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## Review Article

## Ameliorative effects of ginseng and ginsenosides on rheumatic diseases

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## ABSTRACT

**Background:** Inflammation is a host-defensive innate immune response to protect the body from pathogenic agents and danger signals induced by cellular changes. Although inflammation is a host-defense mechanism, chronic inflammation is considered a major risk factor for the development of a variety of inflammatory autoimmune diseases, such as rheumatic diseases. Rheumatic diseases are systemic inflammatory and degenerative diseases that primarily affect connective tissues and are characterized by severe chronic inflammation and degeneration of connective tissues. Ginseng and its bioactive ingredients, ginsenosides, have been demonstrated to have antiinflammatory activity and pharmacological effects on various rheumatic diseases by inhibiting the expression and production of inflammatory mediators.

**Methods:** Literature in this review was searched in a PubMed site of National Center for Biotechnology Information.

**Results:** The studies reporting the preventive and therapeutic effects of ginseng and ginsenosides on the pathogenesis of rheumatic diseases were discussed and summarized.

**Conclusion:** Ginseng and ginsenosides play an ameliorative role on rheumatic diseases, and this review provides new insights into ginseng and ginsenosides as promising agents to prevent and treat rheumatic diseases.

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## 1. Introduction

Inflammation is an innate immune mechanism to protect the body from invading pathogens and cellular danger signals [1–3]. Although an inflammatory response is a host-defense mechanism, chronic inflammation, defined as repeated and prolonged inflammation, is considered a major risk factor for the development of inflammatory and autoimmune diseases. Rheumatic diseases are chronic inflammatory and degenerative autoimmune diseases that primarily affect connective tissues such as cartilage and bones, ligaments, tendons, and muscles but can also affect nonconnective tissues and internal organs, leading to substantial morbidity [4]. More than 100 rheumatic diseases have been identified, and there are numerous patients who suffer from these

diseases worldwide. This has resulted in extensive investigation of the mechanisms of disease pathogenesis and development of effective therapeutics. Representative rheumatic diseases include rheumatoid arthritis (RA), osteoarthritis (OA), systemic lupus erythematosus (SLE), ankylosing spondylitis, and Sjögren's syndrome. Despite uncertainty regarding the etiology of rheumatic diseases, chronic inflammation and autoimmunity are known to play critical roles in both the onset and progression of rheumatic diseases. Ginsengs and their active components, ginsenosides, have strong antiinflammatory properties; they may therefore have an ameliorative effect on the pathogenesis of rheumatic diseases. Indeed, many studies have investigated the therapeutic effects of ginsengs and ginsenosides on rheumatic diseases *in vitro* and *in vivo*.

**Abbreviations:** ACAN, Aggrecan; ACLT, Anterior cruciate ligament transection; BMP, Bone morphogenetic protein; CIA, Collagen-induced arthritis; CK, Compound K; COL, Collagen; DAMP, Danger-associated molecular pattern; LTMMR, Ligament transection and medial meniscus resection; OA, Osteoarthritis; PAMP, Pathogen-associated molecular pattern; PPD, Protopanaxadiol; PPT, Protopanaxatriol; PRR, Pattern-recognition receptor; RA, Rheumatoid arthritis; RNAKL, Receptor activator of NF- $\kappa$ B ligand; SLE, Systemic lupus erythematosus.

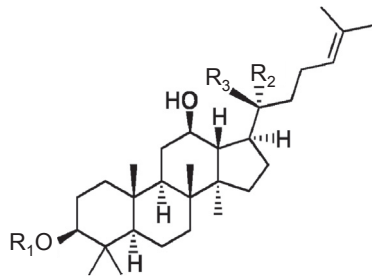
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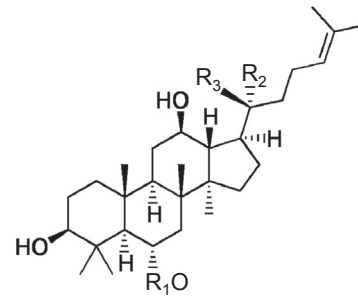
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A



