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EDITED BY
Lu Zhao,
Zhejiang University, China

REVIEWED BY
Prabhat Upadhyay,
Massachusetts General Hospital and
Harvard Medical School, United States
Fatima Rizvi,
Boston University, United States

*CORRESPONDENCE
Yong Xiao,
✉ xiaoyongziji0429@163.com

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Natural compounds protect against the pathogenesis of osteoarthritis by mediating the NRF2/ARE signaling

Zhenyu Wu^{1,2}, Zhouxin Yang², Luying Liu² and Yong Xiao^{3,4*}

¹First Affiliated Hospital of Gannan Medical University, Ganzhou, China, ²First Clinical Medical College of Gannan Medical University, Ganzhou, China, ³Jiangxi University of Traditional Chinese Medicine, Nanchang, China, ⁴Xiaoyong Traditional Chinese Medicine Clinic in Yudu, Ganzhou, China

Osteoarthritis (OA), a chronic joint cartilage disease, is characterized by the imbalanced homeostasis between anabolism and catabolism. Oxidative stress contributes to inflammatory responses, extracellular matrix (ECM) degradation, and chondrocyte apoptosis and promotes the pathogenesis of OA. Nuclear factor erythroid 2-related factor 2 (NRF2) is a central regulator of intracellular redox homeostasis. Activation of the NRF2/ARE signaling may effectively suppress oxidative stress, attenuate ECM degradation, and inhibit chondrocyte apoptosis. Increasing evidence suggests that the NRF2/ARE signaling has become a potential target for the therapeutic management of OA. Natural compounds, such as polyphenols and terpenoids, have been explored to protect against OA cartilage degeneration by activating the NRF2/ARE pathway. Specifically, flavonoids may function as NRF2 activators and exhibit chondroprotective activity. In conclusion, natural compounds provide rich resources to explore the therapeutic management of OA by activating NRF2/ARE signaling.

KEYWORDS

osteoarthritis, oxidative stress, Nrf2/ARE signaling, flavonoids, terpenoids

Introduction

Osteoarthritis (OA), a degenerative and irreversible joint disease, has been associated with chronic inflammation, trauma, and other diseases. No effective strategies are available to cure OA. Clinically, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to alleviate OA symptoms, such as joint pain, stiffness, and movement limitation, which may greatly decrease the quality of life and increase the burden on society and patients (Lane et al., 2017). This awkward situation might be attributed to the incomplete understanding of the pathological molecular mechanisms. It is well-accepted that OA is correlated with the imbalance between anabolism and catabolism in the joint cartilage. Both the reduction of anabolism and the stimulation of catabolism can be driven by chronic inflammatory responses, oxidative stress, and other aberrant signaling pathways. Effective agents used for preventing or inhibiting OA progression are still lacking.

Excessive oxidative stress contributes to the pathological development of OA (Lepetsos and Papavassiliou, 2016). Reactive oxygen/nitrogen species (ROS/RNS), such as hydrogen peroxide (H₂O₂), hydroxyl radical, superoxide anion, nitric oxide (NO), and hypochlorite ion, are free radicals, which have unpaired electrons. ROS can be produced by mitochondrion, non-

mitochondrial membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs), and xanthine oxidase (XO) (Turrens, 2003). Overproduction of ROS may induce damage to macromolecules, including DNA, protein, and fat. In addition, ROS can be the player involved in the intracellular signaling pathways, which orchestrate the homeostasis of joint cartilage. Increasing evidence shows that ROS overproduction and oxidative stress have been observed in the joint cartilage of patients with OA, and oxidative stress has been implicated in the mediation of chondrocyte apoptosis and extracellular matrix (ECM) degradation (Henrotin et al., 1993; Ertürk et al., 2012; Altay et al., 2015). Thus, suppression of oxidative stress has become a therapeutic strategy for OA management.

Nuclear factor erythroid 2-related factor 2 (NRF2), a transcriptional factor, exhibits a central role in maintaining the homeostasis of the intracellular redox system. NRF2 activation has been reported to counteract ROS generation and oxidative stress by binding to antioxidant response elements (AREs) in the promoters of the downstream antioxidant genes, such as heme oxygenase-1 (HO-1) (Baird and Yamamoto, 2020). Potentially, any exogenous bioactive ROS-scavenging or NRF2/ARE-activating agents that balance the redox homeostasis may lead to therapeutic effects against OA development. Naturally occurring compounds from different sources have been explored to develop novel preventive and therapeutic agents for treating various human diseases. Many of them may regulate multiple signaling pathways at DNA, RNA, and protein levels and exhibit favorable safety profiles (Khan et al., 2021). These make them become the ideal options for the therapeutic management of chronic diseases, such as OA. Natural compounds with anti-oxidative activity, such as flavonoids, have been linked to the confrontation of OA progression by inhibiting oxidative stress in chondrocytes (Wang Q. et al., 2022; Zhu et al., 2022a). In this article, we will summarize the protective activities of natural compounds against OA development by mediating the NRF2/ARE signaling pathway in chondrocytes.

The interaction between oxidative stress and OA

The pathological development of OA

OA elucidates a subset of the pathological alterations that are influencing the joints. The pathogenesis of OA includes three overlapping stages (Braaten et al., 2022). Firstly, ECM on the surface of the articular cartilage is damaged. Various factors, such as genetic, metabolic, biochemical, and environmental processes, contribute to the destruction of ECM (Felson et al., 2000; Loeser, 2010). Progressive ECM degeneration may lead to the development of clefts and fibrillation in the articular cartilage. Particularly, these pathological changes may affect the micro-environment of subchondral bone, leading to alterations in joint shape and loading transmission. Secondly, chondrocytes, the unique cell type in the joint cartilage, are affected by the damage of ECM and subchondral tissues. Importantly, many signaling pathways regulating the repair activity, such as bone morphogenic proteins (BMPs), transforming growth factor-beta (TGF- β), and insulin-like growth factor-I (IGF-I), are activated. On the other hand, ECM breakdown may trigger the release of pro-

inflammatory cytokines and facilitate the expression of matrix metalloproteases (MMPs), forming a vicious cycle of cartilage degeneration. In addition, endochondral ossification is also stimulated by up-regulating the expression of type X collagen. The third stage is the failure of cartilage repair during OA development. The repair activity of chondrocytes is rather limited. The continued catabolic activity progressively contributes to the damage to cartilage and subchondral bone and cell death. For example, upregulated expression of MMPs and downregulated expression of tissue inhibitors of metalloproteinase-1 (TIMP-1) are reported in OA chondrocytes (Lotz and Loeser, 2012).

The pathological changes of OA are associated with the dysregulation of signaling pathways, such as NRF2/ARE, NF- κ B, AMPK/Sirt1, HIFs, Wnt/ β -catenin, TGF β /BMP, and JAK2/STAT3 (Park and Lee, 2022; Yao et al., 2023). NRF2/ARE signaling is a major factor in counteracting oxidative stress and ECM degradation. Activation of the NRF2 signaling facilitates to maintain the homeostasis of chondrocytes and joint cartilage (Xiong et al., 2023). In addition, activation of the NRF2 signaling may negatively regulate the phosphorylation and nuclear translocation of p65, suppressing the NF- κ B and RANKL signaling pathways in IL-1 β -treated chondrocytes (Yang et al., 2023). HIF-1 α exhibits protective activity on articular cartilage by suppressing the NF- κ B signaling in mice. Loss of HIF-1 α expression upregulates the expression of MMP-13 and HIF-2 α (Okada et al., 2020). Dysregulation of the Wnt/ β -catenin signaling contributes to the pathological development of OA. Increased expression of β -catenin has been found in OA patients, and genetic activation of β -catenin stimulates the expression of catabolic enzymes, such as MMPs and ADAMTSs (Hui et al., 2018). Similarly, the TGF β /BMP/Smad signaling pathway also plays a key role in cartilage homeostasis. Smad2/3 and Smad1/5/9 may exhibit distinctive effects on chondrocyte biology. In chondrocyte-specific Smad3-null mice, dysregulated expression of MMP-13 and Col10a1 is found, and increased chondrocyte hypertrophy and stimulated cartilage degeneration are observed (Chen et al., 2012). Combined knockout of Smad1, 5, and 8 may induce severe chondrodysplasia (Retting et al., 2009). The JAK2/STAT3 signaling is abnormally activated in OA chondrocytes. Inhibition of JAK2 expression can lead to a significant reduction in aggrecan loss and chondrocyte apoptosis (Lu et al., 2017). Targeting the JAK2/STAT3 signaling has become a potential therapeutic approach for OA treatment (Chen et al., 2023). Thus, the pathological development of OA is related to multi-factors and multi-pathways. Studies have shown that these signaling pathways can be potential targets for the therapeutic management of OA (Cheng et al., 2022; van der Kraan, 2022).

