DFE-induced AD in NC/Nga mouse	(↓) clinical & behavioral score; (↓) immune cell infiltration;	[58]
Gintonin	DNFB-challenged NC/Nga mouse	(↓) MDC, pro-inflammatory cytokine & helper T cell-related cytokine level	[59]
		(↓) ear thickness reduction; (↓) dermatitis index; (↓) IgE, histamine, IL-4, IFN- γ ;	
Rg5:Rk1	TNF- α +IFN- γ -induced inflammation HaCaT cell	(↓) epidermal & dermal thickness; (↓) inflammation; (↓) mast cell infiltration	[60]
		(↓) TARC & MDC level; (↓) pro-inflammatory cytokine & enzyme level;	
Rg5:Rk1	LPS-stimulated RAW 264.7 cell	(↓) STAT1, NF- κ B, p38 MAPK phosphorylation level; (↓) NF- κ B translocation level	[60]
		(↓) NO & ROS production; (↓) pro-inflammatory cytokine & enzyme level	

KRGE, Korean Red Ginseng; TNCB, trinitrochlorobenzene; IgE, immunoglobulin E; TNF- α , tumor necrosis factor alpha; IFN- γ , interferon-gamma; TSLP, thymic stromal lymphopoietin; DNCB, 1-chloro-2,4-dinitrobenzene; IL-4, interleukin-4; IL-10, interleukin-10; MAPK, mitogen-activated protein kinase; DNFB, 1-fluoro-2,4-dinitrobenzene; IL-6, interleukin-6; IL-8, interleukin-8; TARC, thymus and activation-regulated chemokine; MDC, macrophage-derived chemokine; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated b cells; IL-1 β , interleukin-1 β ; MIP-1 α , macrophage inflammatory protein-1 α ; MIP-1 β , macrophage inflammatory protein-1 β ; RANTES, regulated on activation normal T cell expressed and secreted; MCP-1, monocyte chemoattractant protein-1; MCGE, mountain-cultivated ginseng extract; CFE, CK-fortified extract; CK, compound K; DFE, *Dermatophagoides farinae* body extract; STAT1, signal transducer and activator of transcription 1; LPS, lipopolysaccharide; NO, nitric oxide; ROS, reactive oxygen species

model of MS. KRGE has shown preventive effect on a myelin basic protein peptide (MBP_{68–82})–induced acute EAE rat model by ameliorating neurological scores of EAE [33]. The preventive effect of KRGE corresponded to the reduction of demyelination, activation/infiltration of immune cells (microglia and macrophage), expression of pro-inflammatory cytokines/chemokines, adhesion molecules, and inducible nitric oxide (NO) synthase in the spinal cord after immunization [33]. KRGE also reduced the numbers of CD4(+) T, Th1, and Th17 cells in the spinal cord and lymph nodes, corresponding to downregulation of IFN- γ , IL-17, and IL-23 in the spinal cord [33]. On the other hand, KRGE enhanced the numbers of Treg cells in the spinal cord and lymph nodes of the same rats [33]. KRGE also reduced blood-brain barrier (BBB) permeability via protecting BBB disruption in the same model [33]. Additionally, pretreatment and the onset of treatment with KRGE alleviated neurological impairment of myelin oligodendrocyte glycoprotein (MOG)–induced mouse

model of chronic EAE [33], suggesting that KRGE might be beneficial for the early stage of MS. Recently, it has been demonstrated that KRGE can mitigate spinal demyelination in the MBP-induced acute MS rat model. It inhibited the recruitment and activation of immune cells including microglia and decreased mRNA expression of proinflammatory mediators (IL-6, IFN- γ , and cyclooxygenase-2) but increased mRNA expression of anti-inflammatory mediators (insulin-like growth factor beta 1, transforming growth factor beta, and vascular endothelial growth factor-1) [34]. Its underlying mechanisms were associated with significant downregulation of p38 mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated b cell (NF- κ B) signaling pathways in microglia/macrophages, T cells, and astrocytes [34].

When ginsenoside Rd was intraperitoneally administered to MOG-induced EAE mice on the disease onset day, it effectively ameliorated the clinical severity in the EAE mice and reduced the

Table 4
Effects of Panax ginseng on rheumatoid arthritis.

