

Protective effects of ginseng and ginsenosides in the development of osteoarthritis (Review)

JINCAI CHEN^{1*}, LIN HUANG^{2*} and XIAOFEI LIAO³

¹Department of Orthopedics, First Affiliated Hospital of Gannan Medical University;

²Department of Internal Medicine, Ganzhou Hospital of Traditional Chinese Medicine;

³Department of Pharmacy, Ganzhou People's Hospital, Ganzhou, Jiangxi 341000, P.R. China

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Abstract. Osteoarthritis (OA) is a chronic inflammatory joint disease. Traditional Chinese medicine provides a resource for drug screening for OA treatment. Ginseng and the associated bioactive compound, ginsenosides, may reduce inflammation, which is considered a risk factor for the development of OA. Specifically, ginsenosides may exhibit anti-inflammatory and anti-oxidative stress activities, and inhibit extracellular matrix degradation by suppressing the NF- κ B and MAPK signaling pathways. Notably, specific ginsenosides, such as compound K and Rk1, may physically interact with I κ B kinase and inhibit the associated phosphorylation. Thus, ginsenosides exhibit potential as therapeutic candidates in the management of OA. However, the low water solubility limits the clinical applications of ginsenosides. Numerous effective strategies have been explored to improve bioavailability; however, further investigations are still required.

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Correspondence to: Dr Xiaofei Liao, Department of Pharmacy, Ganzhou People's Hospital, 16 Meiguan Road, Ganzhou, Jiangxi 341000, P.R. China
E-mail: xiaofeiliao_gz@163.com

*Contributed equally

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1. Introduction

Osteoarthritis (OA), also known as chronic degenerative arthritis, is characterized by low-grade inflammation in the joints. In total, >250 million patients suffer from OA; thus, posing a serious threat to human health (1). Notably, OA may induce the disability of joints, and cause a loss of labor production and economic burden. At present, there are no effective strategies for the treatment of OA, and the majority of drugs available for the treatment of OA, including non-steroidal anti-inflammatory drugs and glucosamine, only relieve the symptoms. Notably, surgery is often considered last for effectively managing OA of the knee (2). To the best of our knowledge, although numerous previous studies aimed to improve the available treatment options for OA, the results of clinical trials are not satisfactory at present (3,4). This may be explained by a lack of understanding of the potential pathological mechanisms underlying OA.

Pathologically, abnormal metabolic changes may lead to the pathogenesis of OA and these modifications include inflammatory stress, increased chondrocyte apoptosis and extracellular matrix (ECM) degradation (5). Chondrocytes are a unique cell type found in the cartilage that maintains the balance of ECM metabolism (6). However, avascular cartilage with limited capacity for repair is impacted by detrimental stimuli, negatively influencing the biological functions of chondrocytes and subsequently inducing pathological changes (7). Typically, the pathological development of OA is orchestrated by a network of signaling pathways, including the Wnt/ β -catenin (8), PI3K/AKT (9), mitogen-activated protein kinases (MAPK)/NF- κ B (10) and Notch pathways (11). These key signaling pathways are considered potential targets for the development of novel drugs. In recent years, research has focused on the use of Traditional Chinese Medicine (TCM) in the prevention of OA development (12).

Ginseng, belonging to the genus *Panax* in the *Araliaceae* family, is a common TCM used in East Asian countries for the treatment of numerous diseases. Ginseng exhibits dietary, nutraceutical and medicinal uses. The bioactive compounds of ginseng, namely ginsenosides, are classified as steroidal saponins with a triterpene dammarane chemical structure and a steroid-like configuration. To date, ~200 ginsenosides and >40 different subtypes have been discovered (13). Among

these ginsenosides, Rb1, Rb2, Rg1, Rc, Rd, Re and Rg1 are the most abundant (14) (Fig. 1). Moreover, ginsenosides are divided into protopanaxadiol, protopanaxatriol and other subtypes, according to the structure of the backbone. The different modified groups and sugars attached to the backbone produce various distinctive structures of ginsenosides with distinct biological activities (15). Results of recent studies demonstrated that ginsenosides exhibit numerous beneficial properties, including cardiovascular protection (16), neuroprotection (17), liver protection (18), antitumor (19), anti-diabetes (20) and bone protection (21). Moreover, ginsenosides exhibit numerous pharmacological activities, including anti-inflammatory (22), which is the main therapeutic strategy for the clinical management of OA. The present study aimed to review and discuss the protective activities of ginseng and ginsenosides by inhibiting inflammation, oxidative stress and ECM degradation during OA development (Fig. 1).

2. Protective effects of ginseng and ginsenosides against OA development

The pathological development of OA. The pathological development of OA is multifactorial and affected by the activation of signaling cascades. Inflammatory responses and oxidative stress are involved in the progression of OA (23). Inflammation is an innate immune response triggered by pathogens or danger-related signals. Results of a previous study described the association between immune cells and OA development (24). Notably, chondrocytes and synoviocytes are the two cell types responsible for producing inflammatory cytokines and chemokines, and these are involved in the pathogenesis of OA (25). More specifically, the increased production of inflammatory cytokines may induce the aberrant expression of cell signaling pathways, transcriptional expression and joint cartilage destruction. The altered expression of cell signaling pathways may further enhance the release of inflammatory cytokines, forming a positive loop (26). For example, IL-1 β and TNF α are pro-inflammatory cytokines secreted by chondrocytes, synoviocytes and mononuclear cells in early OA. Both IL-1 β and TNF α stimulate the signaling cascade of inflammation, producing IL-6, IL-1 β , TNF α and prostaglandin E2 (PGE2) in chondrocytes (27). In addition, IL-1 β , IL-6 and TNF α are important regulators in the promotion of articular cartilage destruction and synovium inflammatory responses (28). Activation of NF- κ B signaling is associated with increased expression of pro-inflammatory cytokines in OA, including cyclooxygenase-2 (COX-2), PGE2 and inducible nitric oxide synthase (iNOS), the increased expression of MMPs and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs), and the decreased expression of collagen II and aggrecans (29).