The involvement of oxidative stress in the pathogenesis of OA

Oxidative stress contributes to inflammatory responses in OA chondrocytes. Inflammatory responses are involved in the dysregulated balance between anabolism and catabolism in chondrocytes (Scanzello and Goldring, 2012). The balance between PI3K/AKT and MAPK signaling pathways exhibits a critical role in inflammatory responses and OA pathogenesis (Yu and Kim, 2015). Increased ROS production in OA chondrocytes has been demonstrated to suppress the activity of the PI3K/AKT

pathway. In addition, ROS may stimulate the expression of the MAPK pathway. Thymoquinone (TQ), a major metabolite of black seed oil, can induce ROS generation. TQ may increase the production of COX-2 and PGE2 by activating the p38 and ERK pathways in rabbit OA chondrocytes. N-acetyl cysteine (NAC), an antioxidant, may abolish TQ-induced ROS production and inflammatory responses (Yu and Kim, 2015). Advanced oxidation protein products (AOPPs) can enhance the expression of IL-1 β and TNF α by up-regulating the p38-MAPK signaling in OA chondrocytes (Liao et al., 2020). H₂O₂ increases the secretion of IL-6 and TNF α by activating the NF- κ B signaling in OA chondrocytes (Wang et al., 2023).

Oxidative stress facilitates ECM degradation. NOX enzyme family is a key source of superoxide anion and H₂O₂. NOX-4 may enhance IL-1 β -stimulated expression of MMPs, which promote ECM degradation (Grange et al., 2006). NOX4 deficiency decreases MMP-13 and collagen I expression, enhances aggrecan production, and reduces cartilage degradation in DMM-induced OA mice (Renaudin et al., 2023). Another study reports that AOPPs may upregulate the expression of NOX4 in chondrocytes. Apocynin, a NOX inhibitor, can block the detrimental effects of AOPPs, as shown by increased collagen II and GAG expression and attenuated ECM degradation (Liao et al., 2020). Sirt4 deficiency downregulates the expression of antioxidant enzymes, such as SOD1, SOD2, and CAT. Knockdown of Sirt4 may decrease the production of collagen II and aggrecan and increase the generation of MMP-13 in OA chondrocytes (Dai et al., 2020).

Oxidative stress promotes cell death in OA chondrocytes. ROS production increases with aging, due to the decline of mitochondrial functions (Chistiakov et al., 2014). In addition, excessive mechanical loading in chondrocytes may induce the generation of superoxide anion and decrease the expression of superoxide dismutase (SOD), which catalyzes the conversion of superoxide anion to H₂O₂ (Koike et al., 2015). Mitochondrial H₂O₂ can induce human chondrocyte cell death by up-regulating the activity of the MKK3/6-p38 signaling pathway (Collins et al., 2016). Similarly, ROS also promotes chondrocyte cell death by activating protein kinase C (PKC- β 1) expression, and inhibition of PKC- β 1 may abolish ROS-induced chondrocyte cell death (DelCarlo and Loeser, 2006). Advanced glycation end products (AGEs) may induce mitochondrial dysfunction in OA chondrocytes. It has been reported that AGEs can induce oxidative stress and chondrocyte apoptosis by down-regulating the AMPK α /Sirt1/PGC-1 α signaling (Yang et al., 2022). Collectively, inhibiting redox-sensitive factors implicated in cell death and stimulating antioxidant expression may facilitate chondrocyte survival and promote cartilage integrity (Figure 1).

The roles of the NRF2/ARE signaling in the pathological development of OA

It is well-accepted that the NRF2/ARE pathway is negatively mediated by Keap1 (Suraweera et al., 2020; Saha et al., 2021). Under normal conditions, NRF2-Keap1 complex interacts with the E3 ubiquitin ligase complex Cullin 3 (Cul3) and leads to the ubiquitination and proteasomal degradation of NRF2. Under stressed conditions, modification of the cysteine residues may induce the conformational changes of Keap1. Then, the conformational changes of Keap1 induce its dissociation from

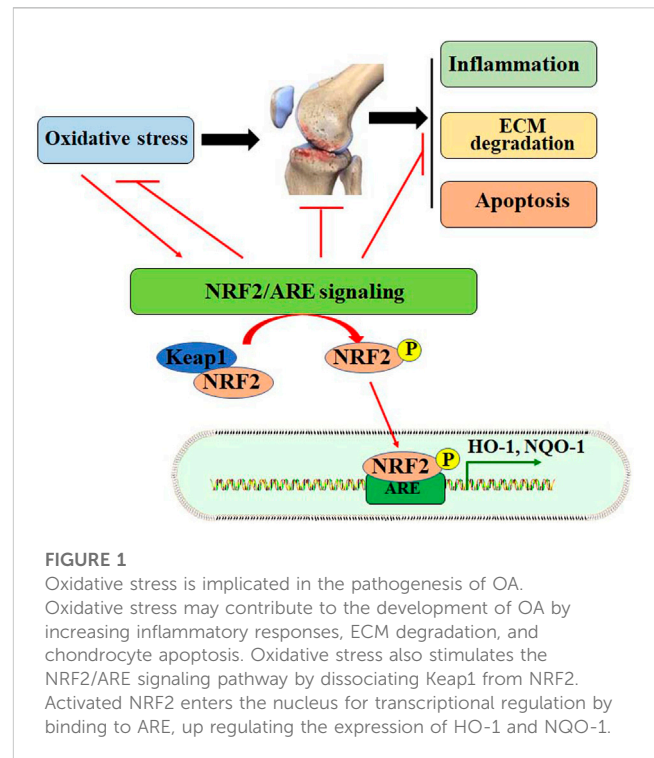


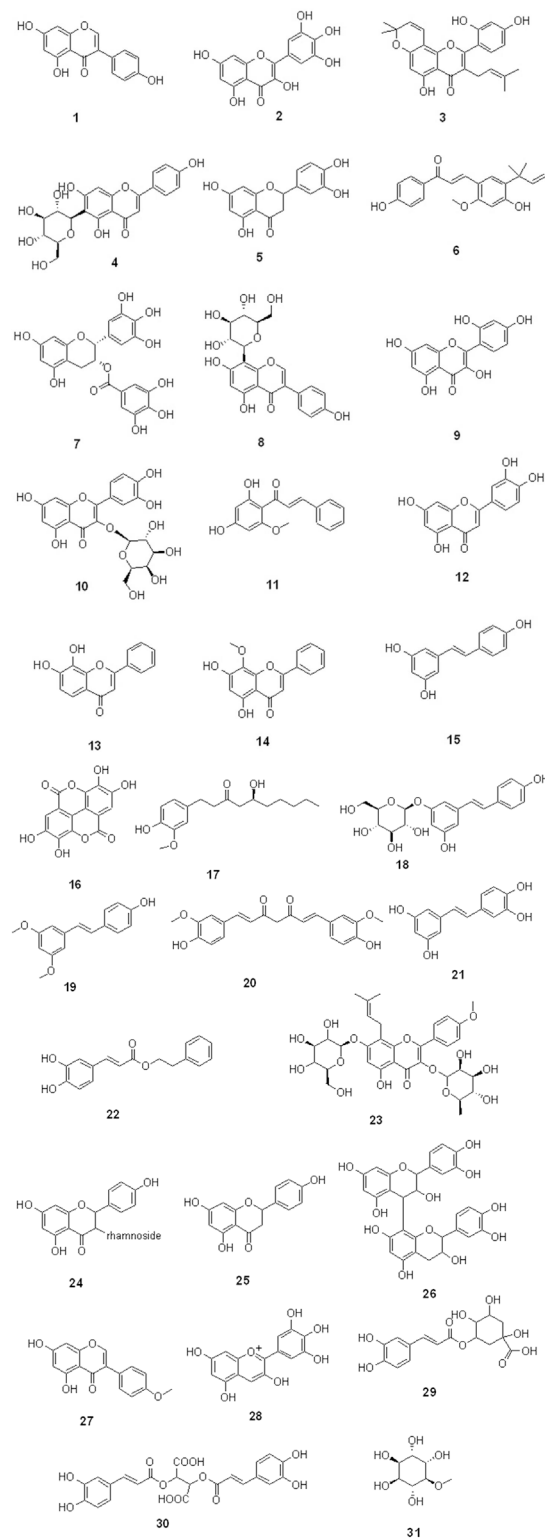
FIGURE 1

Oxidative stress is implicated in the pathogenesis of OA. Oxidative stress may contribute to the development of OA by increasing inflammatory responses, ECM degradation, and chondrocyte apoptosis. Oxidative stress also stimulates the NRF2/ARE signaling pathway by dissociating Keap1 from NRF2. Activated NRF2 enters the nucleus for transcriptional regulation by binding to ARE, up regulating the expression of HO-1 and NQO-1.