Component	Experimental model	Results	References
KRGE	collagen-induced arthritis	(↑) clinical arthritis score; (↓) joint inflammation; (↓) STAT3 phosphorylation; (↓) Th17 cell number; (↓) RANKL-induced osteoclastogenesis	[65]
RGSF-A	collagen-induced arthritis	(↓) proinflammatory cytokine production; (↓) serum antibody production; (↓) leukocyte activation; (↓) immune cell infiltration; (↓) clinical severity; (↑) IL-10 production	[66]
Rg3-, Rk1-, and Rg5-rich saponin extract	collagen-induced arthritis	(↓) progression and severity of arthritis; (↓) MMP-3, nitrotyrosine, SOD expression; (↓) proinflammatory cytokine production; (↓) spleen cell proliferation; (↓) oxidative tissue damage	[67]
CK	adjuvant-induced arthritis	(↓) clinical score and behavioral symptoms; (↓) spleen and joint inflammation; (↑) regulatory T-cell rate; (↓) T-cell proliferation	[68]
	RA-FLS and RAW 264.7 using <i>in vitro</i> study	(↓) MMP secretion; (↓) osteoclastogenesis; (↓) RA-FLS apoptosis; (↓) MAPK signaling	[69]
Rc	collagen-induced arthritis	(↓) clinical score; (↓) inflammation; (↓) collagen deposition; (↓) proinflammatory cytokine levels	[70]
Rg1	adjuvant-induced arthritis	(↑) joint swelling; (↓) proinflammatory cytokine levels; (↑) PPAR- γ protein expression	[71]

KRGE, Korean Red Ginseng extract; STAT3, signal transducer and activator of transcription 3; Th17, helper T cell 17; RANKL, receptor activator of nuclear factor kappa-B ligand; RGSF-A, red ginseng saponin fraction A; IL-10, interleukin-10; MMP-3, matrix metalloproteinase 3; SOD, superoxide dismutase; CK, compound K; RA-FLS, rheumatoid arthritis fibroblast-like synoviocyte; MMP, matrix metalloproteinase; MAPK, mitogen-activated protein kinase; PPAR- γ , peroxisome proliferator-activated receptor gamma

permeability of the BBB, in agreement with downregulation of the IFN- γ level, upregulation of the IL-4 level, and promotion of Th2 shift in splenocytes and cerebral cortex [35]. Interestingly, Rd increased the levels of the neural growth factor and brain-derived neurotrophic factor in both cerebral cortex and lumbar spinal cord of EAE mice, indicating that Rd promoted the release of the nervous system growth factor for repair and restoration from pathological loss [35]. Intrathecal pretreatment of rats with ginsenoside Rg1 and Rb1 also mitigated behavioral impairment in the MOG-induced chronic EAE mouse model [33]. These reports demonstrate the potency of ginsenosides Rd, Rg1, and Rb1 in inhibiting the clinical course of EAE. These findings also suggest that ginsenosides could be promising agents for mitigating neuroimmune dysfunction diseases such as MS.

It has been reported that a purified acidic polysaccharide isolated from *P. ginseng* can downregulate Th1 cytokines and splenic proinflammatory cytokines in an MOG peptide (MOG_{35–55})–induced chronic EAE mouse model [36]. Its effect was dependent on the mitigation of neurological symptoms. In contrast, this acidic polysaccharide upregulated Treg cells [36]. Acidic polysaccharides can also lower the levels of immune cell infiltration in the spinal cord, splenic proinflammatory cytokines, spinal demyelination, and neurological scores in a proteolipid protein peptide–induced RRMS EAE mouse model, similar to their effects in an MOG-induced chronic EAE mouse model [37].

Treatment of MS patients with *P. ginseng* for 3 months can reduce their fatigue (86%; 52 of 60 patients), one of the common complaints of patients with MS [24]. It also significantly improved their quality of life [24]. However, in a single-center, randomized, double-blind, placebo-controlled, crossover pilot study of 56 patients with MS, American ginseng did not significantly improve fatigue (assessed by the Fatigue Severity Scale) in the MS group compared with placebo, although it had no serious adverse effects [38]. Again, clinical study of ginseng is very limited. Therefore, clinical studies using ginseng and its components should be continued. KRGE might be useful as a new therapeutic for autoimmune disorders such as MS.

Taken together, KRGE and its components have beneficial effects on the development and progression of EAE. Clinical studies applying ginseng to MS have shown promising results, supporting the need for further investigation using ginseng in patients with MS. Therapeutic effects are expected which can be exciting for patients with MS in the future.