Dysregulated expression in both pro- and anti-oxidant systems may induce oxidative stress, which is associated with excessive reactive oxygen species (ROS) production (30). Notably, oxidative stress exerts detrimental effects on macromolecules and stimulates various disorders in the human body. Moreover, oxidative stress is considered a complex pathological process that impacts numerous target organelles, including mitochondria and the endoplasmic reticulum (ER). Initiation of oxidative stress may stimulate organelles to

adaptively modify their metabolism, to protect from injury and maintain cellular homeostasis (31). In addition, increased oxidative stress may impair DNA, protein and lipid production, leading to cellular injury (32). Notably, mitochondria are both producers and targets of ROS. Specifically, the mitochondrial respiratory chain produces ROS, which may induce mitochondrial dysfunction and subsequently enhance the production of ROS with a positive loop (33). Under oxidative stress, increased mitochondrial fission and decreased mitochondrial fusion induce the imbalance of mitochondrial metabolism, leading to the increased expression of Bax and cytochrome c, and the initiation of mitochondrial apoptosis (34). Results of a previous study demonstrated the close association between OA progression and oxidative stress; notably, oxidative stress induces the increased production of ROS in OA chondrocytes (35).

Protective activities of ginseng and ginsenosides against OA.

The participation of inflammatory responses and oxidative stress in OA indicates that the cellular processes of OA chondrocytes may be modulated by appropriate anti-inflammatory agents and anti-oxidants. For example, in lipopolysaccharide (LPS)-treated RAW 264.7 macrophage cells, a ginsenoside Rh2 mixture [consisting of 20(S)-Rh2, 20(R)-Rh2, Rk2 and Rh3] exerted anti-inflammatory effects by inhibiting the expression of NF- κ B signaling (36). In IL-1 β -treated SW1353 cells, Korean red ginseng suppressed the expression of MMP-13 and the release of glycosaminoglycan, by inhibiting the activation of p38 MAPK, JNK and STAT1/2 signaling pathways (37). In addition, the results of a previous study demonstrated that extracts of *Notoginseng Radix* and *Rehmanniae Radix Preparata* alleviate joint pain and inhibited cartilage degeneration in rat OA models (38). Similarly, *Panax quinquefolium* saponin, isolated from *Radix panacis quinquefolia* (American ginseng) inhibited IL-1 β -induced ER stress, NF- κ B-mediated inflammatory responses and cell apoptosis in rat chondrocytes (39,40). Red ginseng also exhibits anti-oxidative activity, which may be an advantage in protecting against the destruction of joint cartilages (41). In a double-blind randomized trial, patients treated with red ginseng demonstrated improved joint pain, higher disability of the arm, shoulder and hand scores, increased production of antioxidant enzymes, and decreased expression of oxidative stress markers (42). Maltol, a compound in red ginseng, reduces the levels of pro-inflammatory cytokines and the production of catabolic factors, such as MMP-13 and ADAMTS-5, by suppressing NF- κ B activity and increasing the nuclear factor (erythroid-derived 2)-like 2 (NRF2) pathway (43,44). These results demonstrated the protective activity of ginseng and the corresponding bioactive ginsenosides. Moreover, these results highlighted the molecular mechanisms that may exhibit potential in the suppression of inflammatory responses and oxidative stress in OA chondrocytes.

3. Anti-inflammatory properties of ginsenosides

Results of a previous study suggested that inflammasomes exhibit potential as biomarkers in inflammatory diseases. Activation of inflammasomes may trigger caspase-1, which activates IL-1 β , IL-18 and IL-33 (45). Results of a previous study demonstrated the biological activity of ginsenosides in

