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

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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-κB and MAPK signaling pathways. Notably, specific ginsenosides, such as compound K and Rk1, may physically interact with IκB 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.

Contents

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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-κB (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-1β and TNFα are pro-inflammatory cytokines secreted by chondrocytes, synoviocytes and mononuclear cells in early OA. Both IL-1β and TNFα stimulate the signaling cascade of inflammation, producing IL-6, IL-1β, TNFα and prostaglandin E2 (PGE2) in chondrocytes (27). In addition, IL-1β, IL-6 and TNFα are important regulators in the promotion of articular cartilage destruction and synovium inflammatory responses (28). Activation of NF-κB 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-κB signaling (36). In IL-1β-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-1β-induced ER stress, NF-κB-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-κB 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-1β, IL-18 and IL-33 (45). Results of a previous study demonstrated the biological activity of ginsenosides in

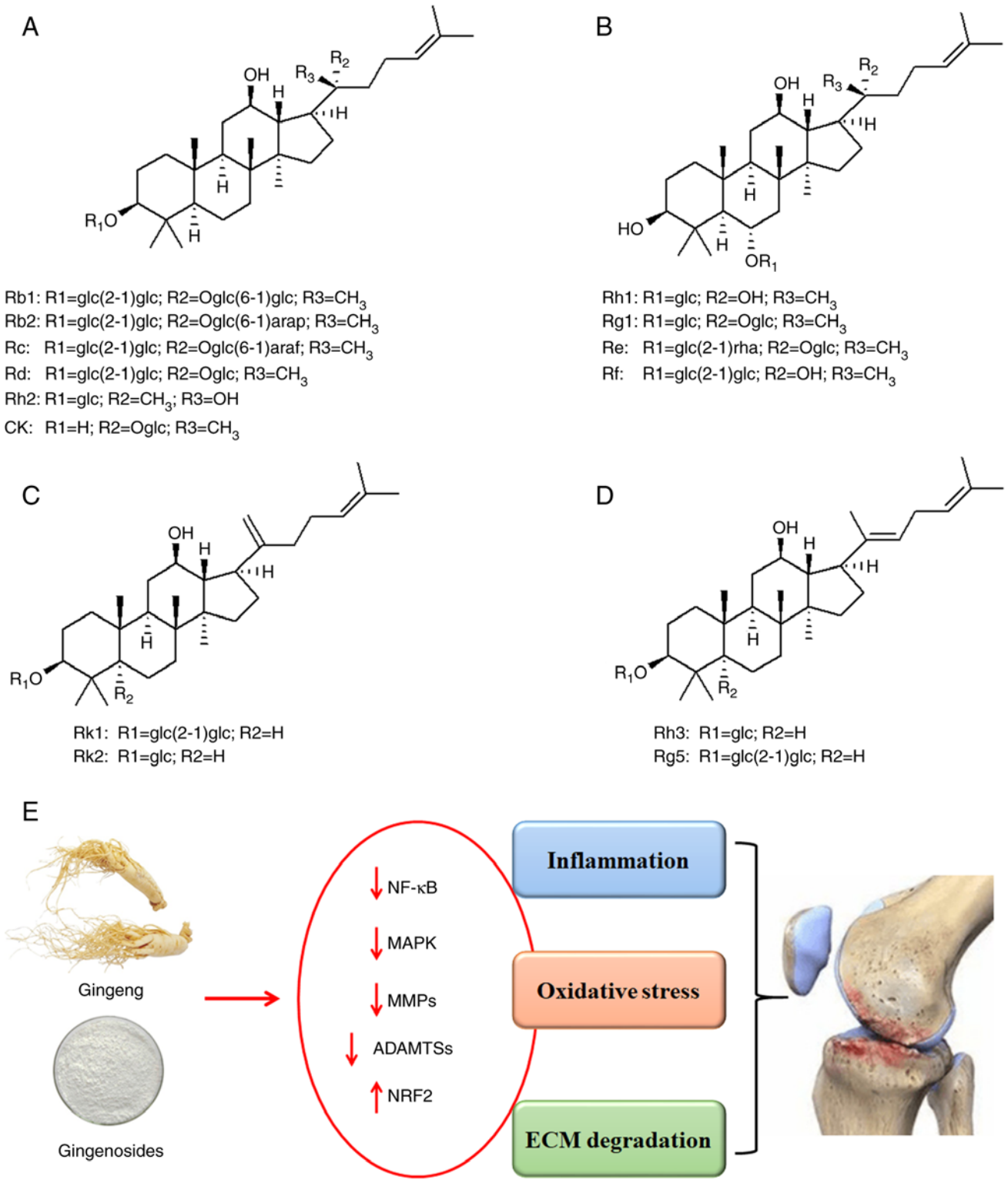

Figure 1. Chemical structures of ginsenosides and the protective effects of ginseng and ginsenosides against osteoarthritis. (A) Different ginsenosides of the protopanaxadiol type. Ginsenoside Rb1 has a glc(2-1)glc group at the R1 position, a Oglc(6-1)glc group at the R2 position, and a methyl group 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, CH_3 and Oglc, and CH_3, OH and CH_3, 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-1β-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 TNFα in RAW 264.7 cells with IC_{50} values of 56.5 and 27.5 μM, respectively, and in U937 cells with IC_{50} values of 51.3 and 26.8 μM, respectively (50). Moreover, Rb1 inhibited the IL-1β-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-1β and TNFα (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-1β, 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-κB signaling plays a crucial role in inflammatory responses. Activation of the NF-κB signaling pathway includes phosphorylation of IκB kinases (IKKs), IκB 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-κB, 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-κB and MAPK signaling pathways (59). Moreover, the expression of NF-κB signaling is activated in primary human OA chondrocytes (60). Ginsenoside Ro also exhibits potential as an inhibitor of inflammation by suppressing NF-κB signaling pathways. Results of a previous study demonstrated that Ro inactivates the TNFα-induced NF-κB signaling pathway (61) (Table I). More specifically, Ro exhibited inhibitory activity against the IL-1β-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-κB-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-1β and TNFα, and suppression of p38 MAPK may lead to the decreased production of inflammation cytokines (64). P38 MAPK is involved in activation of the NF-κB 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-κB signaling pathway, and LPS-induced NF-κB and MAPK (p38, ERK1/2 and JNK) pathways (66). In a rabbit OA