4.2. Effects of *P. ginseng* on CD and UC

CD and UC are autoimmune diseases associated with the gastrointestinal tract. They are the two major types of inflammatory bowel disease (IBD) [27,39]. CD affects any part of the gastrointestinal tract, ranging from the mouth to the anus, whereas UC primarily affects the colon and the rectum [39]. Although mucosal immune response in CD differs from that in UC, both diseases share several common anatomopathological and clinical features such as abdominal pain, vomiting, diarrhea, rectal bleeding, severe internal cramps/muscle spasms in the region of the pelvis, weight loss, and anemia [40,41]. Thus, both CD and UC can seriously limit the quality of life. Additionally, at the turn of the 21st century, they have become global diseases, showing accelerating incidence in newly industrialized countries whose societies have become more Westernized [42]. CD and UC are complex diseases arising from a combination of hereditary factors, genetic factors, and/or environmental factors (diet, microbiota, breach of intestinal barrier, geography, cigarette smoking, sanitation and hygiene, and so on) that can cause autoimmune responses and inflammation in the intestine [43]. A dysregulated mucosal immune response is the central

driver of CD and UC which is characterized by an altered innate immune system along with activated effector T cells, increased presence of B cells, increased antibody production, and increased production of proinflammatory mediators [44]. Although CD and UC are not medically curable, they can be treated by surgery (proctocolectomy for UC), medical therapies [mesalazine and immunosuppressant such as prednisone, tumor necrosis factor (TNF) inhibitors, azathioprine, methotrexate, or 6-mercaptopurine], nutritional and dietetic therapies, microbiome, and alternative medicine [45,46].

In a dextran sodium sulfate–induced colitis model, fermented wild ginseng (FWG) can alleviate the severity of colitis and the infiltration of macrophages in colonic tissue. FWG can also inhibit the expression of proinflammatory cytokines (TNF- α , IL-12 subunit p40, IL-1 β , IL-6, and IFN- γ) in lipopolysaccharide-induced RAW 264.7 macrophage cell lines and peritoneal macrophages. The mechanism underlying favorable effects of FWG involves the attenuation of NF- κ B signaling pathway [47]. Interestingly, beneficial activities of FWG are associated with the presence of FWG metabolites such as compound K (CK), 2-(S)-protopanaxatriol, Rh1, F1, and 20(S)-protopanaxadiol that are not present in wild ginseng. Based on the high-performance liquid chromatography results, fermentation of wild ginseng can increase its metabolites described previously, resulting in enhanced beneficial effects [47]. Ginsenoside Rf can decrease the production of inflammatory mediators [IL-1 β , IL-6, TNF- α , NO, and reactive oxygen species] that are highly activated in IBD and TNF- α –stimulated intestinal epithelial cells (HT-29) and mouse macrophage cells (RAW264.7). In addition, Rf can suppress TNF- α /lipopolysaccharide-induced NF- κ B transcriptional activity [48]. These results suggest that ginseng metabolites such as Rf have potent intestinal anti-inflammatory effects. Thus, they might have potential to treat CD and UC.

Unfortunately, there are no reliable reports showing how *P. ginseng* affects patients with CD and UC, although one study has reported that some patients with IBD are taking *P. ginseng* as a complementary medicine because standard therapy has side effects and low effectiveness for them [49]. In this regard, further research should be performed to investigate how *P. ginseng* affects clinical symptoms of CD and UC. Similar to this, *in vivo* and *in vitro* data are also needed to suggest the possibility of using *P. ginseng* and its components as therapeutics for CD and UC.

4.3. Effects of *P. ginseng* on atopic dermatitis

Atopic dermatitis (AD) is an autoimmune skin disease accompanied by inflammatory responses. The representative symptom of AD is itchiness which can lead to scratching or rubbing the itchy site. This behavior can worsen skin inflammation [26]. Despite the increased numbers of patients with AD, the pathogenesis of AD is still not clearly understood yet. Patients with AD show increased skin levels of Th17-associated cytokines (e.g. IL-17A, IL-6, IL-23) and Th2 cytokines such as IL-4 and IL-13 [50]. In AD, IL-4 is related to Th2 differentiation, IgE production, and eosinophil recruitment. Elevated levels of IL-4 can increase the risk of AD development. Several mouse models have been used to demonstrate the relationship between AD and IL-4 [50]. In addition to IL-4, several other cytokines such as IL-13, IL-5, and epithelial cell–derived cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin are also related to AD.