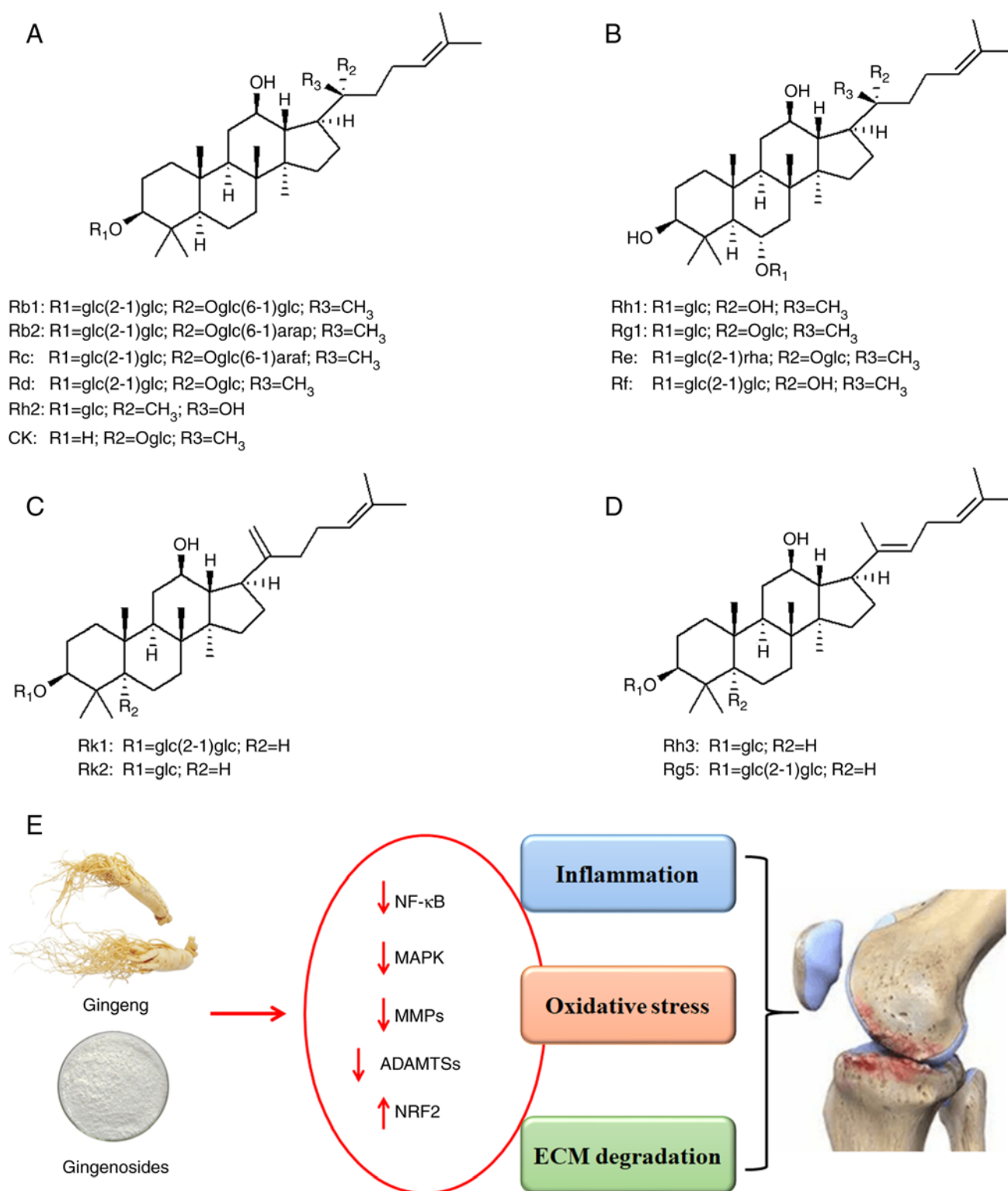


Figure 1. Chemical structures of ginsenosides and the protective effects of ginseng and ginsenosides against osteoarthritis. (A) Different ginsenosides of the protopanaxadiol type. Ginsenoside Rb1 has a glc(2-1)glc group at the R1 position, a Oglc(6-1)glc group at the R2 position, and a methyl group at the R3 position. Ginsenoside Rb2 and Rc have the same groups as Rb1 at the R1 and R3 position, while the R2 position is replaced by Oglc(6-1)arap and Oglc(6-1)araf groups, respectively. The R1, R2 and R3 positions of Ginsenosides Rd, Rh2 and CK are glc(2-1)glc, glc, and H, Oglc, CH₃ and Oglc, and CH₃, OH and CH₃, respectively. (B) Different ginsenosides of the protopanaxatriol type. (C) Derivatives of protopanaxadiol: Ginsenosides Rk1 and Rk2. (D) Derivatives of protopanaxadiol: Ginsenosides Rh3 and Rg5. (E) The protective activity of ginseng and ginsenosides against osteoarthritis development by inhibiting inflammation, oxidative stress and ECM degradation. ECM, extracellular matrix.

the activation of inflammasomes (46). Notably, ginsenoside Rg1 and Rh3 inhibit the activation of inflammasomes by inhibiting NOD-like receptor thermal protein domain associated

protein 3 (NLRP3) and absent in melanoma 2 activity in mouse and human macrophages (47). Moreover, the inhibitory activity of Rg1 against inflammasomes has been demonstrated

in numerous diseases (48). In IL-1 β -treated human OA chondrocytes, Rg1 significantly decreased the production of COX-2 and PGE2 (49) (Table I). In addition, ginsenoside Rb1 and Rb2 may decrease the levels of TNF α in RAW 264.7 cells with IC₅₀ values of 56.5 and 27.5 μ M, respectively, and in U937 cells with IC₅₀ values of 51.3 and 26.8 μ M, respectively (50). Moreover, Rb1 inhibited the IL-1 β -induced expression of COX-2/PGE2 and iNOS/NO, and caspase-3 and PARP mRNA expression in primary human OA chondrocytes (51) (Table I). Results of a previous study demonstrated that ginsenoside Rf decreases the serum levels of IL-6, IL-1 β and TNF α (52).

In monoiodoacetate (MIA)-induced OA in ovariectomized (OVX) rats, Rb1 exhibited inhibitory activity against inflammatory responses, as indicated by the decreased expression of IL-1 β , IL-6, monocyte chemoattractant protein-1/C-C motif chemokine 2 and PGE2/COX-2 (Table I) (53). Fibroblast growth factor 18 (FGF18) plays a critical role in cartilage formation, osteogenesis and bone development (54). Increased expression of FGF18 is associated with anabolic activity in cartilaginous tissues and this may act as a potential target for the therapeutical management of OA (55). Results of a previous study demonstrated that Rb1 enhances the expression of FGF18 by sponging miR-21-5p in MIA-induced OA rats, protecting against OA development. Overexpression of miR-21-5p abolished the chondroprotective effects of Rb1 by stimulating inflammatory responses, decreasing cell viability and attenuating FGF18-mediated chondroprotection (56) (Table I).

NF- κ B signaling plays a crucial role in inflammatory responses. Activation of the NF- κ B signaling pathway includes phosphorylation of I κ B kinases (IKKs), I κ B and p65, nuclear translocation of p65, and transcriptional regulation of target genes (57) (Fig. 2). Moreover, ginsenoside Rk1 may ameliorate inflammation by inhibiting LPS-induced phosphorylation of NF- κ B, JAK2 and STAT3-Ser727/-Tyr705 in RAW 264.7 cells (58). In murine models of sepsis *in vivo* and *in vitro*, ginsenosides exerted inhibitory activity against inflammation by suppressing NF- κ B and MAPK signaling pathways (59). Moreover, the expression of NF- κ B signaling is activated in primary human OA chondrocytes (60). Ginsenoside Ro also exhibits potential as an inhibitor of inflammation by suppressing NF- κ B signaling pathways. Results of a previous study demonstrated that Ro inactivates the TNF α -induced NF- κ B signaling pathway (61) (Table I). More specifically, Ro exhibited inhibitory activity against the IL-1 β -induced upregulation of COX-2, Bax, Bad and caspase-3 expression, the downregulation of Bcl-xL and proliferating cell nuclear antigen expression, and phosphorylation of p65 and p53, inhibiting NF- κ B-associated inflammation and chondrocyte apoptosis (62).