model, Rb1 inhibited the activity of NF-κB, 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 (H_2O_2) exhibits various biological effects by generating ROS, which is associated with oxidative stress and increased chondrocyte apoptosis (68). Mechanistically, H_2O_2 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 H_2O_2-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 H_2O_2, 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-1β-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-1β-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-1β-induced chondrocyte apoptosis by decreasing the PI3K/AKT-mediated mitochondrial signaling pathway (73). TNFα 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-1α expression and reversed the effects of TNFα on the acetylation of cyclophilin D and mitochondrial dysfunction through downregulation of NF-κB 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 *et al*, 2013	Human OA chondrocytes	1, 10 and 100 μg/l	COX-2↓, PGE2↓, iNOS↓, NO↓, MMP-13↓, caspase-3↓, poly (ADP-ribose) polymerase↓, collagen II↑, aggrecan↑	(51)
	Aravinthan *et al*, 2021	MIA-induced rat OA	3-10 μg/kg bw	Bone morphogenetic protein 2↑, collagen II↑, MMP-13↓, IFNγ↓, monocyte chemoattractant protein-1/C-C motif chemokine 2 ↓, IL-1β↓, IL-6↓	(53)
	Luan *et al*, 2022	MIA-induced rat OA	5 and 10 mg/kg bw	Histological improvement, IL-1β↓, IL-6↓, TNFα↓, miR-21-5p↓, fibroblast growth factor 18↑	(56)
	Luan *et al*, 2022	Rat chondrocytes	10 μM	IL-1β↓, IL-6↓, TNFα↓, miR-21-5p↓, fibroblast growth factor 18↑	(56)
	Hossain *et al*, 2022	Rabbit knee OA	30 and 100 μg/kg	MMPs↓, TNFα↓, caspase-3↓, Bax↓, ROS↓, NF-κB↓, p38 MAPK↓, PI3K/AKT↓	(67)
	Na *et al*, 2012	Rat chondrocytes	50 and 100 μM	Caspase-3↓, Bax↓, Bcl-xL↑, apoptosis↓	(70)
	Kim *et al*, 2012	Rat chondrocytes	100 μM	ROS↓, NO↓, iNOS↓, collagen II↑, SOX9↑, MMP-1↓, MMP-13↓	(71)
	Chen *et al*, 2016	ACLT+MMx rat models; C5.18 cells	300 μM; 100 μg/ml	IL-1β↓, histological improvement, MMP-13↓, collagen X↓	(86)
Rg1	Cheng *et al*, 2017	Human OA chondrocytes	0.1, 1 and l0 μg/ml	MMP-13↓, COX-2↓, PGE2↓, collagen II↑, aggrecan↑	(49)
	Cheng *et al*, 2017	ACLT-induced rat OA	30 and 60 mg/kg	MMP-13↓, collagen II↑	(49)
	Huang *et al*, 2014	Rat chondrocytes	10 μg/ml	p-AKT↑, Bcl-2, Bax↓, Cyto c↓, caspase-3↓, MMP-13↓, TIMP-1↑, PI3K/AKT↑	(72)
	Xu *et al*, 2022	Human chondrocytes	10, 50 and 100 μg/ml	Bax↓, Bcl-2↑, caspase-3↓, caspase-8↓, caspase-9↓, Fas ligand↓, apoptosis inducing factor ↓, cytochrome c↓, ROS↓, malondialdehyde↓	(73)
Rg3	Ma *et al*, 2021	TC28a2 cells	3 μM	Sirt1↑, peroxisome proliferator-activated receptor gamma coactivator 1-α↑, Sirt3↑, acetylated CypD↓, mitochondrial functions↑, apoptosis↓, NF-κB↓, MAPK↓	(74)
	So *et al*, 2013	Human OA chondrocytes	1 and 2.5 μM	MMP-1↓, MMP-3↓, MMP-13↓, collagen II↑, ACAN↑, β-galactosidase↓	(85)
Rg5	Zhang, 2017	Rat OA models	1, 2, 5, 10, 15 mg/kg	MMP-13↓, TIMP-1↓, collagen II↑, IL-1β↓, TNFα↓, NO↓, iNOS↓, BMP-2↑, TGFβ1↑	(90)
Ro	Zhang *et al*, 2015	Rat chondrocytes	50, 100 and 200 μM	Bax↓, Bad↓, p-p53↓, Bcl-xL↑, proliferating cell nuclear antigen ↑, caspase-3↓, COX-2↓, MMP-3↓, MMP-9↓, p-p65↓	(62)

OA, osteoarthrosis; 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; ↑, increased; ↓, decreased.

stress (78). In SH-SY5Y cells, Rb1 inhibited the 6-hydroxydopamine-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 α1 chain (Col2a1), which