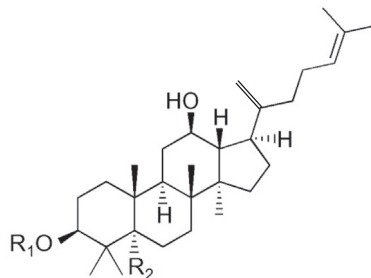
Ginsenosides (G)	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
PPD backbone	H	OH	CH <sub>3</sub>
20(S)-G-Rg3	glc(2-1)glc	OH	CH <sub>3</sub>
20(R)-G-Rg3	glc(2-1)glc	CH <sub>3</sub>	OH
G-Rh2	glc	CH <sub>3</sub>	OH
G-Rb1	glc(2-1)glc	Oglc(6-1)glc	CH <sub>3</sub>
G-Rb2	glc(2-1)glc	Oglc(6-1)araf	CH <sub>3</sub>
G-Rc	glc(2-1)glc	Oglc(6-1)araf	CH <sub>3</sub>
G-Rd	glc(2-1)glc	Oglc	CH <sub>3</sub>
Compound K	H	Oglc	CH <sub>3</sub>

B

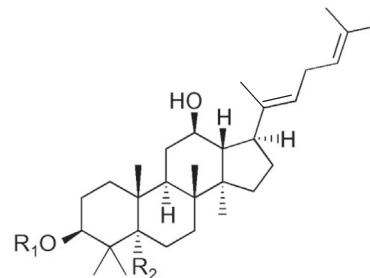


Ginsenosides (G)	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
PPT backbone	H	OH	CH <sub>3</sub>
20(S)-G-Rh1	glc	OH	CH <sub>3</sub>
20(R)-G-Rh1	glc	CH <sub>3</sub>	OH
G-Rg1	glc	Oglc	CH <sub>3</sub>
G-Rg2	glc(2-1)rha	OH	CH <sub>3</sub>
G-Re	glc(2-1)rha	Oglc	CH <sub>3</sub>
G-Rf	glc(2-1)glc	OH	CH <sub>3</sub>
G-F1	H	Oglc	CH <sub>3</sub>

C



Ginsenosides (G)	R <sub>1</sub>	R <sub>2</sub>
G-Rk1	glc(2-1)glc	H
G-Rk2	glc	H
G-Rk3	H	Oglc



Ginsenosides (G)	R <sub>1</sub>	R <sub>2</sub>
G-Rh3	glc	H
G-Rh4	H	Oglc
G-Rg5	glc(2-1)glc	H

**Fig. 1. Types of ginsenosides.** (A) Backbone structure of PPD and the different types of ginsenosides with their side chains (R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>) in the PPD group. (B) Backbone structure of PPT and the different types of ginsenosides with their side chains (R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>) in the PPT group. (C) Backbone structures of rare ginsenosides and the different types of ginsenosides with their side chains (R<sub>1</sub> and R<sub>2</sub>) in this group. PPD, protopanaxadiol; PPT, protopanaxatriol.

Ginseng refers to species of slow-growing plants in the genus *Panax* and has been used to ameliorate and cure various human diseases for thousands of years. Many efforts have been made to purify and identify the bioactive components of ginseng, and ginsenosides have been identified as the main bioactive compounds. A large number of studies have investigated the pharmacological roles of various ginsenosides on the pathogenesis of human diseases, and many studies have reported that various ginsenosides exert an antiinflammatory effect during the inflammatory response and in inflammatory autoimmune diseases [5].

This review provides a brief summary of ginseng and ginsenosides and discusses recent studies that have investigated their pharmacological roles in the pathogenesis of rheumatic diseases. The aim of this review is not only to enhance understanding of the effects of ginseng and ginsenosides in rheumatic diseases but also

to provide new insights that may spur the development of ginseng-containing remedies to prevent and treat rheumatic diseases.