MAPKs exhibit an essential role in cell responses to stimuli, such as inflammatory cytokines. GTPase-induced activation of MAPK kinase kinases induces phosphorylation of MAPK kinases which activate p38 MAPK (63) (Fig. 2). Moreover, P38 MAPK is activated by IL-1 β and TNF α , and suppression of p38 MAPK may lead to the decreased production of inflammation cytokines (64). P38 MAPK is involved in activation of the NF- κ B signaling pathway. Results of a previous study demonstrated that ginsenosides exert their therapeutic effects by targeting p38 MAPK (65). Notably, Rb1 inhibited 2,4,6-trinitrobenzene sulfuric acid-stimulated COX-2 and iNOS expression, the NF- κ B signaling pathway,

and LPS-induced NF- κ B and MAPK (p38, ERK1/2 and JNK) pathways (66). In a rabbit OA model, Rb1 inhibited the activity of NF- κ B, p38 MAPK and PI3K/AKT signaling pathways to inhibit inflammatory responses, ameliorate histopathological changes and protect rabbit knee articular cartilages (67) (Table I).

4. Anti-oxidative activity of ginsenosides

Hydrogen peroxide (H₂O₂) exhibits various biological effects by generating ROS, which is associated with oxidative stress and increased chondrocyte apoptosis (68). Mechanistically, H₂O₂ enhances the permeability of the mitochondrial membrane and promotes the translocation of cytochrome c from the mitochondria to the cytoplasm, leading to the initiation of apoptotic pathways (69). Results of a previous study demonstrated that Rb1 exhibits inhibitory activity against H₂O₂-induced mitochondrial permeability transition and caspase-3 expression, and exerted effects on Bcl-xL expression, leading to suppression of cell apoptosis in rat chondrocytes (70) (Table I). Similarly, Rb1 treatment ameliorated the decreased viability caused by H₂O₂, increased the production of ROS and NO, and decreased the expression of chondrogenic genes, including Sox9 and collagen II in rat chondrocytes (71) (Table I). In IL-1 β -treated rat chondrocytes, Rg1 maintained mitochondrial functions and ameliorated mitochondrial-mediated apoptosis, demonstrated by the increased expression of Bcl-2 and the decreased expression of Bax, cytochrome c and caspase-3. Interestingly, treatment with the PI3K inhibitor, LY294002, may reverse the protective effects of Rg1 (72).

In IL-1 β -treated human OA chondrocytes, Rg1 reduced the levels of ROS, decreased the production of malondialdehyde (MDA), improved the mitochondrial membrane potential, upregulated the expression of Bcl-2, downregulated the expression of Bax, caspase-3, caspase-9, factor-related apoptosis ligand, apoptosis-inducing factor and cytochrome c, and inhibited IL-1 β -induced chondrocyte apoptosis by decreasing the PI3K/AKT-mediated mitochondrial signaling pathway (73). TNF α stimulation may induce the loss of mitochondrial mass, DNA copy number and the generation of ROS, decrease the mitochondrial membrane potential and upregulate IL-8 and MMP-9, eliciting chondrocyte apoptosis and ECM degradation (74). Results of a recent study demonstrated that Rg3 activates Sirt3/PGC-1 α expression and reversed the effects of TNF α on the acetylation of cyclophilin D and mitochondrial dysfunction through downregulation of NF- κ B and p38 MAPK signaling pathways (74) (Table I).

NRF2, a key transcriptional factor in the redox system, regulates the anti-oxidative defence at multiple levels (75). Under physiological conditions, NRF2 is inactivated via interaction with Kelch-like ECH-associated protein 1. Under oxidative stress, NRF2 is released, phosphorylated, activated and translocated into the nucleus to bind with anti-oxidant response elements, mediating the expression of target genes, such as heme oxygenase 1 (HO-1) (76) (Fig. 3). Results of a previous study demonstrated that Rb1 decreases the levels of MDA, increases the production of glutathione and activates the NRF2 signaling pathway (77). Ginsenoside compound K (CK) exhibited neuroprotective activity by stimulating the NRF2/HO-1 signaling pathway and suppressing oxidative

Table I. Protective activity of ginsenosides against OA.