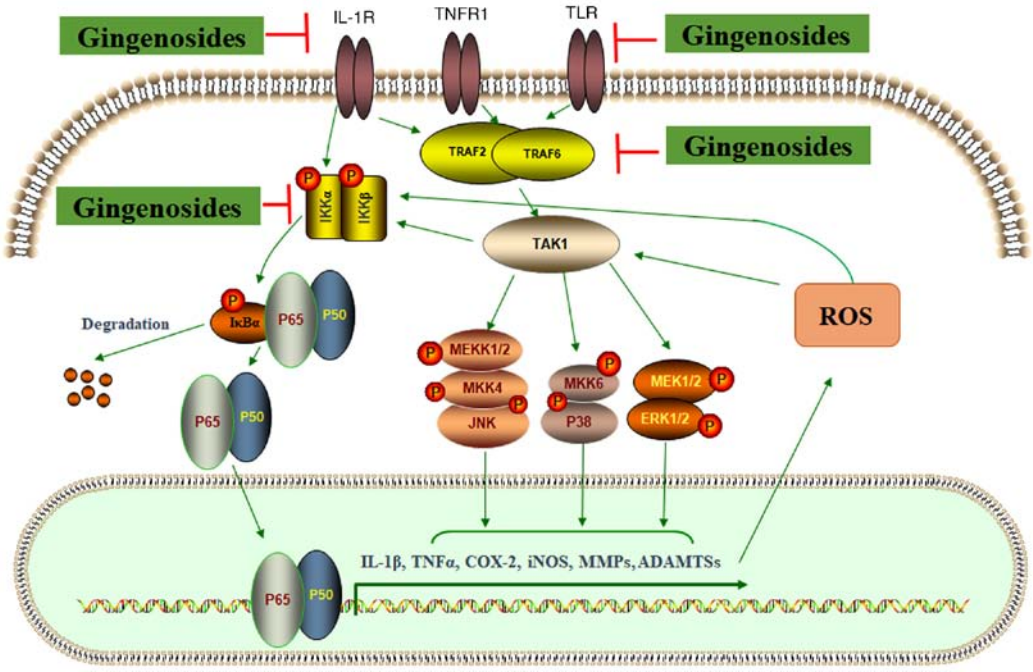

Figure 2. Activation of NF-κB and MAPK signaling pathways regulates the expression of catabolic factors. External signals activate TRAF2/TRAF6, and induce the phosphorylation of MAPK (JNK, p38 MAPK and ERK1/2) by mediating TAK1. The phosphorylation of IKKα/IKKβ is induced by TAK1 and external signals. The IKK-induced phosphorylation of IκBα may lead to its degradation and the release of p65/p50, which enter the nucleus for the transcriptional regulation of target genes, including IL-1β, TNFα, COX-2, iNOS, MMPs and ADAMTSs. Ginsenosides may inhibit NF-κB and MAPK signaling pathways, and suppress inflammatory responses. TRAF, TNF receptor-associated factor; TAK, transforming growth factor-β activated kinase; IKK, inhibitor of IκB kinase; COX, cyclooxygenase; iNOS, inducible isoform of nitric oxide synthase; ADAMTSs, A disintegrin and metalloproteinase with thrombospondin motifs; MEKK, mitogen-activated protein kinase 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-κB, 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-1β-treated SW1353 cells. Moreover, 10, 30 and 50 μM 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-1β-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-1β-treated human OA chondrocytes (Table I) (85).

Results of a previous study demonstrated that Rg1 downregulates the expression of MMP-13 and upregulates the production of aggrecan and collagen II in IL-1β-treated human OA chondrocytes (49). In IL-1β-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-1β-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-1β-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-1β-treated rat chondrocytes, Ro may decrease the expression of MMP-3 and MMP-9 by inhibiting the activity of the NF-κB signaling pathway (62). Moreover, Rb1 downregulated the expression of MMPs, inhibited chondrocyte apoptosis and protected knee articular cartilage by inhibiting NF-κB, 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

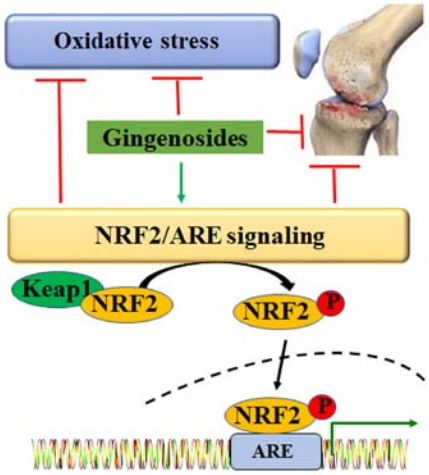

Figure 3. Ginsenosides suppress oxidative stress and inhibit OA development through activation of the NRF2/ARE signaling pathway. Dissociation of Keap1 leads to the phosphorylation and activation of NRF2, which enters the nucleus for the transcriptional regulation of target genes. OA, osteoarthritis;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

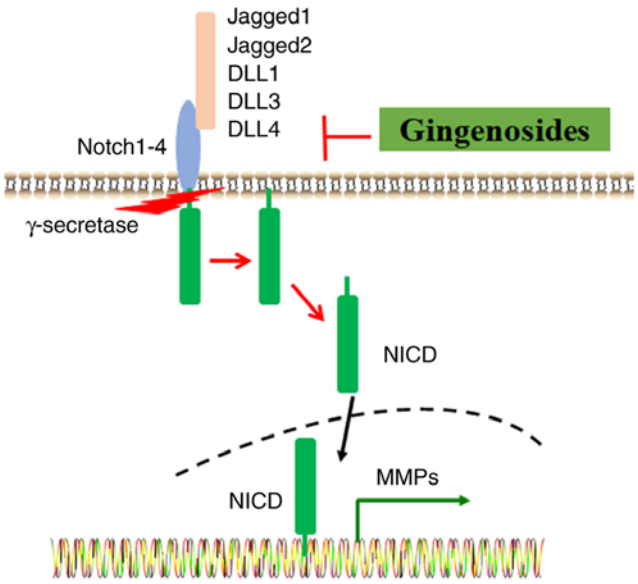

Figure 4. Ginsenosides protect against ECM degradation through the inhibition of Notch signaling. Ligands, such as Jagged1, Jagged2, DLL1, DLL3 and DLL4, bind to the Notch1-4 receptors. A series of proteolytic events are activated by γ-secretase, and these may induce the release of NCID, which enters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

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-1β, TNFα 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-1β and TNFα 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-1β-treated SW1353 cells, protecting against cartilage lesions (93). In addition, H_2O_2 is associated with the inhibition of proteoglycan synthesis and degradation of aggrecan in articular cartilage, leading to ECM degradation and cartilage erosion (94). In H_2O_2-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 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 $(AUC)_{(0-t)}$ and $AUC_{(0-\infty)}$, 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-κB 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-κB 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-κB and MAPK signaling pathways (118). Consistently, a previous study demonstrated that CK can suppress the NF-κB pathway by inhibiting IKK in H_2O_2-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 IκBα and p65, and the nuclear translocation of p65; thus, inhibiting the NF-κB 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-κB 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.