## 2. Ginseng and ginsenosides

Ginseng refers to perennial plant species in the genus *Panax* in the family Araliaceae. Plants in this genus are found worldwide and are cultivated in Eastern Asia and North America. Ginseng has long been used as a traditional herbal medicine and as a health food to improve vitality and physical performance and to reduce or cure spiritlessness and fatigue [6]. There are 13 species in the genus *Panax*, of which the pharmacological properties of five have been investigated: *Panax ginseng* (Asian or Korean ginseng), American ginseng, Vietnamese ginseng, Japanese ginseng, and Pseudo-ginseng. Among these, *Panax ginseng*, also known as Korean

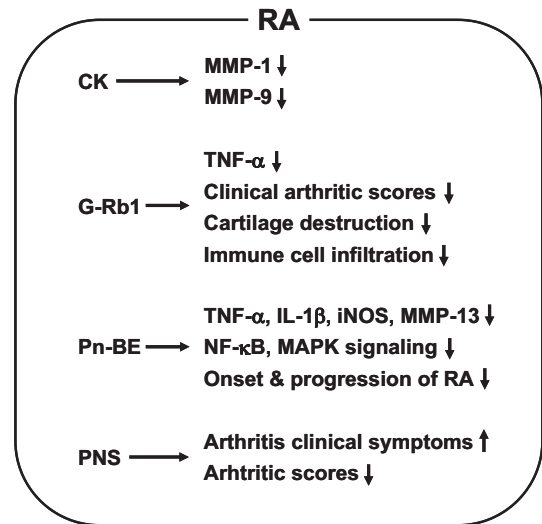
ginseng, is the most popular and commonly used species for therapeutic purposes [7]. The meaning of “*Panax*” is “all healing,” which originates from traditional Oriental medicine beliefs that ginseng could treat all human diseases. A number of studies have demonstrated that ginseng can alleviate the symptoms of various diseases and conditions such as diabetes [8,9], hypertension [10,11], gastric ulcers [12], neuronal disease [13,14], pain [15,16], inflammatory diseases [5,17], and cancers [18,19]. Further studies have revealed the pharmacologically active compounds of ginseng: ginsenosides, ginsenosides, polysaccharides, peptides, phytosterols, polyacetylenes, polyacetylenic alcohols, and fatty acids [20,21]. Among these, ginsenosides are the main bioactive compounds in ginseng, and most studies of the pharmacological and medicinal effects of ginseng have focused on ginsenosides. Ginsenosides are steroidal triterpenoid saponins [22]. More than 100 different types of ginsenosides have been identified, and ginsenosides are presented by G-Rx, where x is determined by the distance moved on thin layer chromatography from the polar segment marked “A” to the least polar segment marked “H” [23]. Ginsenosides are classified as protopanaxadiol, protopanaxatriol, or rare ginsenosides based on the backbone structure (Fig. 1), and various reactive groups and sugars are attached to the different areas of the backbone to generate distinctive ginsenoside molecules. A number of studies have successfully demonstrated that many types of ginsenosides have pharmacological effects in various human diseases, such as cardiovascular diseases [24,25], neuronal diseases [14], diabetes [26], obesity [27], skin diseases [28], and cancers [29,30]. Ginsenosides have also been reported to have antiinflammatory effects during inflammatory responses and in inflammatory diseases [5], and many studies have demonstrated that ginsenosides have a pharmacological effect on rheumatic diseases, which are the most common inflammatory autoimmune diseases.

### 3. Effects of ginseng and ginsenosides in rheumatic diseases

#### 3.1. Rheumatoid arthritis

RA is a long-term inflammatory autoimmune disease that causes chronic joint inflammation with the symptoms of pain, swelling, and stiffness in the hands, feet, knees, and wrists. RA is generally characterized by chronic synovial inflammation of the joints, resulting in the degradation and destruction of cartilages and bones, and has poor outcomes with limited treatment options [31,32]. Despite the lack of robust epidemiological studies in some regions and the difference in RA prevalence between ethnicities, the prevalence of RA is the highest among the inflammatory autoimmune diseases, ranging from 0.5 to 1% of the population worldwide [33,34]. The exact causes of RA pathogenesis remain unknown, but chemokines, pro-inflammatory cytokines [e.g., tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-6], and inflammatory mediators [e.g., reactive oxygen/nitrogen species, prostaglandins, cyclooxygenase-2, matrix metalloproteinases (MMPs)], and the influx of inflammatory immune cells (e.g., macrophages, neutrophils) are thought to play a critical role in RA pathogenesis [32,35]. Therefore, many efforts have been made to develop RA therapies by suppressing these inflammatory products.