NRF2. The dissociation of Keap1 prevents NRF2 from ubiquitination and degradation, and NRF2 is stabilized and then translocated into the nucleus for transcriptional regulation (Dinkova-Kostova et al., 2018). Additionally, NRF2 can also be phosphorylated by PKC, casein kinase II (CKII), protein kinase R-like endoplasmic reticulum kinase (PERK), JNK, and ERK (Zuo et al., 2022).

Activation of the NRF2/ARE signaling pathway exhibits the protective activity against OA pathogenesis by up-regulating the expression of antioxidant factors, such as HO-1, NADPH gene of quinone oxidoreductase 1 (NQO1), GSH, GPx, and SOD, and suppressing oxidative stress in chondrocytes (Ashrafizadeh et al., 2020) (Figure 1). In OA chondrocytes, NRF2/ARE signaling activation is associated with anti-inflammatory effects. Specifically, activation of the NRF2/ARE signaling may suppress M1 polarization and promote M2 polarization through signaling transductions, including TGF β /Smad, JAK/STAT, and NF- κ B pathways (Wang and He, 2022). NLRP3 inflammasome can be stimulated by the TLR/NF- κ B signaling pathway. It is also reported that activation of the NRF2 signaling may alleviate the progression of OA by suppressing NLRP3 inflammasome in primary mouse chondrocytes (Yan et al., 2020). MCC950 is an inhibitor of NLRP3. It has been shown that MCC950 may ameliorate inflammatory responses and protect cartilage against degeneration by up-regulating the expression of NRF2/HO-1/NQO-1 signaling pathway in mouse chondrocytes (Ni et al., 2021).

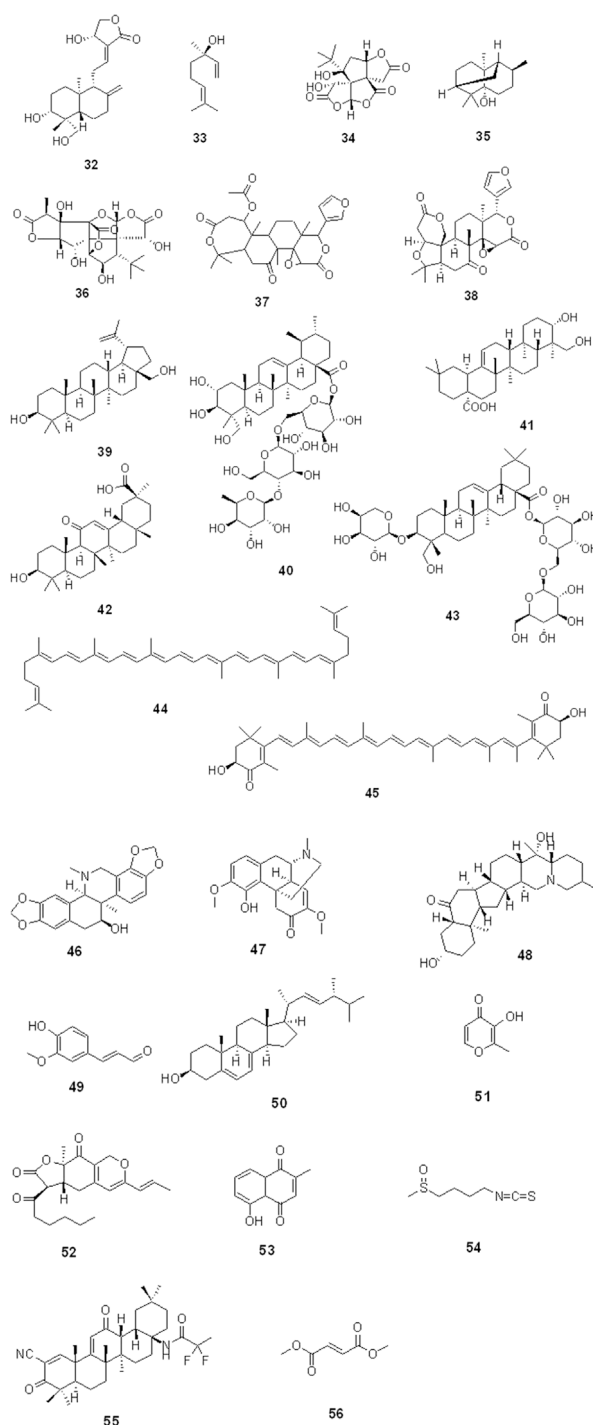
Activation of the NRF2 signaling also contributes to the inhibition of ECM degradation and chondrocyte apoptosis. It has been reported that NRF2 signaling may increase the expression of collagen II and SOX9 and decrease the expression of MMP-13 and ADAMTS5, protecting against IL-1 β -induced ECM degradation in OA chondrocytes (Liang et al., 2022). Manganese (Mn) deficiency



SCHEME 1
Continued.

can negatively affect tibial cartilage development by stimulating oxidative stress and inflammation. Mn deficiency may downregulate NRF2 signaling and upregulate MMP-1, MMP-9, and MMP-13

expression in broiler chicks (Dong et al., 2022). Knockdown of NRF2 may promote MMP-13 expression, decrease aggrecan production, and suppress cell apoptosis in TBHP-treated



SCHEME 1

(Continued). The chemical structures of natural compounds.

chondrocytes (Shao et al., 2020). It has been demonstrated that NRF2 activation may suppress IL-1 β -induced mitochondrial dysfunction, ROS generation, and apoptosis in OA chondrocytes. Mechanically, overexpression of NRF2 upregulates the expression of anti-apoptotic factors, downregulates pro-apoptotic proteins, and activates ERK1/2 and its downstream factors, such as ELK1, P70S6K, and P90RSK (Khan et al., 2018).

However, one study reports that inhibition of the NRF2/ARE signaling can ameliorate LPS-stimulated NLRP3 inflammasome in SW982 cells. Increased expression of NRF2/HO-1 and NLRP3 are also observed in rat OA models (Chen et al., 2019). Another study suggests that there is no difference in NRF2 expression between OA and healthy human cartilage chondrocytes (Cai et al., 2019b). The discrepancy in NRF2 expression in OA chondrocytes might be

TABLE 1 The protective effects of some natural compounds against OA development by mediating the NRF2 signaling pathway in animal models.

Compounds	Sources and availability	Models	Doses	Routines	Biological actions	Ref
Genistein	Soybean; 26.8–102.5 mg/100 g	Rat ACLT	40 mg/kg/day	gavage	OARIS Score↓, GAG↑	Liu et al. (2019)
Myricetin	Garlic; 693 mg/kg	Mouse DMM	20 mg/kg/2 days	gavage	NRF2↑, p-Akt↑, OARIS Score↓	Pan et al. (2019)
moracin	<i>Cortex Mori.</i> ; 0.01%–0.6%	Rat ACLT	30 mg/kg/day	gavage	OARIS Score↓, NRF2↑, collagen II↑	Zhou et al. (2020)
Lico A	licorice root; 4–10 mg/g	Mouse DMM	10 mg/kg/day	gavage	OARIS Score↓, NRF2↑, IL-1β↑, IL-18↑	Yan et al. (2020)
7,8-DHF	<i>Lepisorus ussuriensis</i> ; 0.48 mg/kg	Mouse DMM	5 mg/kg/week	i.p	OARIS Score↓, NRF2↑, HO-1↑, IL-1β↓, IL-6↓, TNFα↓, MMP-1/-3/-13↓	Cai et al. (2019a)
Polydatin	cocoa powder; 7.14 μg/g	Mouse DMM	100 mg/kg/day	i.p	OARIS Score↓, Synovitis Score↓	Tang et al. (2018)
Engeletin	Grape skin; 2.4 mg/kg	Rat ACLT	50 μg/week	i.a	OARIS Score↓	Wang et al. (2021a)
18β-GA	<i>Glycyrrhiza glabra</i> ; 0.1%–1.6%	Mouse DMM	50 mg/kg/day	i.p	OARIS Score↓, NRF2↑	Chen et al. (2021a)
ASD	Rhizome of <i>Dipsacus asper</i> Wall; 15.0 g/kg	Mouse DMM	100 mg/kg/3 days	gavage	OARIS Score↓, NRF2↑	Gu et al. (2020)
AST	<i>Haematococcus lacustris</i> ; 4% of dry weight	Mouse DMM	20 mg/kg twice a week	i.a	OARIS Score↓, NRF2↑	Sun et al. (2019)
COR	<i>Corydalis bungeana Turcz.</i> ; 9 mg/kg	Mouse DMM	15 and 30 mg/kg/day	gavage	OARIS Score↓, NRF2↑, collagen II↑	Li et al. (2022)

Note: i.p., intraperitoneal injections; i.a., intra-articular injection.