References

1. Wu SY, Lin CH, Chang NJ, Hu WL, Hung YC, Tsao Y and Kuo CA: Combined effect of laser acupuncture and electroacupuncture in knee osteoarthritis patients: A protocol for a randomized controlled trial. Medicine (Baltimore) 99: e19541, 2020.
2. Zhang W, Ouyang H, Dass CR and Xu J: Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res 4: 15040, 2016.
3. Jones IA, Togashi R, Wilson ML, Heckmann N and Vangsness CT Jr: Intra-articular treatment options for knee osteoarthritis. Nat Rev Rheumatol 15: 77-90, 2019.
4. Charlesworth J, Fitzpatrick J, Perera NKP and Orchard J: Osteoarthritis-a systematic review of long-term safety implications for osteoarthritis of the knee. BMC Musculoskelet Disord 20: 151, 2019.
5. Wang J, Li J, Song D, Ni J, Ding M, Huang J and Yan M: AMPK: Implications in osteoarthritis and therapeutic targets. Am J Transl Res 12: 7670-7681, 2020.
6. Dilley JE, Bello MA, Roman N, McKinley T and Sankar U: Post-traumatic osteoarthritis: A review of pathogenic mechanisms and novel targets for mitigation. Bone Rep 18: 101658, 2023.
7. Goldring MB and Marcu KB: Cartilage homeostasis in health and rheumatic diseases. Arthritis Res Ther 11: 224, 2009.
8. Jiang J, Feng S, Li Z, Luo Y, Wang Z, Li M and Wu G: The expression of MDM2 gene promoted chondrocyte proliferation in rats with osteoarthritis via the Wnt/β-catenin pathway. Cell Mol Biol (Noisy-le-grand) 67: 236-241, 2022.
9. Wang Y, Zhao H, Jia S, Wang Q, Yao W, Yang Y and Bai L: Senomorphic agent pterostilbene ameliorates osteoarthritis through the PI3K/AKT/NF-κB axis: An in vitro and in vivo study. Am J Transl Res 14: 5243-5262, 2022.
10. Qiu J, Jiang T, Yang G, Gong Y, Zhang W, Zheng X, Hong Z and Chen H: Neratinib exerts dual effects on cartilage degradation and osteoclast production in Osteoarthritis by inhibiting the activation of the MAPK/NF-κB signaling pathways. Biochem Pharmacol 205: 115155, 2022.
11. Minguzzi M, Panichi V, D'Adamo S, Cetrullo S, Cattini L, Flamigni F, Mariani E and Borzì RM: Pleiotropic roles of NOTCH1 signaling in the loss of maturational arrest of human osteoarthritic chondrocytes. Int J Mol Sci 22: 12012, 2021.
12. Yang M, Jiang L, Wang Q, Chen H and Xu G: Traditional Chinese medicine for knee osteoarthritis: An overview of systematic review. PLoS One 12: e0189884, 2017.
13. Kim JH: Pharmacological and medical applications of *Panax ginseng* and ginsenosides: A review for use in cardiovascular diseases. J Ginseng Res 42: 264-269, 2018.
14. Kang OJ and Kim JS: Comparison of ginsenoside contents in different parts of Korean ginseng (*Panax ginseng* C.A. Meyer). Prev Nutr Food Sci 21: 389-392, 2016.
15. Fan M, Lan X, Wang Q, Shan M, Fang X, Zhang Y, Wu D, Luo H, Gao W and Zhu D: Renal function protection and the mechanism of ginsenosides: Current progress and future perspectives. Front Pharmacol 14: 1070738, 2023.
16. Zhao T, Wang X, Liu Q, Yang T, Qu H and Zhou H: Ginsenoside Rd promotes cardiac repair after myocardial infarction by modulating monocytes/macrophages subsets conversion. Drug Des Devel Ther 16: 2767-2782, 2022.
17. Zhou AF, Zhu K, Pu PM, Li ZY, Zhang YY, Shu B, Cui XJ, Yao M and Wang YJ: Neuroprotective effect and possible mechanisms of ginsenoside-Rd for cerebral ischemia/reperfusion damage in experimental animal: A meta-analysis and systematic review. Oxid Med Cell Longev 2022: 7650438, 2022.
18. Liu Y, Liu N, Liu Y, He H, Luo Z, Liu W, Song N and Ju M: Ginsenoside Rb1 reduces D-GalN/LPS-induced acute liver injury by regulating TLR4/NF-κB signaling and NLRP3 inflammasome. J Clin Transl Hepatol 10: 474-485, 2022.
19. Xue X, Liu Y, Qu L, Fan C, Ma X, Ouyang P and Fan D: Ginsenoside Rh3 inhibits lung cancer metastasis by targeting extracellular signal-regulated kinase: A network pharmacology study. Pharmaceuticals (Basel) 15: 758, 2022.
20. Song B, Ding L, Zhang H, Chu Y, Chang Z, Yu Y, Guo D, Zhang S and Liu X: Ginsenoside Rb1 increases insulin sensitivity through suppressing 11β-hydroxysteroid dehydrogenase type I. Am J Transl Res 9: 1049-1057, 2017.
21. Song M, Cui Y, Wang Q, Zhang X, Zhang J, Liu M and Li Y: Ginsenoside Rg3 alleviates aluminum chloride-induced bone impairment in rats by activating the TGF-β1/Smad signaling pathway. J Agric Food Chem 69: 12634-12644, 2021.
22. Xu HL, Chen GH, Wu YT, Xie LP, Tan ZB, Liu B, Fan HJ, Chen HM, Huang GQ, Liu M and Zhou YC: Ginsenoside Ro, an oleanolic saponin of *Panax ginseng*, exerts an anti-inflammatory effect by direct inhibiting toll-like receptor 4 signaling pathway. J Ginseng Res 46: 156-166, 2022.
23. Wu Z, Yang Z, Liu L and Xiao Y: Natural compounds protect against the pathogenesis of osteoarthritis by mediating the NRF2/ARE signaling. Front Pharmacol 14: 1188215, 2023.
24. Scanzello CR and Goldring SR: The role of synovitis in osteoarthritis pathogenesis. Bone 51: 249-257, 2012.
25. Di Nicola V: Degenerative osteoarthritis a reversible chronic disease. Regen Ther 15: 149-160, 2020.
26. Wojdasiewicz P, Poniatowski ŁA and Szukiewicz D: The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014: 561459, 2014.