As discussed earlier, a number of studies have demonstrated the antiinflammatory properties of ginseng and ginsenosides, and their ameliorative effects on RA pathogenesis have also been studied. Joint-protective effects of compound K (CK) on RA pathogenesis were investigated *in vitro*. Choi et al demonstrated that CK significantly decreased the production of MMP-1 and MMP-3 from RA fibroblast-like synoviocytes by inhibiting janus kinase (JNK) and extracellular signal-regulated kinase (ERK) signaling pathways [36]. *In vivo* studies have also investigated the effects of ginseng and ginsenosides on RA pathogenesis using RA animal models. Kim et al



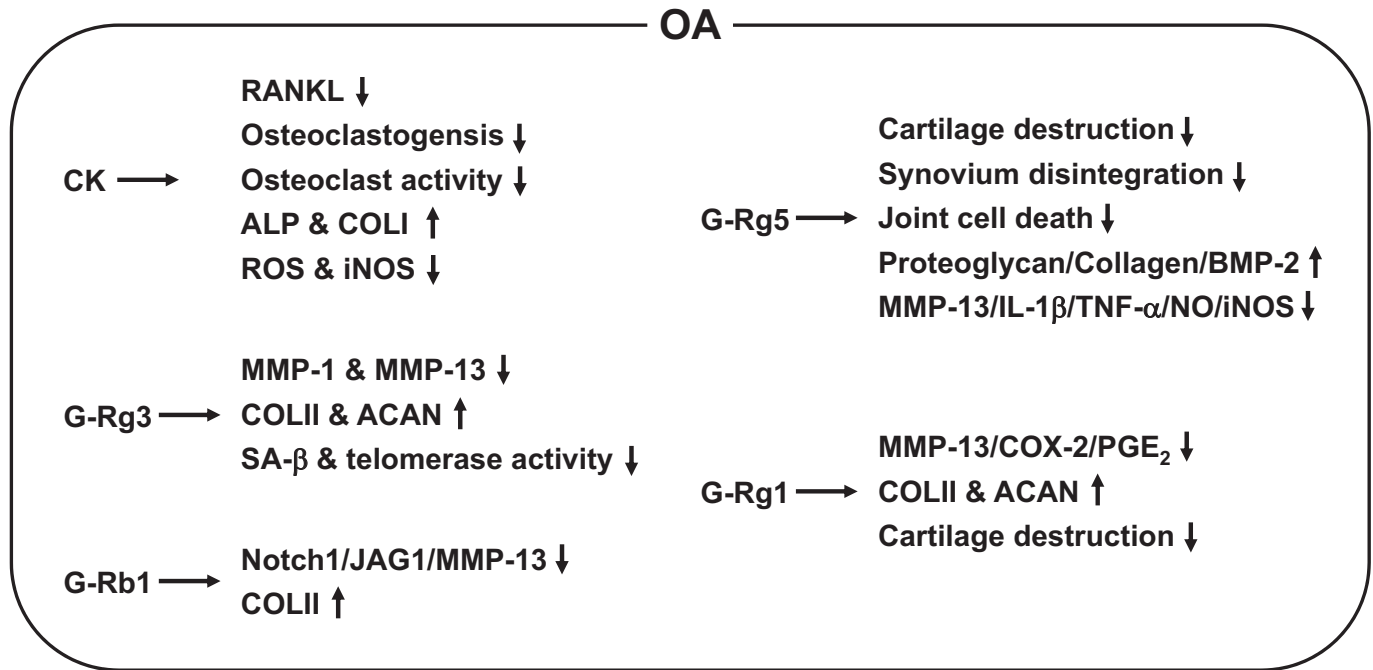
**Fig. 2. Schematic summary of ameliorative effects of ginseng and ginsenosides on RA pathogenesis.** CK, G-Rb1, Pn-BE, and PNS ameliorate RA by decreasing MMP-1, MMP-9, MMP-13, TNF- $\alpha$ , IL-1 $\beta$ , iNOS, and NF- $\kappa$ B/MAPK signaling, clinical arthritis scores, cartilage destruction, immune cell infiltration, and onset/progression of RA and by improving arthritis clinical symptoms in various cells, animal models, and human RA patients.