Several studies have investigated the preventive and therapeutic role of *P. ginseng* in both *in vivo/vitro* models of AD. It has been reported that oral administration of KRGE to trinitrochlorobenzene-challenged NC/Nga mice can attenuate levels of skin condition, serum IgE, epidermal hyperplasia, eosinophil/monocyte infiltration in lesion, and expression of TNF- α and IFN- γ in lesion [51,52]. In the

same model, another group has validated the effect of KRGE on early AD. Oral administration of KRGE reduced the ear thickness and decreased the levels of transepidermal water loss, serum IgE, and lymphocyte infiltration in the ear skin [53]. KRGE also suppressed thymic stromal lymphopoietin and TNF- α expression based on immunohistochemical analysis [53]. Interestingly, direct application of KRGE to skin lesions of 1-chloro-2,4-dinitrobenzene-induced AD mouse improved skin condition and reduced scratching behavior and serum IgE levels associated with reduction in mRNA expression of IL-4 and IL-10 and the lower level of MAPK signaling and Ikaros translocation [54]. In 1-fluoro-2,4-dinitrobenzene-challenged Balb/C mice model, KRGE decreased the levels of serum IgE, IL-6, IL-8, thymus and activation-regulated chemokine (TARC), and macrophage-derived chemokine [55]. In the human keratinocyte cell line HaCaT and human mast cell line HMC-1, KRGE also decreased expression levels of cytokines examined previously. KRGE also suppressed the expression of macrophage inflammatory protein-1 α and macrophage inflammatory protein-1 β , regulated on activation normal T cell expressed and secreted, monocyte chemoattractant protein-1, and IL-8 in HMC-1 cells [55]. Additionally, KRGE lowered NF- κ B and MAPK signaling in both *in vivo* and *in vitro* experiments described previously [54,55]. In 1-chloro-2,4-dinitrobenzene-challenged NC/Nga mice, it has been reported that mountain-cultivated ginseng extract can alleviate the development of AD-like skin symptoms by regulating Th1 and Th2 responses/balances in skin lesions and TARC expression by suppressing TNF- α /IFN- γ -induced NF- κ B activation in human keratinocytes (HaCaT cells) [56].

Modification of *P. ginseng* may alter its compounds, resulting in better therapeutic effects for various disorders. 20-O- β -D-glucopyranosyl-20(S)-pro-topanaxadiol, also known as CK, is derived from ginsenosides Rb1, Rb2, and Rc [57]. CK-fortified extract has been used to treat AD-induced mouse models [58]. In *Dermatophagoides farinae* body extract-induced AD-like symptoms in NC/Nga mice, oral administration of CK can attenuate the dermatitis score, ear thickness, scratching time, and severity of skin lesions. CK treatment also reduced the levels of macrophage-derived chemokines in serum, infiltration of eosinophils and mast cells in skin, and production of proinflammatory/T cell-related cytokines in splenocytes [58]. Gintonin, a recently discovered fraction of *P. ginseng*, mainly consists of lysophosphatidic acids and *P. ginseng* proteins such as GLP151 and GMP [10]. In 1-fluoro-2,4-dinitrobenzene-challenged NC/Nga mice, oral administration of gintonin can reduce ear thickness, lower dermatitis index, and decrease serum levels of IgE, histamine, IL-4, and IFN- γ , in paralleled to decreased levels of epidermal/dermal thickness and inflammatory/mast cell infiltration with involvement of autotaxin regulation [59].

Rg5:Rk1, a mixture of protopanaxadiol-type ginsenoside, can reduce NO and reactive oxygen species production in lipopolysaccharide-stimulated RAW 264.7 cells [60]. It can also decrease RNA expression levels of proinflammatory cytokines and expression levels of TARC and macrophage-derived chemokine in TNF- α /IFN- γ -incubated human keratinocytes (HaCaT) and RAW 264.7 cells by suppressing NF- κ B/p38 MAPK/signal transducer and activator of transcription 1 signaling [60]. Although clinical studies of *P. ginseng* on AD are very limited, one study has reported that daily intake of KRGE by patients with AD can ameliorate symptoms of AD associated with reduction of transepidermal water loss and improvement of skin hydration [61].

These findings and reports have demonstrated that *P. ginseng*, CK, gintonin, and ginsenosides have therapeutic effects on patients with AD and *in vivo/vitro* models. Because both oral application and dermal application of *P. ginseng* are available and the effects of *P. ginseng* on treating AD are promising, *P. ginseng* might be useful as an alternative medicine for AD. Further studies are needed to assess its outcome indicators.