27. Chow YY and Chin KY: The role of inflammation in the pathogenesis of osteoarthritis. Mediators Inflamm 2020: 8293921, 2020.
28. Zahan OM, Serban O, Gherman C and Fodor D: The evaluation of oxidative stress in osteoarthritis. Med Pharm Rep 93: 12-22, 2020.
29. Wang H, Liao R, Tang W, Su W, Zeng M, Yang J, Fan X, Xie J and Hu Y: Dietary inflammation index and osteoarthritis in the elderly: Is there a mediating role of physical activity? Br J Nutr 128: 2258-2266, 2022.
30. Zarezadeh M, Mahmoudinezhad M, Hosseini B, Khorraminezhad L, Razaghi M, Alvandi E and Saedisomeolia A: Dietary pattern in autism increases the need for probiotic supplementation: A comprehensive narrative and systematic review on oxidative stress hypothesis. Clin Nutr 42: 1330-1358, 2023.
31. Ott M, Gogvadze V, Orrenius S and Zhivotovsky B: Mitochondria, oxidative stress and cell death. Apoptosis 12: 913-922, 2007.
32. Sadasivam N, Kim YJ, Radhakrishnan K and Kim DK: Oxidative stress, genomic integrity, and liver diseases. Molecules 27: 3159, 2022.
33. Park J, Lee J and Choi C: Mitochondrial network determines intracellular ROS dynamics and sensitivity to oxidative stress through switching inter-mitochondrial messengers. PLoS One 6: e23211, 2011.
34. Youle RJ and Karbowski M: Mitochondrial fission in apoptosis. Nat Rev Mol Cell Biol 6: 657-663, 2005.
35. Sirše M: Effect of dietary polyphenols on osteoarthritis-molecular mechanisms. Life (Basel) 12: 436, 2022.
36. Baatar D, Siddiqi MZ, Im WT, Ul Khaliq N and Hwang SG: Anti-inflammatory effect of ginsenoside Rh_2-Mix on lipopolysaccharide-stimulated RAW 264.7 murine macrophage cells. J Med Food 21: 951-960, 2018.
37. Lee JH, Shehzad O, Ko SK, Kim YS and Kim HP: Matrix metalloproteinase-13 downregulation and potential cartilage protective action of the Korean red ginseng preparation. J Ginseng Res 39: 54-60, 2015.
38. Jhun JY, Na HS, Shin JW, Jung KA, Seo HB, Ryu JY, Choi JW, Moon SJ, Park HJ, Oh SW, *et al*: Notoginseng Radix and Rehmanniae Radix Preparata extract combination (YH23537) reduces pain and cartilage degeneration in rats with monosodium iodoacetate-induced osteoarthritis. J Med Food 21: 745-754, 2018.
39. Xie JJ, Chen J, Guo SK, Gu YT, Yan YZ, Guo WJ, Yao CL, Jin MY, Xie CL, Wang X, *et al*: Panax quinquefolium saponin inhibits endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and attenuates the progression of osteoarthritis in rat. Biomed Pharmacother 97: 886-894, 2018.
40. Zhang Y, Cai W, Han G, Zhou S, Li J, Chen M and Li H: Panax notoginseng saponins prevent senescence and inhibit apoptosis by regulating the PI3K-AKT-mTOR pathway in osteoarthritic chondrocytes. Int J Mol Med 45: 1225-1236, 2020.
41. Seo SK, Hong Y, Yun BH, Chon SJ, Jung YS, Park JH, Cho S, Choi YS and Lee BS: Antioxidative effects of Korean red ginseng in postmenopausal women: A double-blind randomized controlled trial. J Ethnopharmacol 154: 753-757, 2014.
42. Kim HI, Chon SJ, Seon KE, Seo SK and Choi YR: Clinical effects of Korean red ginseng in postmenopausal women with hand osteoarthritis: A double-blind, randomized controlled trial. Front Pharmacol 12: 745568, 2021.
43. Zhu DC, Wang YH, Lin JH, Miao ZM, Xu JJ and Wu YS: Maltol inhibits the progression of osteoarthritis via the nuclear factor-erythroid 2-related factor-2/heme oxygenase-1 signal pathway in vitro and in vivo. Food Funct 12: 1327-1337, 2021.
44. Lu H, Fu C, Kong S, Wang X, Sun L, Lin Z, Luo P and Jin H: Maltol prevents the progression of osteoarthritis by targeting PI3K/Akt/NF-κB pathway: In vitro and in vivo studies. J Cell Mol Med 25: 499-509, 2021.
45. Yang SM, Ka SM, Hua KF, Wu TH, Chuang YP, Lin YW, Yang FL, Wu SH, Yang SS, Lin SH, *et al*: Antroquinonol mitigates an accelerated and progressive IgA nephropathy model in mice by activating the Nrf2 pathway and inhibiting T cells and NLRP3 inflammasome. Free Radic Biol Med 61: 285-297, 2013.
46. Yi YS: Roles of ginsenosides in inflammasome activation. J Ginseng Res 43: 172-178, 2019.
47. Kim J, Ahn H, Han BC, Lee SH, Cho YW, Kim CH, Hong EJ, An BS, Jeung EB and Lee GS: Korean red ginseng extracts inhibit NLRP3 and AIM2 inflammasome activation. Immunol Lett 158: 143-150, 2014.
48. Gao Y, Li J, Wang J, Li X, Li J, Chu S, Li L, Chen N and Zhang L: Ginsenoside Rg1 prevent and treat inflammatory diseases: A review. Int Immunopharmacol 87: 106805, 2020.
49. Cheng W, Jing J, Wang Z, Wu D and Huang Y: Chondroprotective effects of ginsenoside Rg1 in human osteoarthritis chondrocytes and a rat model of anterior cruciate ligament transection. Nutrients 9: 263, 2017.
50. Cho JY, Yoo ES, Baik KU, Park MH and Han BH: In vitro inhibitory effect of protopanaxadiol ginsenosides on tumor necrosis factor (TNF)-alpha production and its modulation by known TNF-alpha antagonists. Planta Med 67: 213-218, 2001.
51. Cheng W, Wu D, Zuo Q, Wang Z and Fan W: Ginsenoside Rb1 prevents interleukin-1 beta induced inflammation and apoptosis in human articular chondrocytes. Int Orthop 37: 2065-2070, 2013.
52. Kim MK, Kang H, Baek CW, Jung YH, Woo YC, Choi GJ, Shin HY and Kim KS: Antinociceptive and anti-inflammatory effects of ginsenoside Rf in a rat model of incisional pain. J Ginseng Res 42: 183-191, 2018.
53. Aravinthan A, Hossain MA, Kim B, Kang CW, Kim NS, Hwang KC and Kim JH: Ginsenoside Rb_1 inhibits monoiodoacetate-induced osteoarthritis in postmenopausal rats through prevention of cartilage degradation. J Ginseng Res 45: 287-294, 2021.
54. Hung IH, Schoenwolf GC, Lewandoski M and Ornitz DM: A combined series of Fgf9 and Fgf18 mutant alleles identifies unique and redundant roles in skeletal development. Dev Biol 411: 72-84, 2016.
55. Ellsworth JL, Berry J, Bukowski T, Claus J, Feldhaus A, Holderman S, Holdren MS, Lum KD, Moore EE, Raymond F, *et al*: Fibroblast growth factor-18 is a trophic factor for mature chondrocytes and their progenitors. Osteoarthritis Cartilage 10: 308-320, 2002.
56. Luan J, Che G, Man G and Xiao F: Ginsenoside Rb1 from Panax ginseng attenuates monoiodoacetate-induced osteoarthritis by inhibiting miR-21-5p/FGF18-mediated inflammation. J Food Biochem 46: e14340, 2022.
57. Hayden MS and Ghosh S: Shared principles in NF-kappaB signaling. Cell 132: 344-362, 2008.
58. Yu Q, Zeng KW, Ma XL, Jiang Y, Tu PF and Wang XM: Ginsenoside Rk1 suppresses pro-inflammatory responses in lipopolysaccharide-stimulated RAW264.7 cells by inhibiting the Jak2/Stat3 pathway. Chin J Nat Med 15: 751-757, 2017.
59. Saba E, Jeong D, Irfan M, Lee YY, Park SJ, Park CK and Rhee MH: Anti-inflammatory activity of Rg3-enriched korean red ginseng extract in murine model of sepsis. Evid Based Complement Alternat Med 2018: 6874692, 2018.
60. Olivotto E, Borzi RM, Vitellozzi R, Pagani S, Facchini A, Battistelli M, Penzo M, Li X, Flamigni F, Li J, *et al*: Differential requirements for IKKalpha and IKKbeta in the differentiation of primary human osteoarthritic chondrocytes. Arthritis Rheum 58: 227-239, 2008.
61. Xing L, Jiang M, Dong L, Gao J, Hou Y, Bai G and Luo G: Cardioprotective effects of the YiQiFuMai injection and isolated compounds on attenuating chronic heart failure via NF-κB inactivation and cytokine suppression. J Ethnopharmacol 148: 239-245, 2013.
62. Zhang XH, Xu XX and Xu T: Ginsenoside Ro suppresses interleukin-1β-induced apoptosis and inflammation in rat chondrocytes by inhibiting NF-κB. Chin J Nat Med 13: 283-289, 2015.
63. Braicu C, Buse M, Busuioc C, Drula R, Gulei D, Raduly L, Rusu A, Irimie A, Atanasov AG, Slaby O, *et al*: A comprehensive review on MAPK: A promising therapeutic target in cancer. Cancers (Basel) 11: 1618, 2019.
64. Chen Y, Shou K, Gong C, Yang H, Yang Y and Bao T: Anti-inflammatory effect of geniposide on osteoarthritis by suppressing the activation of p38 MAPK signaling pathway. Biomed Res Int 2018: 8384576, 2018.
65. Arafa EA, Refaey MS, Abd El-Ghafar OAM, Hassanein EHM and Sayed AM: The promising therapeutic potentials of ginsenosides mediated through p38 MAPK signaling inhibition. Heliyon 7: e08354, 2021.
66. Joh EH, Lee IA, Jung IH and Kim DH: Ginsenoside Rb1 and its metabolite compound K inhibit IRAK-1 activation-the key step of inflammation. Biochem Pharmacol 82: 278-286, 2011.
67. Hossain MA, Alam MJ, Kim B, Kang CW and Kim JH: Ginsenoside-Rb1 prevents bone cartilage destruction through down-regulation of p-Akt, p-P38, and p-P65 signaling in rabbit. Phytomedicine 100: 154039, 2022.