CK, compound K; IL-1 $\beta$ , interleukin-1 $\beta$ ; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF- $\kappa$ B, nuclear factor-kappa B; Pn-BE, *Panax notoginseng* butanol extract; PNS, *Panax notoginseng* saponin; RA, rheumatoid arthritis; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

demonstrated the antiarthritic effects of ginsenoside Rb1 (G-Rb1) in collagen-induced arthritic (CIA) mice and reported that oral administration of G-Rb1 markedly ameliorated clinical arthritis scores and also reduced immune cell infiltration and cartilage destruction by suppressing TNF- $\alpha$  expression, which is upregulated during inflammatory responses in CIA mice [37]. This study also demonstrated that G-Rb1 significantly inhibited TNF- $\alpha$  expression induced by interferon- $\gamma$  in peripheral blood mononuclear cells, chondrocytes, and fibroblast-like synoviocytes isolated from human RA patients [37]. Chang et al investigated the antiinflammatory effects of BT-201, a *Panax notoginseng* butanol extract, in CIA mice and reported that BT-201 attenuated the onset and progression of arthritic symptoms and reduced arthritic histological scores [38]. The antiarthritic effects of BT-201 were achieved by inhibiting TNF- $\alpha$  and IL-1 $\beta$  secretion from THP-1 cells, inhibiting inducible nitric oxide synthase production in RAW264.7 cells, MMP-13 production in SW1353 cells by suppressing nuclear factor-kappa B, and mitogen-activated protein kinase signaling pathways [38]. Antiarthritic effects of ginseng were also investigated in 84 RA patients. Zhang et al demonstrated that *Panax notoginseng* saponin significantly improved the clinical symptoms and reduced arthritic indexes in RA patients [39]. Although protein-based antiarthritic blockbuster drugs, such as TNF-blockers, IL-1-blockers, and IL-6-blockers, are currently used to treat RA, alternative approaches are in great demand because of the instability of the protein drugs and existence of TNF-failure patient groups. Collectively, the studies described previously strongly suggest that ginseng and ginseng-derived components can suppress inflammatory responses and ameliorate RA pathogenesis (Fig. 2) and could therefore potentially be used as antiarthritic agents to prevent and treat RA.

#### 3.2. Osteoarthritis

OA is a complex and multifactorial joint degenerative disease resulting from the breakdown of cartilage and the underlying



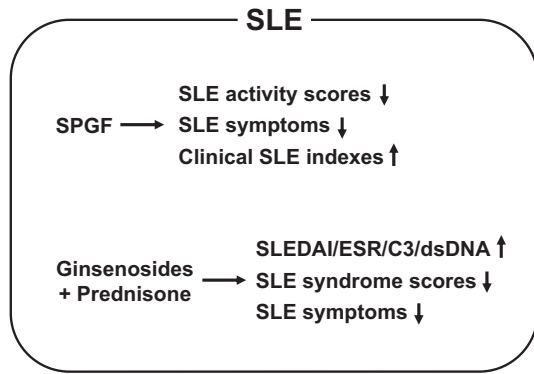
**Fig. 3. Schematic summary of the ameliorative effects of ginsenosides on OA pathogenesis.** CK, G-Rg1, G-Rg3, G-Rg5, and G-Rb1 ameliorate OA by decreasing RANKL, ROS, NO, iNOS, MMP-1, MMP-13, Notch1/JAG1, SA-β, IL-1β, TNF-α, COX-2, PGE<sub>2</sub>, osteoclastogenesis, osteoclast activity, telomerase activity, cartilage destruction, synovium disintegration, and joint cell death, by increasing expression of ALP, collagens, ACAN, proteoglycan, and BMP-2, and by improving OA clinical symptoms in cells and animal models. ALP, alkaline phosphatase; ACAN, aggrecan; BMP-2, bone morphogenetic protein 2; CK, compound K; COLI, type 1 collagen; COLII, type 2 collagen; COX-2, cyclooxygenase-2; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; JAG1, jagged 1; MMP, matrix metalloproteinase; NF-κB, nuclear factor-kappa B; NO, nitric oxide; OA, osteoarthritis; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; RANKL, receptor activator of NF-κB ligand; ROS, reactive oxygen species; SA-β, senescence-associated β; TNF-α, tumor necrosis factor-α.