TABLE 2 The protective effects of some natural compounds against OA development by mediating the NRF2 signaling pathway in vitro

Compounds	Cell lines	Concentrations	Biological actions	Ref
moracin	Rat chondrocytes	5, 10, and 15 μM	NRF2↑, HO-1↑, p65 nuclear translocation↓, IL-6↓, TNFα↓, COX-2↓, PGE2↓, iNOS↓, NO↓, MMP-13↓, ADAMTS5↓	Zhou et al. (2020)
Lico A	Mouse chondrocytes	5, 25, and 50 μM	NRF2↑, HO-1↑, p65↓, NLRP3↓, Cleaved GSDMD↓, Cleaved caspase-1↓, collagen II↑, aggrecan↑	Yan et al. (2020)
Hyperoside	Mouse chondrocytes	10, 20, and 40 μM	ROS↓, COX-2↓, iNOS↓, MMP-3↓, MMP-13↓, ADAMTS5↓, collagen II↑, aggrecan↑, SOX9↑, cleaved caspase-3/-9↓, Bax↓, Bcl-xL↑, cytochrome c↓	Sun et al. (2021)
7,8-DHF	Mouse chondrocytes	1, 3, and 9 μM	NRF2↑, HO-1↑, MDA↓, SOD↑	Cai et al. (2019a)
Pterostilbene	Rat chondrocytes	4, 8, 10, and 20 μM	NRF2↑, COX-2↓, PGE2↓, iNOS↓, NO↓, ROS↓	Xue et al. (2017)
Engeletin	Rat chondrocytes	10 and 20 μM	NRF2↑, HO-1↑, NQO-1↑, P-p65↓, MAPK↓, MMP-3↓, MMP-9↓, collagen II↑, aggrecan↑	Wang et al. (2021a)
Biochanin A	Mouse chondrocytes	12 and 24 μM	MMP-3↓, collagen II↑, Bcl-2↑, TFR1↓, ROS↓, GPX4↑, xCT↑, NRF2↑, HO-1↑	He et al. (2022)
18β-GA	Mouse chondrocytes	10, 25, and 50 μM	NRF2↑, HO-1↑, IL-6↓, TNFα↓, COX-2↓, PGE2↓, iNOS↓, NO↓, MMP-13↓, ADAMTS5↓	Chen et al. (2021a)
ASD	Mouse chondrocytes	50, 100, and 200 μM	NRF2↑, HO-1↑, p65↓, IL-6↓, TNFα↓, COX-2↓, PGE2↓, iNOS↓, NO↓, MMP-13↓, ADAMTS5↓, collagen II↑, aggrecan↑	Gu et al. (2020)
AST	Mouse chondrocytes	5, 10, and 20 μM	NRF2↑, HO-1↑, p-p65/p65↓, MAPK↓, TNFα↓, COX-2↓, iNOS↓, MMP-3/-13↓, ADAMTS5↓, collagen II↑	Sun et al. (2019)
COR	Mouse chondrocytes	2 and 4 μM	NRF2↑, HO-1↑, p-p65/p65↓, IL-6↓, COX-2↓, iNOS↓, MMP-3/-13↓, ADAMTS5↓, collagen II↑, aggrecan↑	Li et al. (2022)

TABLE 3 The clinical studies of natural compounds against OA development by mediating the NRF2/ARE signaling pathway.

Compounds	Models/Doses	Biological actions	Conclusions	Ref
Genistein	IL-1 β -treated human chondrocytes/10 μ M	NRF2 \uparrow , HO-1 \uparrow , COX-2 \downarrow , iNOS \downarrow , MMP-1 \downarrow , MMP-3 \downarrow , MMP-13 \downarrow , collagen II \uparrow , aggrecan \uparrow	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Liu et al. (2019)
Myricetin	IL-1 β -treated human chondrocytes/5, 10, and 15 μ M	NRF2 \uparrow , HO-1 \uparrow , p65 \downarrow , IL-6 \downarrow , TNF α \downarrow , COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , MMP-13 \downarrow , ADAMTS5 \downarrow , collagen II \uparrow , aggrecan \uparrow	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Pan et al. (2019)
Morin	IL-1 β -treated human OA chondrocytes/2.5, 5, and 10 μ M	PGE2 \downarrow , NO \downarrow , p65 \downarrow , NRF2 \uparrow , HO-1 \uparrow , MMP-1 \downarrow , MMP-3 \downarrow , MMP-13 \downarrow	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Qu et al. (2018)
Wogonin	IL-1 β -treated human OA chondrocytes/10, 25, and 50 μ M	IL-6 \downarrow , TNF α \downarrow , COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , MMP-3 \downarrow , MMP-9 \downarrow , MMP-13 \downarrow , ADAMTS5 \downarrow , collagen II \uparrow , ACAN \uparrow , NRF2 \uparrow , HO-1 \uparrow , NQO-1 \uparrow , p-ERK1/2 \uparrow	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Khan et al. (2017)
Polydatin	IL-1 β -treated human chondrocytes/25, 50, and 100 μ g/mL	NRF2 \uparrow , HO-1 \uparrow , IL-6 \downarrow , TNF α \downarrow , COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , MMP-13 \downarrow	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Tang et al. (2018)
Curcumin	IL-1 β -treated human chondrocytes/20 and 40 μ M	IL-6 \downarrow , TNF α \downarrow , COX-2 \downarrow , iNOS \downarrow , MMP-1 \downarrow , MMP-3 \downarrow , MMP-9 \downarrow , MMP-13 \downarrow , ADAMTS4 \downarrow , ADAMTS5 \downarrow , COL2A1 \uparrow , ACAN \uparrow , NRF2 \uparrow , HO-1 \uparrow , NQO-1 \uparrow , GCLC \uparrow , SOD-2 \uparrow	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Jiang et al. (2020a)
Piceatannol	IL-1 β -treated human chondrocytes/1, 5, and 10 μ M	IL-6 \downarrow , TNF α \downarrow , COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , MMP-13 \downarrow , ADAMTS5 \downarrow , collagen II \uparrow , aggrecan \uparrow , p65 \downarrow , NRF2 \uparrow , HO-1	Inhibits inflammation and ECM degradation by activating the NRF2/ARE signaling	Tang et al. (2017)
ICA	IL-1 β -treated HC-A/10 ⁻⁹ M	ROS \downarrow , GPX \uparrow , SOD \uparrow , MMP-3 \downarrow , MMP-9 \downarrow , MMP-13 \downarrow , ADAMTS4 \downarrow , GAG \uparrow , NRF2 \uparrow , NQO-1 \uparrow	Inhibits oxidative stress and ECM degradation by activating the NRF2/ARE signaling	Zuo et al. (2019)
CA	TNF α -treated C28/I2 cells/5, 10, and 20 μ M	IL-1 β \downarrow , IL-6 \downarrow , IL-12 \downarrow , COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , MMP-3 \downarrow , MMP-9 \downarrow , MMP-13 \downarrow , ADAMTS5 \downarrow , collagen II \uparrow , aggrecan \uparrow , ROS \downarrow , p-PI3K \downarrow , p-AKT \downarrow , p65 \downarrow	Inhibits inflammation, oxidative stress, and ECM degradation by activating the NRF2/ARE signaling	Qu et al. (2022)
Hederagenin	IL-1 β -treated C28/I2 cells/5, 10, and 20 μ M	IL-6 \downarrow , TNF α \downarrow , COX-2 \downarrow , PGE2 \downarrow , iNOS \downarrow , NO \downarrow , ROS \downarrow , MMP-1 \downarrow , MMP-3 \downarrow , MMP-9 \downarrow , MMP-13 \downarrow , ADAMTS5 \downarrow , collagen II \uparrow , aggrecan \uparrow , Bax \downarrow , Bcl-2 \uparrow , cleaved caspase-3 \downarrow , p-JAK2 \downarrow , p-STAT3 \downarrow , MAPK \downarrow , NRF2 \uparrow	Inhibits inflammation, oxidative stress, chondrocyte apoptosis, and ECM degradation by activating the NRF2/ARE signaling	Shen et al. (2022)
SFN	H ₂ O ₂ -treated human OA chondrocytes/7 μ M	NRF2 \uparrow , NOX4 \downarrow , COL2 \uparrow , ACAN \uparrow , SOX9 \uparrow , IL-6 \downarrow , TNF α \downarrow , MMP-13 \downarrow , ADAMTS5 \downarrow	Inhibits inflammation, oxidative stress, and ECM degradation by activating the NRF2/ARE signaling	Yang et al. (2020a)

related to various factors, such as experimental conditions, cell types, and cell situations. Thus, more efforts are still needed for elucidating the roles of NRF2 in the pathological development of OA.