Compound	First author/s, year	Model	Concentrations	Biological functions	(Refs.)
Rb1	Cheng <i>et al</i> , 2013	Human OA chondrocytes	1, 10 and 100 μ g/l	COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , MMP-13 \downarrow , caspase-3 \downarrow , poly (ADP-ribose) polymerase \downarrow , collagen II \uparrow , aggrecan \uparrow	(51)
	Aravinthan <i>et al</i> , 2021	MIA-induced rat OA	3-10 μ g/kg bw	Bone morphogenetic protein 2 \uparrow , collagen II \uparrow , MMP-13 \downarrow , IFN γ \downarrow , monocyte chemoattractant protein-1/C-C motif chemokine 2 \downarrow , IL-1 β \downarrow , IL-6 \downarrow	(53)
	Luan <i>et al</i> , 2022	MIA-induced rat OA	5 and 10 mg/kg bw	Histological improvement, IL-1 β \downarrow , IL-6 \downarrow , TNF α \downarrow , miR-21-5p \downarrow , fibroblast growth factor 18 \uparrow	(56)
	Luan <i>et al</i> , 2022	Rat chondrocytes	10 μ M	IL-1 β \downarrow , IL-6 \downarrow , TNF α \downarrow , miR-21-5p \downarrow , fibroblast growth factor 18 \uparrow	(56)
	Hossain <i>et al</i> , 2022	Rabbit knee OA	30 and 100 μ g/kg	MMPs \downarrow , TNF α \downarrow , caspase-3 \downarrow , Bax \downarrow , ROS \downarrow , NF- κ B \downarrow , p38 MAPK \downarrow , PI3K/AKT \downarrow	(67)
	Na <i>et al</i> , 2012	Rat chondrocytes	50 and 100 μ M	Caspase-3 \downarrow , Bax \downarrow , Bcl-xL \uparrow , apoptosis \downarrow	(70)
	Kim <i>et al</i> , 2012	Rat chondrocytes	100 μ M	ROS \downarrow , NO \downarrow , iNOS \downarrow , collagen II \uparrow , SOX9 \uparrow , MMP-1 \downarrow , MMP-13 \downarrow	(71)
Rg1	Cheng <i>et al</i> , 2016	ACLT+MMx rat models; C5.18 cells	300 μ M; 100 μ g/ml	IL-1 β \downarrow , histological improvement, MMP-13 \downarrow , collagen X \downarrow	(86)
	Cheng <i>et al</i> , 2017	Human OA chondrocytes	0.1, 1 and 10 μ g/ml	MMP-13 \downarrow , COX-2 \downarrow , PGE2 \downarrow , collagen II \uparrow , aggrecan \uparrow	(49)
	Cheng <i>et al</i> , 2017	ACLT-induced rat OA	30 and 60 mg/kg	MMP-13 \downarrow , collagen II \uparrow	(49)
	Huang <i>et al</i> , 2014	Rat chondrocytes	10 μ g/ml	p-AKT \uparrow , Bcl-2, Bax \downarrow , Cyto c \downarrow , caspase-3 \downarrow , MMP-13 \downarrow , TIMP-1 \uparrow , PI3K/AKT \uparrow	(72)
	Xu <i>et al</i> , 2022	Human chondrocytes	10, 50 and 100 μ g/ml	Bax \downarrow , Bcl-2 \uparrow , caspase-3 \downarrow , caspase-8 \downarrow , caspase-9 \downarrow , Fas ligand \downarrow , apoptosis inducing factor \downarrow , cytochrome c \downarrow , ROS \downarrow , malondialdehyde \downarrow	(73)
Rg3	Ma <i>et al</i> , 2021	TC28a2 cells	3 μ M	Sirt1 \uparrow , peroxisome proliferator-activated receptor gamma coactivator 1- α \uparrow , Sirt3 \uparrow , acetylated CypD \downarrow , mitochondrial functions \uparrow , apoptosis \downarrow , NF- κ B \downarrow , MAPK \downarrow	(74)
	So <i>et al</i> , 2013	Human OA chondrocytes	1 and 2.5 μ M	MMP-1 \downarrow , MMP-3 \downarrow , MMP-13 \downarrow , collagen II \uparrow , ACAN \uparrow , β -galactosidase \downarrow	(85)
Rg5	Zhang, 2017	Rat OA models	1, 2, 5, 10, 15 mg/kg	MMP-13 \downarrow , TIMP-1 \downarrow , collagen II \uparrow , IL-1 β \downarrow , TNF α \downarrow , NO \downarrow , iNOS \downarrow , BMP-2 \uparrow , TGF β 1 \uparrow	(90)
Ro	Zhang <i>et al</i> , 2015	Rat chondrocytes	50, 100 and 200 μ M	Bax \downarrow , Bad \downarrow , p-p53 \downarrow , Bcl-xL \uparrow , proliferating cell nuclear antigen \uparrow , caspase-3 \downarrow , COX-2 \downarrow , MMP-3 \downarrow , MMP-9 \downarrow , p-p65 \downarrow	(62)

OA, osteoarthritis; bw, body weight; p-phosphorylated; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; TIMP-1, tissue inhibitor of matrix metalloproteinase-1; Sirt, sirtuin; \uparrow , increased; \downarrow , decreased.

stress (78). In SH-SY5Y cells, Rb1 inhibited the 6-hydroxy-dopamine-induced expression of caspase-3 by upregulating the activity of the PI3K/AKT/NRF2 signaling pathway (79). However, further investigations into the specific effects of ginsenosides on the NRF2 signaling pathway in chondrocytes are required.

5. Inhibitory activity of ginsenosides against ECM degradation

ECM in articular cartilage mainly consists of collagen II and aggrecan. Collagen II is a fibrillar collagen with triple-helical homotrimers of collagen type II α 1 chain (Col2a1), which