bones of the joint tissues and is characterized by the symptoms of pain, swelling, and stiffness in the hands, knees, and hips. Although the prevalence of OA varies based on the specific joints affected and characteristics of the study population, the prevalence of knee OA in the population aged above 60 years has been estimated to be 13% in women and 10% in men [40], and the proportion of the population with symptomatic knee OA is strongly associated with obesity and aging [41]. Prevalence of OA is expected to increase in the next few decades, with risk factors for OA pathogenesis thought to be damage from mechanical stress due to congenital causes, pathogen infection, excessive body weight, loss of strength in the muscles, and insufficient self-repair of damaged joint tissues [42]. Acetaminophen and nonsteroidal antiinflammatory drugs are prescribed to relieve pain, and several types of therapies, such as physical, occupational, and yoga therapies, have been applied to OA patients to improve their disease symptoms. Knee replacement surgery using titanium can relieve pain and disability. However, there are ongoing studies to develop disease-modifying agents for OA to target disease processes, not symptoms [43–46], such as cell-mediated therapy with intraarticular injection [47–50].

The *in vitro* and *in vivo* ameliorative effects of ginseng and ginsenosides on OA have been investigated using various cell types and OA animal models, respectively. Choi et al demonstrated that CK reduced the expression of reduced receptor activator of nuclear factor-kappa B ligand (RANKL) in fibroblast-like synoviocytes and significantly inhibited RANKL-induced osteoclastogenesis or osteoclast activity in RAW264.7 cells and human CD14<sup>+</sup> monocytes by suppressing RANKL-mediated inhibitor of kappa B degradation and nuclear factor of activated T cells c1 expression [36]. Therapeutic potential of CK for treating OA was further investigated *in silico* and *in vitro*. Kang et al reported that CK had strong binding affinity for inhibitor of kappa B kinase based on *in silico* analysis and demonstrated that CK significantly increased the expression of the

osteoblast differentiation markers alkaline phosphatase and type I collagen and reduced the production of reactive oxygen species and nitric oxide, which are critical molecules required for the development of OA, in H<sub>2</sub>O<sub>2</sub>-stimulated mouse osteoblast precursor cells (MC3T3-E1 cells) [51]. Another *in vitro* study investigated the protective effects of ginsenoside Rg3 (G-Rg3) on human osteoarthritic chondrocytes. So et al isolated chondrocytes from OA patients and demonstrated that G-Rg3 markedly reduced the expression of MMP-1 and MMP-13, which are chondrodegenerative proteins, and increased the expression of type 2 collagen (COLII) and aggrecan, which are chondroprotective proteins, in IL-1β-stimulated chondrocytes [52]. Moreover, G-Rg3 suppressed the expression of senescence-associated β-GAL, a biomarker of cellular senescence, and increased telomerase activity, which is known to be reduced during cellular aging, in chondrocytes [52].

*In vivo* studies have also investigated the therapeutic potential of ginseng and ginsenosides for treating OA in animal models. Wang et al generated an OA rat model by anterior cruciate ligament transection (ACLT) and demonstrated that intraarticular injection of G-Rb1 lowered levels of Notch1 and its ligand, jagged 1, which are overexpressed in OA [53], in the cartilage [54]. G-Rb1 treatment was strongly associated with decrease in levels of Notch1, jagged 1, and MMP-13 and increased level of COLII in IL-1β-stimulated human osteosarcoma cells (SW1353 cells) [53]. In addition, Zhang investigated the effect of ginsenoside Rg5 (G-Rg5) on the degradation of articular cartilage in an OA rat model prepared by ligament transection and medial meniscus resection. Histopathological analysis showed that G-Rg5 significantly alleviated OA symptoms by preventing cartilage degradation, synovial membrane disintegration, and apoptotic cell death in the knee joints in ligament transection and medial meniscus resection OA rats [55]. An *in vitro* study revealed that G-Rg5 increased proteoglycan, collagen, and bone morphogenetic protein 2 levels and decreased MMP-13, IL-1β,



**Fig. 4.** Schematic summary of ameliorative effects of ginseng and ginsenosides on SLE pathogenesis. SPGF and combination therapy with ginsenosides and prednisone ameliorate SLE by decreasing SLE activity scores; increasing SLEDAI, ESR, C3, and dsDNA expression; and improving SLE clinical indexes and SLE symptoms in human SLE patients. C3, complement 3; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SPGF, saponins of ginseng fruit.