Natural compounds activate the NRF2/ARE signaling to protect against OA development

The important roles of oxidative stress in the development of OA indicate that suppression of oxidative stress can be a useful strategy for OA treatment. Exploration of natural compounds with anti-oxidative activity has become one of the research interests in treating redox-imbalanced diseases, such as OA. Dietary supplements and nutraceuticals are also involved in the therapeutic management of OA. For example, allicin, sulforaphane (SFN), and lycopene are the antioxidants isolated from garlic, broccoli, and tomato, respectively, and they may decrease oxidative stress and inflammatory responses. It has been reported that allicin, SFN, and lycopene can effectively inhibit H₂O₂-induced oxidative stress and chondrocytes apoptosis by activating

the Keap1/NRF2 signaling pathway (Yang J. et al., 2020). Most natural compounds with anti-oxidative activity by activating the NRF2/ARE signaling pathway are mainly polyphenols and terpenoids (Scheme 1). Particularly, natural flavonoids may act as NRF2 activators to protect against oxidative stress.

Polyphenols/flavonoids activate the NRF2 signaling

Flavonoids have various pharmacological activities, including anti-inflammation, anti-oxidation, anti-cancer, anti-apoptosis, and bone system protection (Ghitti et al., 2022). Natural flavonoids provide health-benefiting effects against chronic diseases, such as OA. Particularly, isoflavones can act as phytoestrogens due to their structural similarity to estrogen. The estrogen-like effects of flavonoids greatly trigger the research interest because they may provide similar effects to the hormones (Guo et al., 2022). Natural flavonoids can inhibit inflammatory responses, attenuate ECM degradation, and suppress cell death in OA chondrocytes.

Inhibition of inflammatory responses

Genistein (**1**) acts as a selective estrogen receptor modulator (SERM) due to its structural similarity to estrogen. It has been reported that genistein (10 μ M) decreases the expression of COX-2, NOS2, and NO in IL-1 β -treated chondrocytes by activating the NRF2 signaling (Liu et al., 2019). Myricetin (**2**), extracted from Garlic (*Allium ampeloprasum* L., *Amaryllidaceae*) with the availability of 693 mg/kg (Agraharam et al., 2022), at the dose of 15 μ M has been reported to decrease the expression of IL-6, TNF α , COX-2, PGE2, iNOS, and NO and inhibit the NF- κ B signaling in IL-1 β -treated chondrocytes by activating the NRF2 signaling (Pan et al., 2019). In addition, Moracin (**3**, isolated from *Cortex Mori. Radicis, Moraceae*), Isovitexin (**4**, isolated from the passion flower (*Passiflora edulis* Sims, *Passifloraceae*), Cannabis (*Cannabis sativa* L., *Moraceae*), and palm (*Elaeis guineensis* Jacq., *Arecaceae*)), Eriodictyol (**5**, isolated from citrus fruits (*Citrus reticulata* Blanco, *Rutaceae*)), Licochalcone A (Lico A, **6**, isolated from the licorice root (*Glycyrrhiza uralensis* Fisch., *Leguminosae*)), and Epigallocatechin-3-O-gallate (EGCG, **7**, isolated from tea leaves) exhibit similar effects against inflammatory responses by activating the NRF2 signaling in OA chondrocytes (Jia et al., 2017; Wang Y. et al., 2018; Zhou et al., 2020; Hu et al., 2021; Zhu et al., 2022a) (Tables 1, 2). In addition, EGCG (100 μ M) also suppresses the JNK/MAPK signaling and inhibits inflammatory responses in IL-1 β -treated human chondrocytes (Akhtar and Haqqi, 2011).

Puerarin (**8**), separated from the root of *Pueraria lobata* var. *Lobata* (Willd.) Ohwi (Leguminosae), at the doses of 100 mg/kg/day and 200 mg/kg/day for 14 days by gavage ameliorates the pathological changes of OA cartilage by activating AMPK and NRF2 signaling pathways in MIA-induced rat OA models (Wang L. et al., 2018). Additionally, puerarin (10, 25, and 50 μ M) decreases the production of IL-6, TNF α , COX-2, PGE2, iNOS, and NO and inhibits the NF- κ B signaling in IL-1 β -treated mouse chondrocytes (Chen X. et al., 2021). Morin (**9**, isolated from the Chinese botanical drugs *Ficus religiosa* L.) of the *Moraceae* family) decreases IL-1 β -induced enhancement of NO and PGE₂ production and activation of the NF- κ B signaling in human chondrocytes. NRF2 siRNA transfection may abolish the suppressive activity of Morin against inflammatory responses (Qu et al., 2018) (Table 3). Hyperoside (**10**, isolated from *Epimedium brevicornu* Maxim (*Berberidaceae*), *Hypericum attenuatum* Fisch. (*Guttiferae*), and *Hypericum perforatum* L. (*Guttiferae*)) and Cardamonin (**11**, isolated from *Alpinia katsumadai* Hayata, *Zingiberaceae*) consistently protect mouse chondrocytes against IL-1 β -induced COX-2 and iNOS expression by suppressing PI3K/AKT/NF- κ B and MAPK signaling pathways via activating the NRF2 signaling (Peng et al., 2021; Sun et al., 2021) (Table 2). Luteolin (**12**) and 7,8-dihydroxyflavone (7,8-DHF, **13**) inhibit H₂O₂-induced inflammatory responses in mouse chondrocytes by inhibiting the MAPK pathway and activating the NRF2 signaling (Cai et al., 2019a; Zhou et al., 2022) (Tables 1, 2). Wogonin (5,7-dihydroxy-8-methoxyflavone, **14**), isolated from *Scutellaria baicalensis* Georgi (*Lamiaceae*), at the doses of 10, 25, and 50 μ M has been reported the anti-inflammatory effects, which are not associated with the inhibition of NF- κ B and MAPK signaling pathways in IL-1 β -treated human chondrocytes (Khan et al., 2017) (Table 3).

Resveratrol (**15**), firstly extracted from the root of *Veratrum grandiflorum* O. Loes (*Liliaceae*), has been demonstrated to be an activator of Sirt1, which may mediate Wnt/ β -catenin and Foxo1 signaling pathways in OA chondrocytes (Liang et al., 2023). Resveratrol at the dose of 50 mg/kg/3 days for 8 weeks can inhibit oxidative stress and suppress inflammatory responses in MIA-induced rat OA models by triggering the NRF2/HO-1 signaling and inhibiting the NF- κ B pathway (Wei et al., 2018). TLR4/NF- κ B/STAT3 and JAK2/STAT3 signaling pathways are also implicated in OA development, and they can be inhibited by Resveratrol (Limagne et al., 2016; Jiang M. et al., 2020). Ellagic acid (EA, **16**), a natural polyphenol from fruits and nuts, has anti-inflammatory and anti-oxidative activities. EA (10 and 25 μ M) has been demonstrated to inhibit IL-1 β -induced oxidative stress by activating the NRF2/HO-1-NQO-1 signaling pathway in C28/I2 chondrocytes (Zhu et al., 2022b). 6-Gingerol (**17**) at the doses of 2, 5 and 10 μ M exhibits protective activity against 4-hydroxynonenal-induced chondrocyte cell death by activating the NRF2 signaling pathway. In addition, 6-gingerol suppresses inflammatory responses and oxidative stress. However, IL-1 β -induced activation of MAPK and NF- κ B is not mediated by 6-gingerol (Abusarah et al., 2017). Other polyphenols, such as Polydatin (**18**, extracted from the roots of *Polygonum cuspidatum* Sieb. Et Zucc, *Polygonaceae*), Pterostilbene (**19**, derived from berries), Curcumin (**20**, a major turmeric component), piceatannol (**21**, derived from the seeds of *Euphorbia lagascae* Spreng, *Euphorbiaceae*), and Caffeic acid phenethyl ester (CAPE, **22**, one of the major bioactive ingredients of propolis), also exhibit inhibitory activities against inflammatory responses by activating the NRF2 signaling pathway in IL-1 β -treated chondrocytes (Tang et al., 2017; Xue et al., 2017; Tang et al., 2018; Jiang C. et al., 2020; Sun et al., 2022).