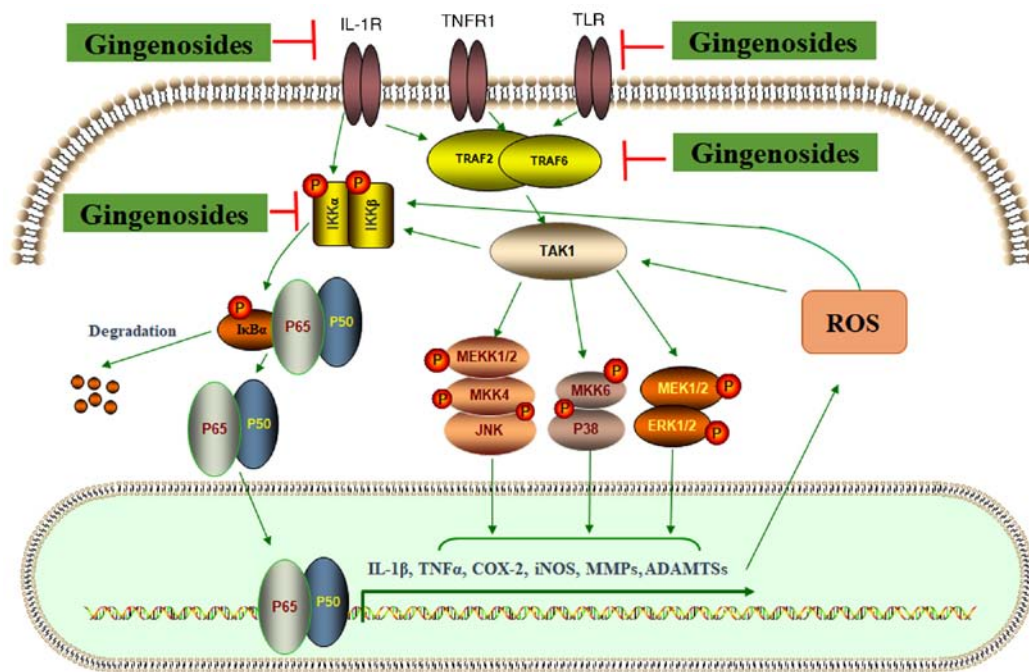


Figure 2. Activation of NF- κ B and MAPK signaling pathways regulates the expression of catabolic factors. External signals activate TRAF2/TRAF6, and induce the phosphorylation of MAPK (JNK, p38 MAPK and ERK1/2) by mediating TAK1. The phosphorylation of IKK α /IKK β is induced by TAK1 and external signals. The IKK-induced phosphorylation of I κ B α may lead to its degradation and the release of p65/p50, which enter the nucleus for the transcriptional regulation of target genes, including IL-1 β , TNF α , COX-2, iNOS, MMPs and ADAMTSs. Ginsenosides may inhibit NF- κ B and MAPK signaling pathways, and suppress inflammatory responses. TRAF, TNF receptor-associated factor; TAK, transforming growth factor- β activated kinase; IKK, inhibitor of I κ B kinase; COX, cyclooxygenase; iNOS, inducible isoform of nitric oxide synthase; ADAMTSs, A disintegrin and metalloproteinase with thrombospondin motifs; MEKK, mitogen-activated protein kinase kinase 1.

form heterotypic fibrils with collagen IX and XI in the cartilage. Aggrecan is formed by a core protein with the attachment of ~200 glycosaminoglycan chains (80). MMPs play a critical role in ECM degradation. Notably, MMP-13 is the key degrading enzyme in collagen II cleavage (81). ADAMTSs, namely ADAMTS-4 and ADAMTS-5, degrade aggrecan (82). Several signaling pathways, such as NF- κ B, MAPK and PI3K/AKT, are involved in mediating the corresponding catabolic activity (27). Inhibition of catabolic enzymes is considered an effective therapeutic strategy for the clinical management of OA.

A previous study screened 11 ginseng saponins and the results demonstrated that these ginseng saponins inhibit the activity of MMP-13, which degrades the major collagens in rabbit OA cartilage (83). Ginsenoside Rc, Rd, Rf, Rg3 and F4 may decrease the expression of MMP-13 in IL-1 β -treated SW1353 cells. Moreover, 10, 30 and 50 μ M F4 decreased the expression of MMP-13 by 33.5, 57.9 and 90.0%, respectively, by suppressing the MAPK pathway (83). *Panax ginseng* and the associated bioactive compounds, ginsenosides Rd and Rb3, decreased MMP-3 expression and increased collagen II expression in IL-1 β -treated S12 murine cartilage cells by suppressing the phosphorylation of p38 MAPK but not ERK (84). Results of a previous study suggested that Rg3 may decrease MMP-1, MMP-13 and β -galactosidase expression, and increase collagen II and aggrecan production in IL-1 β -treated human OA chondrocytes (Table I) (85).

Results of a previous study demonstrated that Rg1 down-regulates the expression of MMP-13 and upregulates the production of aggrecan and collagen II in IL-1 β -treated human

OA chondrocytes (49). In IL-1 β -treated rat chondrocytes, Rg1 also suppressed the expression of MMP-13 and enhanced the expression of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) by mediating the PI3K/AKT signaling pathway (72). In anterior cruciate ligament transection-induced rat OA models, Rg1 exhibited protective activity against cartilage erosion by decreasing MMP-13 expression and increasing collagen II production (49). Moreover, Rb1 reduced MMP-13 mRNA expression and enhanced aggrecan and Col2a1 mRNA expression in IL-1 β -treated human OA chondrocytes (Table I) (51). In addition, Rb1 increased the expression of BMP2 and collagen II, decreased the expression of MMP-13 and ameliorated the histopathological changes in MIA-induced OA in OVX rats (53). Results of a previous study demonstrated that Rb1 may attenuate IL-1 β -induced MMP-13 and collagen type X (ColX) expression in C5.18 cells (86). In anterior cruciate ligament transection and medial meniscus resection-induced OA rat models, Rb1 ameliorated cartilage degeneration and histological damage scores, and decreased the percentage of chondrocytes with positive MMP-13 and ColX staining; thus, inhibiting the progression of arthritis (86) (Table I).

In IL-1 β -treated rat chondrocytes, Ro may decrease the expression of MMP-3 and MMP-9 by inhibiting the activity of the NF- κ B signaling pathway (62). Moreover, Rb1 down-regulated the expression of MMPs, inhibited chondrocyte apoptosis and protected knee articular cartilage by inhibiting NF- κ B, p38 MAPK and PI3K/AKT signaling pathways in rabbit OA models (67). Results of a recent study demonstrated the inhibition of MMPs and anti-inflammatory activity of Rg1 in various tissues (87). Rg1 synergistically increased MMP inhibition in

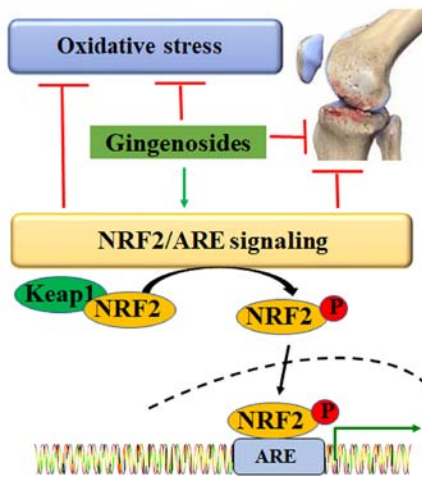


Figure 3. Ginsenosides suppress oxidative stress and inhibit OA development through activation of the NRF2/ARE signaling pathway. Dissociation of Keap1 leads to the phosphorylation and activation of NRF2, which enters the nucleus for the transcriptional regulation of target genes. OA, osteoarthritis; NRF2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant responsive elements; Keap1, Kelch-like ECH-associated protein 1.

combination with other drugs, such as Timosaponin AIII in MG63 and U2OS cells (88). TIMP-1 is an inhibitor of MMPs and is associated with the inhibition of ECM degradation and chondrocyte apoptosis in OA cartilage (89). Results of a previous study demonstrated that ginsenoside Rg5 exhibits protective activity against OA development by decreasing the expression of MMP-13 by 45% and increasing the expression of TIMP-1 by 67% in OA rat knee cartilages. In addition, following treatment with Rg5, the production of collagen II and proteoglycan were enhanced, the expression levels of IL-1 β , TNF α and NO/iNOS were decreased, and the apoptotic ratio of OA chondrocytes was decreased (90) (Table I).