TNF- $\alpha$ , nitric oxide, and inducible nitric oxide synthase levels in the chondrocytes of OA rats [55]. Chang et al investigated the chondroprotective effects of ginsenoside Rg1 (G-Rg1) in human OA patients and an OA rat model by preparing articular chondrocytes from OA patients and an OA rat model that underwent ACLT.

Histological analyses showed that G-Rg1 suppressed gene and protein expression of MMP-13, COX-2, and prostaglandin E<sub>2</sub> and prevented the degradation of COLII and aggrecan in IL-1 $\beta$ -stimulated human OA articular chondrocytes [56]. G-Rg1 also ameliorated OA symptoms in ACLT OA rats by attenuating cartilage degradation and decreasing COLII loss and MMP-13 level [56]. Taken together, these results suggest that ginsenosides attenuate OA pathogenesis by decreasing the expression of cartilage-degrading factors and increasing the expression of cartilage-protecting factors (Fig. 3) and could therefore be useful as anti-OA remedies to prevent and treat OA.

### 3.3. Systemic lupus erythematosus

SLE, the most common form of lupus, is a chronic autoimmune disease in which the immune system attacks healthy self-tissues in almost any part of the body. It is characterized by a wide range of clinical manifestations, including painful and swollen joints, fever, hair loss, chest pain, feeling tired, and malar “butterfly” rash. Despite the wide range of symptoms, one of the common clinical hallmarks of SLE is circulating autoantibodies and immune complexes that recognize host-derived substances, such as nucleic acids and insufficiently removed apoptotic bodies [57,58]. The prevalence of SLE varies according to geographical region, study design, age, sex, and ethnicity, and SLE is much more common in women than in men (ratio of approximately 6:1) [59]. The highest prevalence of SLE was reported in North America (214 cases per 100,000 people),

**Table 1**  
Effects of ginseng and ginsenosides on rheumatic diseases

Disease	Compound	Effects	Experimental models	Ref.
RA	CK	Decreases MMP-1 and MMP-9 production	Human RA fibroblast-like synoviocytes	[36]
	G-Rb1	Decreases TNF- $\alpha$ expression Ameliorates clinical arthritic scores Reduces immune cell infiltration and cartilage destruction	Human RA fibroblast-like synoviocytes Human PBMCs Human chondrocytes Collagen-induced arthritic mice	[37]
	Pn-BE	Inhibits TNF- $\alpha$ , IL-1 $\beta$ , iNOS, and MMP-13 expression Suppresses NF- $\kappa$ B and MAPK signaling pathways Attenuates onset and progression of CIA	Human THP-1 cells Mouse RAW264.7 cells Human SW1353 cells Collagen-induced arthritic mice	[38]
PNS	Improves clinical symptoms Reduces arthritic indexes Reduces RANKL expression	Human RA patients	[39]	
OA	CK	Reduces RANKL expression Inhibits RANKL-induced osteoclastogenesis/osteoclast activity Increases ALP and COLI levels Reduces ROS and NO levels	Human RA fibroblast-like synoviocytes Mouse RAW264.7 cells Human CD14 <sup>+</sup> monocytes Mouse MC3T3-E1 cells	[36] [51]
	G-Rg3	Decreases MMP-1 and MMP-13 expression Increases COLII and ACAN expression Suppresses SA- $\beta$ -GAL level and telomerase activity	Human chondrocytes	[52]
	G-Rb1	Decreases Notch1, JAG1, and MMP-13 expression Increases COLII expression	Human SW1353 cells ACLT OA rats	[53]
	G-Rg5	Prevents cartilage destruction, synovial membrane disintegration, and apoptotic cell death in knee joints Increases proteoglycan, collagen, and BMP-2 expression Decreases MMP-13, IL-1 $\beta$ , TNF- $\alpha$ , NO, and iNOS expression	LTMMR OA rat chondrocytes LTMMR OA rats	[55]
	G-Rg1	Decreases MMP-13, COX-2, and PGE <sub>2</sub> expression Increases COLII and ACAN expression Attenuates cartilage destruction	Human OA chondrocytes ACLT OA rats	[56]
SLE	SPGF	Decreases disease activity scores Ameliorates SLE symptoms Improves clinical SLE indexes	Human SLE patients	[62]
	Ginsenosides + prednisone	Improves SLEDAI, ESR, C3, and anti-dsDNA levels Decreases disease syndrome scores Improves disease symptoms	Human SLE patients Human SLE patients	[63] [64]