68. Cui T, Lan Y, Lu Y, Yu F, Lin S, Fu Y, Qiu J and Niu G: Isoorientin ameliorates H_2O_2-induced apoptosis and oxidative stress in chondrocytes by regulating MAPK and PI3K/Akt pathways. Aging (Albany NY) 15: 4861-4874, 2023.
69. Nuttall ME, Nadeau DP, Fisher PW, Wang F, Keller PM, DeWolf WE Jr, Goldring MB, Badger AM, Lee D, Levy MA, *et al*: Inhibition of caspase-3-like activity prevents apoptosis while retaining functionality of human chondrocytes in vitro. J Orthop Res 18: 356-363, 2000.
70. Na JY, Kim S, Song K, Lim KH, Shin GW, Kim JH, Kim B, Kwon YB and Kwon J: Anti-apoptotic activity of ginsenoside Rb1 in hydrogen peroxide-treated chondrocytes: Stabilization of mitochondria and the inhibition of caspase-3. J Ginseng Res 36: 242-247, 2012.
71. Kim S, Na JY, Song KB, Choi DS, Kim JH, Kwon YB and Kwon J: Protective effect of ginsenoside rb1 on hydrogen peroxide-induced oxidative stress in rat articular chondrocytes. J Ginseng Res 36: 161-168, 2012.
72. Huang Y, Wu D and Fan W: Protection of ginsenoside Rg1 on chondrocyte from IL-1β-induced mitochondria-activated apoptosis through PI3K/Akt signaling. Mol Cell Biochem 392: 249-257, 2014.
73. Xu Z, Li X, Shen G, Zou Y, Zhang H, Yang K and Zhu Y: The protective effect of ginsenoside Rg1 on apoptosis in human ankle joint traumatic arthritis chondrocytes. Evid Based Complement Alternat Med 2022: 6798377, 2022.
74. Ma CH, Chou WC, Wu CH, Jou IM, Tu YK, Hsieh PL and Tsai KL: Ginsenoside Rg3 attenuates TNF-α-induced damage in chondrocytes through regulating SIRT1-mediated anti-apoptotic and anti-inflammatory mechanisms. Antioxidants (Basel) 10: 1972, 2021.
75. Zhang J, Xu HX, Zhu JQ, Dou YX, Xian YF and Lin ZX: Natural Nrf2 inhibitors: A review of their potential for cancer treatment. Int J Biol Sci 19: 3029-3041, 2023.
76. Bellezza I, Giambanco I, Minelli A and Donato R: Nrf2-Keap1 signaling in oxidative and reductive stress. Biochim Biophys Acta Mol Cell Res 1865: 721-733, 2018.
77. Dong C, Liu P, Wang H, Dong M, Li G and Li Y: Ginsenoside Rb1 attenuates diabetic retinopathy in streptozotocin-induced diabetic rats1. Acta Cir Bras 34: e201900201, 2019.
78. Yang Q, Lin J, Zhang H, Liu Y, Kan M, Xiu Z, Chen X, Lan X, Li X, Shi X, *et al*: Ginsenoside compound K regulates amyloid β via the Nrf2/Keap1 signaling pathway in mice with scopolamine hydrobromide-induced memory impairments. J Mol Neurosci 67: 62-71, 2019.
79. Hwang YP and Jeong HG: Ginsenoside Rb1 protects against 6-hydroxydopamine-induced oxidative stress by increasing heme oxygenase-1 expression through an estrogen receptor-related PI3K/Akt/Nrf2-dependent pathway in human dopaminergic cells. Toxicol Appl Pharmacol 242: 18-28, 2010.
80. Vincent TL, McClurg O and Troeberg L: The extracellular matrix of articular cartilage controls the bioavailability of pericellular matrix-bound growth factors to drive tissue homeostasis and repair. Int J Mol Sci 23: 6003, 2022.
81. Hu Q and Ecker M: Overview of MMP-13 as a promising target for the treatment of osteoarthritis. Int J Mol Sci 22: 1742, 2021.
82. Yang CY, Chanalaris A and Troeberg L: ADAMTS and ADAM metalloproteinases in osteoarthritis-looking beyond the 'usual suspects'. Osteoarthritis Cartilage 25: 1000-1009, 2017.
83. Lee JH, Lim H, Shehzad O, Kim YS and Kim HP: Ginsenosides from Korean red ginseng inhibit matrix metalloproteinase-13 expression in articular chondrocytes and prevent cartilage degradation. Eur J Pharmacol 724: 145-151, 2014.
84. Shin JS, Park N, Ra J, Kim Y, Shin M, Hong M, Kim SH, Kwon HJ, Hong SP, Kim J and Bae H: Panax ginseng C.A. Meyer modulates the levels of MMP3 in S12 murine articular cartilage cell line. J Ethnopharmacol 124: 397-403, 2009.
85. So MW, Lee EJ, Lee HS, Koo BS, Kim YG, Lee CK and Yoo B: Protective effects of ginsenoside Rg3 on human osteoarthritic chondrocytes. Mod Rheumatol 23: 104-111, 2013.
86. Chen Y, Lin S, Sun Y, Pan X, Xiao L, Zou L, Ho KW and Li G: Translational potential of ginsenoside Rb1 in managing progression of osteoarthritis. J Orthop Translat 6: 27-33, 2016.
87. Lee SY: Anti-metastatic and anti-inflammatory effects of matrix metalloproteinase inhibition by ginsenosides. Biomedicines 9: 198, 2021.