Attenuation of ECM degradation

Myricetin (**2**), Moracin (**3**), and Puerarin (**8**) can protect against IL-1 β -induced upregulation of MMP-13 and ADAMTS5 expression and downregulation of collagen II and aggrecan expression. Knockdown of NRF2 ameliorates the inhibitory effects of myricetin, moracin, and Puerarin on IL-1 β -induced ECM degradation, respectively (Pan et al., 2019; Zhou et al., 2020; Chen X. et al., 2021) (Table 1). Hyperoside (**10**) and EGCG (**7**) inhibit IL-1 β -induced ECM degradation by up-regulating collagen II, aggrecan, and SOX9 expression and down-regulating MMP-3, MMP-13, and ADAMTS5 expression via the activation of NRF2 signaling in mouse chondrocytes (Sun et al., 2021; Zhu et al., 2022a) (Table 2). Icariin (ICA, **23**, isolated from *herba epimedium* L. (*Berberidaceae*)) and Wogonin (**14**, derived from the root extract of *Scutellaria baicalensis* Georgi, *Lamiaceae*) may alleviate ECM degradation by activating the NRF2 signaling in IL-1 β -treated human chondrocytes, as shown by decreased generation of ROS, downregulated expression of MMP-3, MMP-9, MMP-13, and ADAMTS-4, and increased expression of GAG (Zuo et al., 2019). Curcumin (**20**) promotes the

expression of Col2a, aggrecan, and SOX9, suppresses ECM degradation, and increases chondrocyte viability by inhibiting the NF- κ B/HIF-2 α signaling (Wang P. et al., 2021).

Similarly, Lico A (6) suppresses the expression of MMP-1, MMP-13, and ADAMTS4/5 and enhances the expression of collagen II by inhibiting NF- κ B and Wnt/ β -catenin signaling pathways in rat chondrocytes (Chen et al., 2017). Isovitexin (4) at the doses of 25 and 50 μ g/mL inhibits MMP-3, MMP-13, and ADAMTS5 expression and increases collagen II and aggrecan expression by activating the NRF2 signaling in IL-1 β -treated mouse chondrocytes (Hu et al., 2021). Pterostilbene (19) at the doses of 10 and 20 μ M also inhibits IL-1 β -induced ECM degradation and chondrocyte senescence by suppressing the PI3K/AKT/NF- κ B signaling pathway and reducing senop-associated secretory phenotype (SASP) expression (Wang Y. et al., 2022). In addition, pterostilbene (20 mg/kg/3 days for 5 weeks by intraperitoneal injection) protects against cartilage degradation in ACLT + DMM-induced OA rat models (Wang Y. et al., 2022). Luteolin (12) at the doses of 10 and 20 μ M may suppress MMP-13 and ADAMTS5 expression and stimulate collagen II and aggrecan expression in H₂O₂-treated mouse chondrocytes (Zhou et al., 2022). 7,8-dihydroflavone (7,8-DHF, 13) also suppresses the expression of MMP-1, MMP-3, and MMP-13 by activating the NRF2 signaling in H₂O₂-treated mouse chondrocytes (Cai et al., 2019a) (Tables 1, 2). Pre-treatment with engeletin (dihydrokaempferol 3-rhamnoside, 24) may ameliorate TNF α -induced upregulation of MMP-3/-9 expression and downregulation of collagen II and aggrecan expression in rat chondrocytes (Wang H. et al., 2021) (Tables 1, 2). In ACLT-induced rat OA models, intraarticular injection of engeletin (50 μ g/week for 5 weeks) effectively protects against histopathological changes (Wang H. et al., 2021). Iron is an essential trace element in the human body. Iron overload may induce chondrocyte apoptosis and ECM degradation, exacerbating the progression of OA. It has been reported that naringenin (25) at the doses of 10 and 20 μ M exhibits protective effects against iron overload-induced cartilage damage by activating the NRF2/HO-1 signaling pathway in IL-1 β -treated human chondrocytes (Pan et al., 2022).

Suppression of cell death in OA chondrocytes

Hyperoside (10) can decrease ROS production, inhibit Bax, cytochrome c, cleaved caspase-9, and cleaved caspase-3 expression, and increase Bcl-xL expression in IL-1 β -treated mouse chondrocytes by activating the NRF2 signaling (Sun et al., 2021). 6-Gingerol (17) upregulates the expression of ubiquitin-specific peptidase 49 (USP49), promotes the deubiquitination of Axin, and increases the degradation of β -catenin, resulting in the inhibition of Wnt/ β -catenin signaling and the attenuation of apoptosis in IL-1 β -treated rat chondrocytes (Yang L. et al., 2020). Polydatin (18) (25, 50, and 100 μ g/mL) may promote chondrocyte survival by improving mitochondrial homeostasis via increasing the expression of Parkin and NRF2 in H₂O₂-treated chondrocytes (Kang et al., 2020). Procyanidin B2 (PCB2, 26) at the doses of

20 and 40 μ M can suppress IL-1 β -induced apoptosis by mediating the NRF2/Bax/Bcl-2 signaling pathway in rat chondrocytes (Cai et al., 2022). Similarly, Luteolin (12) can suppress H₂O₂-induced ROS production and cell apoptosis in mouse chondrocytes by activating the NRF2 signaling, as detected by decreased caspase-3 and ssDNA expression (Zhou et al., 2022).

Engeletin (24, widely distributed in vegetables and fruits) may suppress ROS generation, maintain mitochondrial membrane potential, decrease Bax and cleaved caspase-3 expression, and increase Bcl-2 expression in TNF α -treated rat chondrocytes (Wang H. et al., 2021). Iron overload can induce mitochondrial dysfunctions, trigger oxidative stress, and promote chondrocyte apoptosis. However, naringenin (25, a naturally occurring flavanone in citrus fruits) inhibits iron overload-induced chondrocyte apoptosis (Pan et al., 2022). Similarly, Biochanin A (4'-methoxy-5,7-dihydroxy isoflavone, BCA, 27, extracted from *Astragali Radix* (*Astragalus membranaceus* (Fisch.) Bunge, *Leguminosae*) can regulate iron homeostasis, suppress oxidative stress, and inhibit iron overload-induced mitochondrial dysfunction by up-regulating the NRF2/system xc-/GPX4 signaling pathway in mouse chondrocytes (He et al., 2022) (Table 2). Delphinidin (28, a flavonoid present in red wine and berries) at the dose of 40 μ M exhibits protective activity against OA development by suppressing oxidative stress, inhibiting apoptosis, and stimulating autophagy. The possible mechanism might be associated with upregulation of the NRF2/ARE signaling and downregulation of the NF- κ B pathway in C28/I2 chondrocytes (Lee et al., 2020). Puerarin (8) also protects chondrocytes by promoting Beclin-1-dependent autophagy and maintaining homeostasis (Li et al., 2021). Curcumin (20) maintains mitochondrial homeostasis, induces mitophagy, and protects chondrocytes by mediating the AMPK/PINK1/Parkin signaling pathway (Jin et al., 2022). Curcumin (20) also promotes autophagy and reduces apoptosis by inhibiting the PI3K/AKT/mTOR pathway in TNF α -treated chondrocytes (Han et al., 2021).

Licochalcone A (Lico A, 6) may protect mouse chondrocytes against LPS-induced pyroptosis by down-regulating the NRF2 signaling, as shown by decreased expression of caspase-1, IL-1 β , IL-18, and NLRP3 inflammasome (Yan et al., 2020). Consistently, cardamonin (11) suppresses IL-1 β -induced chondrocyte apoptosis by inhibiting the activity of NLRP3 inflammasome via activating the NRF2 signaling (Jiang and Cai, 2021). Chlorogenic acid (CGA, 29), a polyphenolic compound, has anti-oxidative activity. It has been demonstrated that CGA (250 μ M) can inhibit the expression of pro-apoptotic markers, such as cleaved caspase-3 and PARP, and stimulate the expression of Bcl-xL by attenuating the NF- κ B pathway and enhancing the NRF2/ARE signaling, leading to the amelioration of apoptosis in human C28/I2 cells (Zada et al., 2021). Chicoric acid (CA, 30), extracted from *Taraxacum mongolicum* Hand (Composite), can suppress the expression of pro-inflammatory cytokines, such as IL-6, IL-12, TNF α , COX-2, PGE2, iNOS, NO, and ECM catabolic factors, such as MMP-13 and ADAMTS-5, and increase the production of collagen II and aggrecan by activating the NRF2/HO-1 signaling and inhibiting the PI3K/AKT and NF- κ B pathways in C28/I2 cells (Qu et al., 2022). Pinitol (31), an ethanolic ingredient from *Pinaceae*, *Leguminosae*, and *Argyrolobium* family, has shown insulin-like

effects. It has been reported that pinitol (5 and 10 μM) can ameliorate TNF α -induced chondrocyte senescence and cell cycle arrest by rescuing the NRF2 signaling pathway in C28/I2 cells (Lou et al., 2020).