4.4. Effects of *P. ginseng* on RA

RA is a long-term autoimmune disease primarily affecting joints [25]. It typically results in warm, swollen, and painful joints [25]. Although the pathogenesis of RA remains unclear, it is believed to involve a combination of a genetic factor and environmental factors [25]. Harmful environmental factors such as smoking can induce mutations in genes to form neoantigens. Additionally, matrix protein citrullination can occur owing to these neoantigens, resulting in the production of deiminated peptide [25]. The underlying mechanism involves the body's immune system (e.g., lymphocyte activation) attacking joints which results in inflammatory response and thickening of the joint capsule, cartilage, and the underlying bone [25]. RA has been treated using several approved drugs, such as infliximab, tocilizumab, abatacept, and rapamycin. However, these drugs can only ameliorate RA symptoms without successfully curing RA [62]. In addition, they might have adverse effects such as nausea, rash, and respiratory tract disorder [63,64].

KRGE can ameliorate the clinical arthritis score and joint inflammation by histological analysis in a collagen-induced arthritis (CIA) mouse model [65]. The underlying mechanism was associated with reduction of the phosphorylation rate of signal transducer and activator of transcription 3, the number of Th17 cells, and receptor activator of nuclear factor kappa-B ligand. The effect of KRGE was similar to that of human peripheral blood mononuclear cells. Saponin fraction fortified in ginsenoside Rb1, Rc, and Rb2 can decrease the production of proinflammatory cytokine and serum antibody in circulation, reduce leukocyte activation, and increase the serum IL-10 level in the CIA mouse model [66]. Similar to this report, another study has shown that saponin including ginsenosides Rg3, Rk1, and Rg5 can protect against oxidative tissue damage, contribute to the recovery of superoxide dismutase, and inhibit matrix metalloproteinase-3 expression in the CIA mouse model [67]. Effect of *P. ginseng* on RA has been verified using CK, a ginsenoside metabolite [68]. CK reduced the clinical score and behavioral symptoms in adjuvant arthritis-induced mouse associated with decrease of inflammation scores in spleen and joints and T-cell proliferation in *in vivo* and *in vitro* studies but an increase of Treg cells [68]. In another *in vitro* study, CK has also suppressed matrix metalloproteinase secretion, osteoclastogenesis, and MAPK signaling [69]. Ginsenosides Rc or Rg1 can alleviate clinical scores, inflammatory response, and collagen deposition or increase peroxisome proliferator-activated receptor gamma protein expression in CIA mouse models [70,71]. Taken together, these results demonstrate that *P. ginseng* extracts, fraction, and ginsenosides all have favorable effects on RA in both *in vivo* and *in vitro* studies, suggesting that *P. ginseng* might have preventive and therapeutic effects on RA.

To the best of our knowledge, investigating the effect of *P. ginseng* on patients with RA has not been performed yet, although one study has shown that KRGE can inhibit the differentiation of Th17 cells and increase Treg cell population [70]. Further investigation is needed to examine the effect of *P. ginseng* on patients with RA through *in vivo* and *in vitro* studies.

5. Conclusions

P. ginseng and its components might provide powerful intervention for immunological and inflammatory diseases [15,72]. However, the role of *P. ginseng* in autoimmune diseases has been insufficiently investigated. Recently, the continuous increase in the number of patients suffering from autoimmune diseases worldwide has prompted vigorous efforts to develop an appropriate cure for such diseases [73]. However, not much research has been performed on how the immune system is regulated by *P. ginseng*. There

can be some doubts about using *P. ginseng* as a cure for treating autoimmune diseases because *P. ginseng* can boost the immune system and exacerbate such autoimmune diseases at the same time. However, there are reports showing that *P. ginseng* can regulate the immune system in a balanced manner. It has been reported that the ginsenoside Rb1 fraction can balance Th1 and Th2 cell differentiation [74]. Another report has shown that ginsenoside Rd and Re can improve both Th1- and Th2-related cytokine release, suggesting that *P. ginseng* can regulate the immune system in proinflammation- and anti-inflammation-balanced manner [13]. Taken together, these reports suggest that *P. ginseng* might be able to regulate the immune system in a well-balanced way. This supports the idea that *P. ginseng* can become an autoimmune disease-curing medicine. In this regard, future investigations are needed to investigate how *P. ginseng* can regulate both proinflammation and anti-inflammation in autoimmune diseases. Limited preclinical and clinical data for the role of *P. ginseng* in autoimmune diseases suggest that *P. ginseng* should be studied as a possible 'panacea' for autoimmune diseases.

Conflicts of interest

The authors have declared no conflict of interest.

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