88. Lee SY: Ginsenoside Rg1 drives stimulations of timosaponin AIII-induced anticancer effects in human osteosarcoma cells. Evid Based Complement Alternat Med 2020: 8980124, 2020.
89. Young DA, Barter MJ and Wilkinson DJ: Recent advances in understanding the regulation of metalloproteinases. F1000Res 8: F1000 Faculty Rev-195, 2019.
90. Zhang P: Ginsenoside-Rg5 treatment inhibits apoptosis of chondrocytes and degradation of cartilage matrix in a rat model of osteoarthritis. Oncol Rep 37: 1497-1502, 2017.
91. Deshotels L, Safa FM and Saba NS: NOTCH signaling in mantle cell lymphoma: Biological and clinical implications. Int J Mol Sci 24: 10280, 2023.
92. Wang H, Tian Y, Wang J, Phillips KLE, Binch ALA, Dunn S, Cross A, Chiverton N, Zheng Z, Shapiro IM, *et al*: Inflammatory cytokines induce NOTCH signaling in nucleus pulposus cells: Implications in intervertebral disc degeneration. J Biol Chem 288: 16761-16774, 2013.
93. Wang W, Zeng L, Wang ZM, Zhang S, Rong XF and Li RH: Ginsenoside Rb1 inhibits matrix metalloproteinase 13 through down-regulating Notch signaling pathway in osteoarthritis. Exp Biol Med (Maywood) 240: 1614-1621, 2015.
94. Jallali N, Ridha H, Thrasivoulou C, Underwood C, Butler PEM and Cowen T: Vulnerability to ROS-induced cell death in ageing articular cartilage: The role of antioxidant enzyme activity. Osteoarthritis Cartilage 13: 614-622, 2005.
95. Kim JK, Choi MS, Jeung W, Ra J, Yoo HH and Kim DH: Effects of gut microbiota on the pharmacokinetics of protopanaxadiol ginsenosides Rd, Rg3, F2, and compound K in healthy volunteers treated orally with red ginseng. J Ginseng Res 44: 611-618, 2020.
96. Kim DH: Gut microbiota-mediated pharmacokinetics of ginseng saponins. J Ginseng Res 42: 255-263, 2018.
97. Kim HJ, Oh TK, Kim YH, Lee J, Moon JM, Park YS and Sung CM: Pharmacokinetics of ginsenoside Rb1, Rg3, Rk1, Rg5, F2, and compound K from red ginseng extract in healthy korean volunteers. Evid Based Complement Alternat Med 2022: 8427519, 2022.
98. Wang W, Wang GJ, Xie HT, Sun JG, Zhao S, Jiang XL, Li H, Lv H, Xu MJ and Wang R: Determination of ginsenoside Rd in dog plasma by liquid chromatography-mass spectrometry after solid-phase extraction and its application in dog pharmacokinetics studies. J Chromatogr B Analyt Technol Biomed Life Sci 852: 8-14, 2007.
99. Zeng X, Deng Y, Feng Y, Liu Y, Yang L, Huang Y, Sun J, Liang W and Guan Y: Pharmacokinetics and safety of ginsenoside Rd following a single or multiple intravenous dose in healthy Chinese volunteers. J Clin Pharmacol 50: 285-292, 2010.
100. Gao XY, Liu GC, Zhang JX, Wang LH, Xu C, Yan ZA, Wang A, Su YF, Lee JJ, Piao GC and Yuan HD: Pharmacological properties of ginsenoside Re. Front Pharmacol 13: 754191, 2022.
101. Joo KM, Lee JH, Jeon HY, Park CW, Hong DK, Jeong HJ, Lee SJ, Lee SY and Lim KM: Pharmacokinetic study of ginsenoside Re with pure ginsenoside Re and ginseng berry extracts in mouse using ultra performance liquid chromatography/mass spectrometric method. J Pharm Biomed Anal 51: 278-283, 2010.
102. Zhao J, Su C, Yang C, Liu M, Tang L, Su W and Liu Z: Determination of ginsenosides Rb1, Rb2, and Rb3 in rat plasma by a rapid and sensitive liquid chromatography tandem mass spectrometry method: Application in a pharmacokinetic study. J Pharm Biomed Anal 64-65: 94-97, 2012.
103. Miao L, Yang Y, Li Z, Fang Z, Zhang Y and Han CC: Ginsenoside Rb2: A review of pharmacokinetics and pharmacological effects. J Ginseng Res 46: 206-213, 2022.
104. Xie F, Li S, Cheng Z, Liu X, Zhang H, Li P, Liu Z, Guo X and Yu P: Determination of 20(S)-protopanaxadiol in human plasma by HPLC-MS/MS: Application to a pharmacokinetic study. Acta Pharmaceutica Sinica B 3: 385-391, 2013.
105. Li L, Chen X, Li D and Zhong D: Identification of 20(S)-protopanaxadiol metabolites in human liver microsomes and human hepatocytes. Drug Metab Dispos 39: 472-483, 2011.
106. Ren HC, Sun JG, Wang GJ, A JY, Xie HT, Zha WB, Yan B, Sun FZ, Hao HP, Gu SH, *et al*: Sensitive determination of 20(S)-protopanaxadiol in rat plasma using HPLC-APCI-MS: Application of pharmacokinetic study in rats. J Pharm Biomed Anal 48: 1476-1480, 2008.
107. Kim H, Lee JH, Kim JE, Kim YS, Ryu CH, Lee HJ, Kim HM, Jeon H, Won HJ, Lee JY and Lee J: Micro-/nano-sized delivery systems of ginsenosides for improved systemic bioavailability. J Ginseng Res 42: 361-369, 2018.