Potential mechanisms of flavonoids in activating NRF2 signaling

Myricetin (2) may promote NRF2 nuclear translocation and activate the NRF2 signaling in IL-1 β -treated human chondrocytes. Ly294002, a PI3K/AKT inhibitor, can block the stimulatory effects of myricetin on the activation of NRF2 signaling (Pan et al., 2019). Icariin (ICA, 23) and EGCG (7) may downregulate Keap1 expression, upregulate NRF2 expression, and promote the dissociation of Keap1 from NRF2, exhibiting anti-oxidative and chondroprotective activity (Zuo et al., 2019; Zhu et al., 2022a). Similarly, luteolin (12) can interrupt the interaction between Keap1 and NRF2, increase the stability of NRF2, and promote NRF2 nuclear translocation by activating AMPK α 1 expression in H₂O₂-treated mouse chondrocytes (Zhou et al., 2022). Wogonin (14) can directly interact with the Kelch domain of Keap1 protein and interrupt the association of Keap1 with NRF2, leading to the stability of NRF2 (Khan et al., 2017). Isovitexin (4) has been reported to interact with NRF2 and promote its nuclear translocation (Hu et al., 2021). Another study reports that Procyanidin B2 (PCB2, 26) can directly bind to the cavity of NRF2 by forming hydrogen bonds, salt bridge, alkyl, and van der Waals, promoting the stability and nuclear translocation of NRF2 in IL-1 β -treated rat chondrocytes (Cai et al., 2022).

Terpenes and terpenoids activate the NRF2 signaling

Terpenoids are a class of natural compounds made up of molecules with the formula (C₅H₈)_n. The structure of terpenes is constructed by the linkage of isoprene units (C₅H₈)_n. Various terpene compounds can be generated by head-to-tail condensation of C5 building blocks. Regarding the number of linked isoprene units, terpenoids can be divided into hemi-, mono-, sesqui-, di-, sester-, tri-, tetra-, and polyterpenes (Arnesen and Borodina, 2022). Terpenoids are excellent candidates for new drug development, due to their multiple pharmacological properties (Atriya et al., 2022). For example, andrographolide (32) is a diterpene from *Andrographis paniculata* Burm. f. (Acanthaceae) and has been reported to increase the expression of the NRF2/ARE signaling and decrease the NF- κ B, MAPK, and JAK/STAT pathways (Burgos et al., 2020). Recently, terpenoids have been the research focus for the therapeutic management of OA.

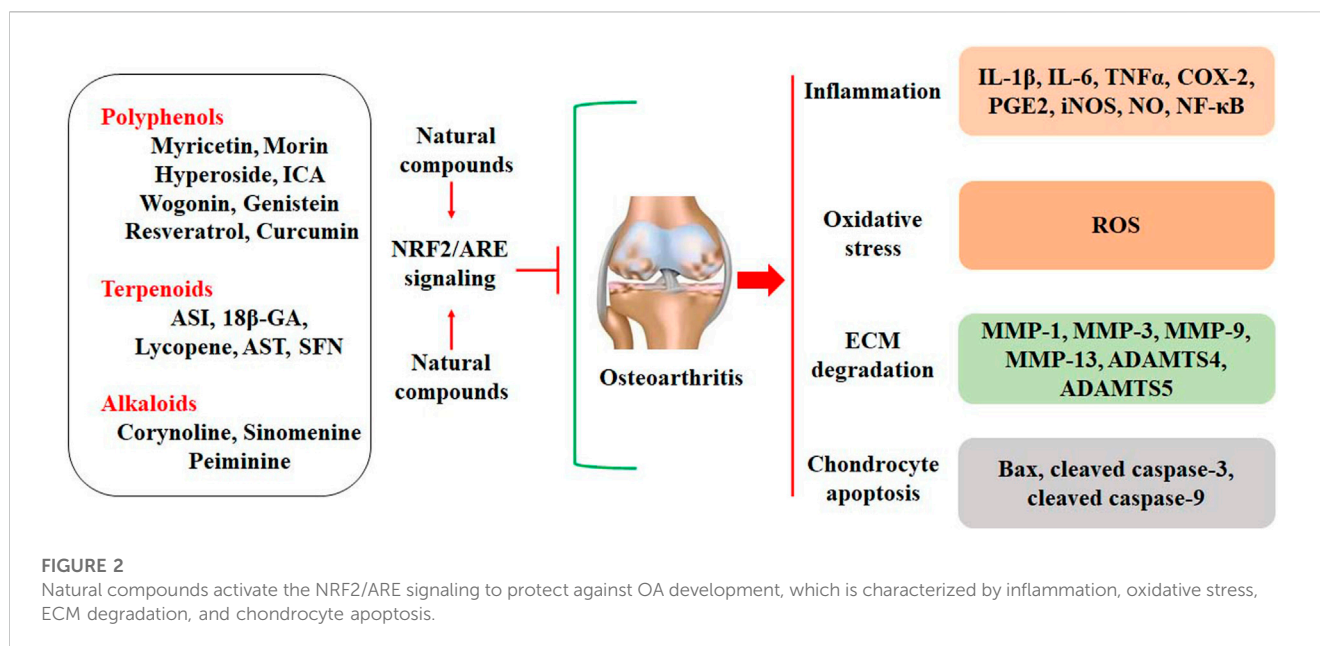
Monoterpenes Linalool (33), an acyclic monoterpene alcohol from *comfrey* (*Symphytum officinale* L., Boraginaceae) and *cruciferous* family, has been demonstrated to suppress IL-1 β -induced expression of COX-2/PGE2, iNOS/NO, TNF α , IL-6, MMP-13, and ADAMTS5 and increase the production of collagen II and aggrecan in mouse chondrocytes by activating the NRF2/HO-1 pathway and suppressing the NF- κ B pathway (Miao et al., 2022).

Sesquiterpenoids Bilobalide (34), a sesquiterpenoid isolated from *Ginkgo biloba* L. (*Ginkgoaceae*), has shown various pharmacological activities, such as anti-inflammatory, anti-oxidative, and anti-apoptosis. In a papain intra-articular rabbit OA model, bilobalide (40 mg/kg and 80 mg/kg by gavage administration) has been shown to decrease the expression of MMP-3 and MMP-13 and improve the biomechanical properties by activating the NRF2/HO-1 signaling pathway (Ma et al., 2022a). In addition, bilobalide may induce autophagy and suppress apoptosis in ATDC5 chondrocytes by activating the AMPK/Sirt1/mTOR signaling (Ma et al., 2022c). Patchouli alcohol (PA, 35) is also a sesquiterpene from *Pogostemon cablin* (Blanco) Benth. (*Lamiaceae*). It has been reported that PA may ameliorate ECM degradation in D-galactose-induced senescent chondrocytes by stimulating the NRF2/HO-1 signaling pathway in mouse chondrocytes (Chen M. et al., 2022).

Diterpenoids Andrographolide (AP, 32), a natural antioxidant, has been clinically used for treating inflammatory and cancer diseases. In H₂O₂-treated rat chondrocytes, AP may suppress oxidative stress by activating the NRF2/ARE signaling pathway. Specifically, AP can inhibit H₂O₂-induced expression of MMP-13 and IL-6 and improve chondrocyte apoptosis (Li et al., 2018). Ginkgolide C (36), derived from *Ginkgo biloba* L. (*Ginkgoaceae*), has been demonstrated to inhibit H₂O₂-induced apoptosis, oxidative stress, and ECM degradation by activating the NRF2/HO-1 pathway and suppressing the NF- κ B pathway in rat chondrocytes (Ma et al., 2022b).

Triterpenoids Nomilin (NOM, 37) is a triterpenoid isolated from some edible citrus fruits and has demonstrated inflammation-modulatory properties. NOM may alleviate the development of OA by decreasing the expression of pro-inflammatory cytokines, such as COX-2/PGE2, iNOS/NO, TNF α , and IL-6, and suppressing ECM degradation by mediating the NRF2 and NF- κ B signaling pathways in mouse chondrocytes (Xue et al., 2020). Limonin (LIM, 38), isolated from lemons and other citrus fruits, has been demonstrated to inhibit IL-1 β -induced generation of pro-inflammatory cytokines, such as COX-2/PGE2, iNOS/NO, TNF α , and IL-6, and the expression of MMP-13 and ADAMTS5 in mouse chondrocytes by mediating the NRF2/HO-1/NF- κ B signaling pathway (Jin et al., 2021).