The Notch signaling pathway mediates cell-to-cell interactions and determines cell fate. It consists of Notch 1-4 receptors and five ligands [jagged1, jagged2, delta-like 1 (DLL1), DLL3 and DLL4] (Fig. 4) (91). Of note, Notch signaling is involved in the pathophysiological alterations of OA. Expression levels of ligand jagged1 and Notch1 are upregulated in OA chondrocytes, and inflammatory cytokines, such as IL-1 β and TNF α may increase Notch signaling (92). Similar to the effects of Notch inhibitor γ -secretase inhibitor N-[N-(3,5difluorophenacetyl-L-alanyl)]-S-phenylglycine t-butyl ester, results of a previous study demonstrated that Rb1 inhibits the expression of MMP-13, collagen II, Notch1 and jagged1 in experimental OA rats and IL-1 β -treated SW1353 cells, protecting against cartilage lesions (93). In addition, H₂O₂ is associated with the inhibition of proteoglycan synthesis and degradation of aggrecan in articular cartilage, leading to ECM degradation and cartilage erosion (94). In H₂O₂-treated rat chondrocytes, Rb1 reversed the increased expression of MMP-1 and MMP-13, and the decreased expression of collagen II (71) (Table I).

6. Pharmacokinetic properties of ginsenosides

Rb1 is a hydrophile and the most abundant ginsenoside in ginseng. In addition, Rb1 is the parent compound of less

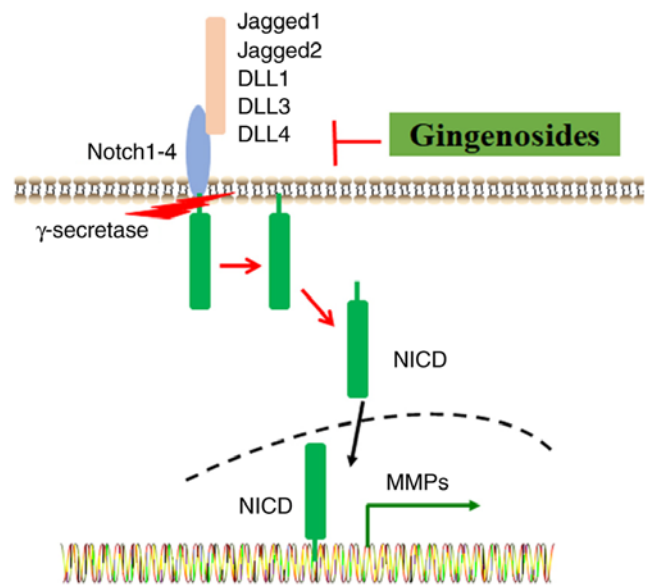


Figure 4. Ginsenosides protect against ECM degradation through the inhibition of Notch signaling. Ligands, such as Jagged1, Jagged2, DLL1, DLL3 and DLL4, bind to the Notch1-4 receptors. A series of proteolytic events are activated by γ -secretase, and these may induce the release of NICD, which enters the nucleus and regulates the expression of target genes, such as MMPs. ECM, extracellular matrix; DLL, delta-like 1; NICD, Notch intracellular domain.

hydrophilic ginsenosides, such as Rd, Rg3, Rg5, Rk1, F2 and CK (95). Notably, gut microbiota carries out hydrolysis of hydrophilic ginsenosides via deglycosylation, to convert them into hydrophobic ginsenosides (96). This conversion may be associated with increased bioavailability. A recent study aimed to determine the safety of red ginseng extract via oral administration in 13 healthy Korean male participants, and the results demonstrated that there are no associated adverse events. In addition, the bioconverted red ginseng extract possesses a higher maximum plasma concentration, area under curve (AUC)₍₀₋₁₎ and AUC_(0- ∞), and a shorter time to maximum plasma concentration following oral administration, compared with those of the red ginseng extract (97). Rd is distributed to various organs and oxidation and glycosylation are the main metabolic pathways of Rd in rats. Results of a previous study demonstrated that the absolute bioavailability of Rd is 0.26% in dogs (98). The recommended intravenous administration dose range of Rd is 10-75 mg and this range was generally well tolerated in clinical trials (99). The main pharmacokinetic parameters of Re have been comprehensively discussed (100) and Re exhibits a poor bioavailability of ~0.24% (101). Similarly, following oral administration of 50 mg/kg Rb1, Rb2 and Rb3 in rats, the AUC values were 66.8, 9.7 and 55.1 mg h/l, respectively, and the C_{max} values were 6.1, 0.4 and 3.3 mg/l, respectively. These results may be associated with poor bioavailability, respectively ~0.78, 0.08 and 0.52% for Rb1, Rb2 and Rb3 (102,103). 20(S)-Protopanaxadiol [20(S)-PPD] is a ginsenoside metabolite with full deglycosylation. Notably, 20(S)-PPD exhibits a half-life of 3 h in rats and 10.6-16.7 h in humans (104). The bioavailability of 20(S)-PPD following oral administration was 31.0 and 9.6% in rats and dogs, respectively (105). This indicates that deglycosylation significantly enhances bioavailability. Results of a previous

study demonstrated that the absolute bioavailability of PDD in rats is 36.8%, which is ~10 times higher than that of Rg3 and Rh2 (106).