108. Wang H, Zheng Y, Sun Q, Zhang Z, Zhao M, Peng C and Shi S: Ginsenosides emerging as both bifunctional drugs and nanocarriers for enhanced antitumor therapies. J Nanobiotechnology 19: 322, 2021.
109. Yang L, Zhang Z, Hou J, Jin X, Ke Z, Liu D, Du M, Jia X and Lv H: Targeted delivery of ginsenoside compound K using TPGS/PEG-PCL mixed micelles for effective treatment of lung cancer. Int J Nanomedicine 12: 7653-7667, 2017.
110. Dong Y, Fu R, Yang J, Ma P, Liang L, Mi Y and Fan D: Folic acid-modified ginsenoside Rg5-loaded bovine serum albumin nanoparticles for targeted cancer therapy in vitro and in vivo. Int J Nanomedicine 14: 6971-6988, 2019.
111. Liu Y, Zhu H, Zhou W and Ye Q: Anti-inflammatory and anti-gouty-arthritic effect of free ginsenoside Rb1 and nano ginsenoside Rb1 against MSU induced gouty arthritis in experimental animals. Chem Biol Interact 332: 109285, 2020.
112. Singh H, Du J, Singh P, Mavlonov GT and Yi TH: Development of superparamagnetic iron oxide nanoparticles via direct conjugation with ginsenosides and its in-vitro study. J Photochem Photobiol B 185: 100-110, 2018.
113. Liu X, Tang I, Wainberg ZA and Meng H: Safety considerations of cancer nanomedicine-A key step toward translation. Small 16: e2000673, 2020.
114. Wu B, Yang L, Chen L, Ma L and Guo Y: Traditional Chinese medicine therapies for patients with knee osteoarthritis: A protocol for systematic review and network meta-analysis. Medicine (Baltimore) 101: e29404, 2022.
115. Ju L, Hu P, Chen P, Xue X, Li Z, He F, Qiu Z, Cheng J and Huang F: Huoxuezhitong capsule ameliorates MIA-induced osteoarthritis of rats through suppressing PI3K/Akt/NF-κB pathway. Biomed Pharmacother 129: 110471, 2020.
116. Liu T, Zhu L and Wang L: A narrative review of the pharmacology of ginsenoside compound K. Ann Transl Med 10: 234, 2022.
117. Chen L, Zhou L, Wang Y, Yang G, Huang J, Tan Z, Wang Y, Zhou G, Liao J and Ouyang D: Food and sex-related impacts on the pharmacokinetics of a single-dose of ginsenoside compound K in healthy subjects. Front Pharmacol 8: 636, 2017.
118. Liu Y, Perumalsamy H, Kang CH, Kim SH, Hwang JS, Koh SC, Yi TH and Kim YJ: Intracellular synthesis of gold nanoparticles by Gluconacetobacter liquefaciens for delivery of peptide CopA3 and ginsenoside and anti-inflammatory effect on lipopolysaccharide-activated macrophages. Artif Cells Nanomed Biotechnol 48: 777-788, 2020.
119. Kang S, Siddiqi MH, Yoon SJ, Ahn S, Noh HY, Kumar NS, Kim YJ and Yang DC: Therapeutic potential of compound K as an IKK inhibitor with implications for osteoarthritis prevention: An in silico and in vitro study. In Vitro Cell Dev Biol Anim 52: 895-905, 2016.
120. Hassamal S: Chronic stress, neuroinflammation, and depression: An overview of pathophysiological mechanisms and emerging anti-inflammatories. Front Psychiatry 14: 1130989, 2023.
121. Schaaf MJ and Cidlowski JA: Molecular mechanisms of glucocorticoid action and resistance. J Steroid Biochem Mol Biol 83: 37-48, 2002.
122. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, *et al*: OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 27: 1578-1589, 2019.
123. Guermazi A, Neogi T, Katz JN, Kwoh CK, Conaghan PG, Felson DT and Roemer FW: Intra-articular corticosteroid injections for the treatment of hip and knee osteoarthritis-related pain: Considerations and controversies with a focus on imaging-radiology scientific expert panel. Radiology 297: 503-512, 2020.
124. Li J, Du J, Liu D, Cheng B, Fang F, Weng L, Wang C and Ling C: Ginsenoside Rh1 potentiates dexamethasone's anti-inflammatory effects for chronic inflammatory disease by reversing dexamethasone-induced resistance. Arthritis Res Ther 16: R106, 2014.
125. Barnes PJ and Adcock IM: Glucocorticoid resistance in inflammatory diseases. Lancet 373: 1905-1917, 2009.