ACAN, aggrecan; ACLT, anterior cruciate ligament transection; ALP, alkaline phosphatase; BMP-2, bone morphogenetic protein 2; C3, complement 3; CIA, collagen-induced arthritic; CK, compound K; COLI, type 1 collagen; COLII, type 2 collagen; COX-2, cyclooxygenase-2; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; IL-1 $\beta$ , interleukin-1 $\beta$ ; iNOS, inducible nitric oxide synthase; JAG1, jagged 1; LTMMR, ligament transection and medial meniscus resection; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF- $\kappa$ B, nuclear factor-kappa B; NO, nitric oxide; OA, osteoarthritis; PBMCs, peripheral blood mononuclear cells; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; RA, rheumatoid arthritis; RANKL, receptor activator of NF- $\kappa$ B ligand; ROS, reactive oxygen species; SA- $\beta$ -GAL, senescence-associated  $\beta$ -GAL; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SPGF, saponins of ginseng fruit; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .



whereas the lowest prevalence was reported in Northern Australia (0 cases per 847 people) [60]. Current treatment options for SLE include inflammation-directed treatment, immune cell-targeted therapies, costimulatory signaling-targeted therapies, anticytokine therapies, anti-IgE therapy, and antikinase therapies [61]. Nevertheless, adverse effects related to treatment of SLE and active SLE refractory to traditional therapies remain major challenges, highlighting the need for complementary and alternative strategies to treat SLE.

Several studies have reported that ginseng had an ameliorative effect on SLE pathogenesis. Yang and Zhang investigated the therapeutic effect of saponins of ginseng fruit on SLE pathogenesis in patients with active disease and demonstrated that saponins of ginseng fruit significantly decreased disease activity scores and ameliorated SLE symptoms by improving the clinical efficacy of current medications in SLE patients [62]. You et al evaluated the efficacy of ginsenosides combined with prednisone, a synthetic corticosteroid immunosuppressant drug used for SLE treatment, and reported that the clinical efficacy of the combined therapy was better than that of the corticosteroid alone, as evidenced by a significant improvement in SLE disease activity index, erythrocyte sedimentation rate, and complement 3 and anti-double-stranded DNA levels [63]. In another study, the same research group reported that combined prednisone and ginsenoside therapy significantly decreased disease syndrome scores and improved disease symptoms compared with the prednisone plus placebo group [64]. These studies suggest that ginseng itself as well as combined ginsenoside and current anti-SLE drug therapy could alleviate SLE symptoms and improve clinical outcomes of SLE patients (Fig. 4).

#### 4. Conclusions and perspectives

Inflammation is an innate immune response to defend the host from infectious agents and alter cellular homeostasis. Although inflammation is a defensive response, chronic inflammation has been implicated in the development of several human inflammatory autoimmune diseases, among which rheumatic diseases are some of the most common. Ginseng and its main bioactive ingredients, ginsenosides, have well-documented pharmacological effects on the pathogenesis of inflammatory autoimmune diseases and rheumatic diseases such as RA, OA, and SLE, as described in Table 1. No studies to date have investigated the effects of ginseng and ginsenosides on the pathogenesis of other types of rheumatic diseases, such as ankylosing spondylitis, spondyloarthritis, and Sjögren's syndrome. Moreover, the effects of other types of ginsenosides and ginseng-derived ingredients on the pathogenesis of RA, OA, and SLE have not been explored. Future studies that address these knowledge gaps are required if ginseng and ginsenosides are to be used as novel therapeutics to treat rheumatic diseases.

#### Conflicts of interest

The author declares no conflicts of interest.

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