The majority of ginsenosides are characterized by a lipophilic steroid skeleton, a low oral absorption rate, rapid clearance and a short half-life, with low levels of bioavailability at <5% (107). Interestingly, novel drug delivery systems may provide improved solubility, oral absorption rates and bioavailability. A series of nano delivery systems, such as liposomes, polymeric nanoparticles (NPs), micelles, microemulsions, metal and inorganic NPs, biomimetic NPs, and protein NPs, have been developed to improve efficiency and reduce associated adverse effects, such as hypertension, insomnia, anxiety, diarrhea and vomiting (107,108). Notably, ginsenoside CK prepared with polymer micelles exhibits good biodegradability and biocompatibility, with antitumor effects stronger than those of free CK (109). Folic acid (FA) is considered an optimal targeting moiety that is used for antitumor drug delivery. Results of a previous study demonstrated that Rg5 released from FA-modified bovine serum albumin NPs may accumulate at the tumor site within 8 h, improving the therapeutic efficacy and tumor targetability (110). To improve levels of bioavailability, polymeric nano-capsules have been employed to encapsulate Rb1 to become nano-Rb1, which significantly inhibited the activity of NF- κ B and NLRP3 inflammasomes (111). The conjugation of superparamagnetic iron oxide nanoparticles (SPIONs) with Rg3 has been developed. Results of a previous study demonstrated that SPION-Rg3 exhibits increased anti-oxidative and anti-inflammatory activities in RAW 264.7 cells (112). A variety of ginsenoside nanodrugs, such as Doxil, Onivyde and Vyxeos, were developed with different physiochemical properties, leading to differences in pharmacokinetics, biodistribution, efficacy and safety (113).

7. Clinical perspectives

Results of a recent study demonstrated the effective use of TCM in the management of OA (114). Huoxuezhitong capsule (HXZT), a compound derived from *Angelica sinensis* (Oliv.) Diels, *Panax notoginseng* (Burkill) F. H. Chen ex C. H., *Boswellia sacra*, *Borneol*, *Eupolyphaga sinensis* Walker and Pyritum, demonstrated efficacy against OA (115). Ginsenosides Rg1 and Rb1, and Noto-ginsenoside R1, are the main effective compounds of HXZT, which inhibited inflammatory responses by inhibiting NF- κ B and PI3K/AKT signaling pathways in LPS-treated RAW264.7 and ATDC5 cells, and in MIA-induced rat OA models (115). However, the limited water solubility of ginsenosides may impact the potential clinical applications.

Ginsenosides are not directly absorbed with intact structures *in vivo* and deglycosylation by intestinal bacteria or gastric acid is required before absorption in the intestinal tract. Ginsenoside CK, the main metabolite of ginsenosides, exhibits a pharmacological activity higher than that of ginsenosides (116). However, to the best of our knowledge, there are no CK preparations that are available for use in patients, despite advances in TCM development. At present, CK capsules are undergoing clinical trials for the treatment of rheumatoid arthritis (117). In LPS-treated RAW 264.7 cells, CK decreased the levels of NO/iNOS and PGE2/COX-2, and exhibited inhibitory activity against inflammation by suppressing the NF- κ B and MAPK signaling

pathways (118). Consistently, a previous study demonstrated that CK can suppress the NF- κ B pathway by inhibiting IKK in H₂O₂-treated MC3T3-E1 cells (119).

Glucocorticoids (GCs) have been extensively used for the treatment of inflammation and immune disorders (120). However, the use of GCs in clinical practice is complex due to reduced sensitivity and the potential resistance to GCs. Moreover, the acquired resistance to GCs may lead to the abnormal upregulation of inflammatory transcriptional factors, such as activator protein 1, to interrupt the competitive binding of GC receptor (GR) to DNA (121). In clinic practice, GCs are frequently used in the treatment and improvement of OA; however, the recommendations for treatment with GCs have not been updated since 2013 (122). This may be due to associated negative outcomes, such as accelerated progression of OA and increased joint destruction (123). Notably, the results of a previous study demonstrated that Rh1 inhibited GC-induced downregulation of GR expression and DNA binding in RAW 264.7 cells (124). Mechanistically, a combination of Rh1 with dexamethasone (DEX) may inhibit the phosphorylation of I κ B α and p65, and the nuclear translocation of p65; thus, inhibiting the NF- κ B signaling pathway. Combined with DEX, Rh1 enhanced the expression of Dual specificity phosphatase 1, which specifically blocks the phosphorylation and activation of the MAPK family, including p38, MAPK, ERK1/2 and JNK (124,125).

Poor levels of bioavailability and the metabolites of ginsenosides may impact the corresponding clinical applications. Therefore, the development of strategies to increase structural stability and enhance absorption in the gastrointestinal tract is required. Moreover, research should focus on effective delivery systems within the human body. Results of previous studies demonstrated the therapeutic effects of ginsenosides both *in vivo* and *in vitro*; however, further studies into the absorption, distribution, metabolism, excretion and toxicity of ginsenosides in humans are required. Notably, animal models have been used for evaluating the safety of potential drugs for the treatment of OA. However, there are numerous differences between animals and humans, and toxicological responses in animals may not be applicable in humans. Moreover, additional clinical trials are required to assess the safety and associated adverse events of ginsenosides, to determine levels of toxicity and facilitate their use in the clinic.

8. Conclusions

OA is characterized by low-grade chronic inflammation and its pathological development is orchestrated by a complex network of signaling pathways. Further understanding of the molecular mechanisms underlying OA is essential for the development of novel drugs. TCM and associated bioactive compounds may exhibit potential in drug screening. Results of previous studies have demonstrated the anti-inflammatory activity of ginseng and ginsenosides in OA development (67). Mechanistically, ginsenosides may inhibit inflammation and oxidative stress, and suppress ECM degradation by targeting NF- κ B and MAPK signaling pathways. Numerous strategies, including nanotechnologies, have been developed to improve bioavailability. However, further clinical trials are required to determine the potential pharmacological effects of ginsenosides. The pathological development of OA is multifactorial and the present

literature review focused on inflammatory responses, oxidative stress and ECM degradation. The present review exhibits numerous limitations; for example, aging, metabolic diseases and drug-drug interactions were not discussed. Moreover, a combination of ginsenosides with other drugs may exhibit potential in the management of OA and ginsenosides may also be used as carriers to deliver other drugs. Thus, further investigations into the synergic pharmacology between ginsenosides and other drugs are required.

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Availability of data and materials

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Authors' contributions

XL was responsible for conceptualization and methodology. JC, LH and XL were responsible for data curation, writing the final article, draft preparation, data curation, data authentication, validation, reviewing and editing. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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