Betulin (39), isolated from birch bark, is often used for anti-inflammation treatment. Betulin can decrease IL-1 β -induced expression of pro-inflammatory cytokines, such as IL-6, TNF α , COX-2, PGE2, iNOS, and NO, and ECM catabolic factors, such as MMP-13 and ADAMTS-5, by activating the AKT/NRF2 pathway and inhibiting the NF- κ B pathway in mouse chondrocytes (Ren et al., 2021). Asiaticoside (ASI, 40), a triterpenoid saponin isolated from *Centella Asiatica* L. (*Apiaceae*), may ameliorate TBHP-induced chondrocyte apoptosis by stimulating the NRF2/HO-1 signaling pathway. Additionally, ASI enhances the production of aggrecan and collagen II and suppresses the expression of MMP-13 and ADAMTS5, improving the degradation of ECM and the progression of OA (Luo et al., 2022). Hederagenin (41), a pentacyclic triterpenoid saponin, has been reported anti-inflammatory and anti-oxidative activities by inhibiting the JAK2/STAT3/MAPK signaling pathway and activating the Keap1-NRF2/HO-1/ROS/Bax/Bcl-2 axis, leading to the suppression of ECM degradation and upregulation of collagen II and aggrecan expression in IL-



1 β -treated C28/I2 cells (Shen et al., 2022) (Table 3). 18 β -Glycyrrhetic acid (18 β -GA, 42), one of the effective metabolites from *Glycyrrhiza glabra* L. (*Leguminosae*), is widely used for treating inflammatory diseases. 18 β -GA may suppress IL-1 β -induced expression of pro-inflammatory cytokines, such as IL-6, TNF α , COX-2, PGE2, iNOS, and NO, and ECM catabolic factors, such as MMP-13 and ADAMTS-5, by activating the activity of the NRF2/HO-1 pathway in mouse chondrocytes (Chen B. et al., 2021) (Tables 1, 2). In addition, 18 β -GA acts as an inhibitor of connexin 43 (Cx43), which plays a role in mechanotransduction. The fluid flow shear stress (FFSS) can upregulate the expression of Cx43 and PGE2, and 18 β -GA may abolish FFSS-induced PGE2 expression (Zhang et al., 2014). Akebia saponin D (ASD, 43), an effective triterpenoid from Rhizome of *Dipsacus asper* Wall (*Caprifoliaceae*), can suppress inflammatory actions by stimulating the NRF2/HO-1 pathway and inhibiting the NF- κ B pathway in mouse chondrocytes, protecting against OA development (Gu et al., 2020) (Table 1).

Tetraterpenoids Lycopene (44) is often found in vegetables and fruits and has been demonstrated anti-inflammatory activity against OA development by activating the NRF2/HO-1 pathway and reversing the NF- κ B/STAT3 pathway, leading to the decreased degradation of ECM in mouse chondrocytes (Zhan et al., 2021). Lycopene also promotes chondrocyte autophagy and suppresses apoptosis by inhibiting MAPK and PI3K/AKT/NF- κ B signaling pathways (Wu et al., 2021). Astaxanthin (AST, 45), also named marine carotenoid, exhibits remarkable anti-oxidative activity by activating the NRF2/ARE signaling. AST has been demonstrated to suppress IL-1 β -induced inflammatory responses, cell apoptosis, and ECM degradation by inhibiting the MAPK/NF- κ B signaling and stimulating the NRF2 pathway in mouse chondrocytes (Sun et al., 2019) (Table 1).

Alkaloids activate the NRF2 signaling

Corynoline (COR, 46), an alkaloid from *Corydalis bungeana* Turcz. (*Papaveraceae* Juss.), has been reported to inhibit

inflammatory responses and suppress the NF- κ B signaling. COR may suppress IL-1 β -induced expression of pro-inflammatory cytokines and ECM degradation by binding and activating NRF2 activity in mouse chondrocytes (Li et al., 2022) (Table 1). Sinomenine (SIN, 47), isolated from *Sinomenium acutum* Thunb. (*Menispermaceae*), has demonstrated anti-inflammatory effects. It has been reported that SIN reduces the expression of COX-2, PGE2, iNOS, NO, IL-6, and TNF α , inhibits the production of MMPs and ADAMTS5, and suppresses the degradation of collagen II and aggrecan in mouse chondrocytes by activating the NRF2/HO-1 signaling pathway (Wu et al., 2019). Another study reports that SIN can suppress IL-1 β -induced MMPs expression by interrupting the interaction between TRAF6 and TAK1, inhibiting JAK2/STAT3 signaling, and increasing SOCS3 expression in SW1353 cells (Qi et al., 2020). Peiminine (PM, 48) is a bioactive metabolite from *Fritillaria thunbergii* Miq. (*Liliaceae*), which is widely used to treat various diseases. PM has been shown to decrease the production of COX-2, PGE2, iNOS, NO, IL-6, and TNF α in mouse chondrocytes. In addition, PM can decrease the expression of MMP-13 and ADAMTS5 and increase the production of collagen II and aggrecan by stimulating the NRF2/HO-1 signaling and inhibiting the AKT/NF- κ B pathway (Luo et al., 2019).

Miscellaneous types

Coniferaldehyde (49), a food flavoring, is a potential NRF2 activator. Coniferaldehyde may ameliorate H₂O₂-induced IL-1, IL-6, MMP-1, and MMP-13 expression by activating the NRF2/HO-1 signaling pathway in mouse chondrocytes (Cai et al., 2021a). Ergosterol (50) is isolated from the fungus *Agaricus campestris*. Ergosterol has shown chondroprotective activity by activating the NRF2/HO-1 signaling pathway in mouse chondrocytes (Cai et al., 2021b). Maltol (51), an aromatic natural metabolite isolated from red ginseng, has shown various biological effects, including anti-inflammation and anti-oxidative stress. It has been reported that maltol exhibits chondroprotective activity *in vivo* and

in vitro. Specifically, maltol suppresses the production of pro-inflammatory cytokines and the expression of MMP-13 and ADAMTS5 and increases the expression of collagen II and aggrecan by modulating the NRF2 and NF- κ B signaling pathways in mouse chondrocytes (Zhu et al., 2021). Monascin (52), an azaphilone pigment isolated from *Monascus purpureus*-fermented rice, has demonstrated protectiveness in the development of OA. Specifically, monascin can reduce inflammatory responses and suppress ECM degradation by activating the NRF2 signaling and inhibiting the NF- κ B pathway in mouse chondrocytes (Zheng et al., 2018). Plumbagin (4-aphthoquinone, 53) can be found in *Plumbaginaceae*, *Droseraceae*, and *Ebenaceae* family. It has been demonstrated that plumbagin exhibits anti-oxidative stress in H₂O₂-treated human chondrocytes by activating the NRF2 signaling and inhibiting the NF- κ B pathway (Guo et al., 2017).

Pharmacological applications of NRF2 activators against OA development

Sulforaphane (SFN, 54), an isothiocyanate widely found in the *Brassicaceae* family and most abundant in broccoli and 3-day-old broccoli sprout extracts (Yagishita et al., 2019), has demonstrated pharmacological effects, such as anti-inflammation and anti-oxidation. Particularly, the anti-oxidative capacity of SFN is associated with the activation of NRF2/ARE signaling pathway (Lu et al., 2023). SFN (50 μ M) can significantly decrease H₂O₂-induced chondrocyte apoptosis and cartilage degradation by enhancing the expression of Sirt1 (Chen M. et al., 2021). Further study shows that SFN protects human OA chondrocytes against H₂O₂-induced oxidative stress, matrix degradation, and hypertrophic differentiation by activating the Keap1/NRF2 signaling pathways (Yang J. et al., 2020) (Table 3). However, SFN (10 μ M) may effectively suppress the expression of MMP-1, MMP-13, ADAMTS4, and ADAMTS5 in a NRF2-independent manner in human chondrocytes and SW1353 cells (Davidson et al., 2013). Another study reports that Sulforadex (SFX-01, 100 mg/kg/day for 3 months by oral administration), a stable synthetic form of SFN, can improve the microarchitecture of mouse bone and the symmetry of gait, without producing significant effects on cartilage lesion severity in STR/Ort OA mice (Javaheri et al., 2017). The effective biological effects of SFN against OA have been demonstrated. To achieve a prolonged and sustained activity, an intra-articular injectable SFN-FLGA microsphere system has been designed. SFN-FLGA may significantly decrease inflammatory responses, as indicated by decreased expression of COX-2, MMP-2, and ADAMTS5 in human OA chondrocytes (Ko et al., 2013). Two preparations for SFN have been developed as Sulforadex (SFX-01, 300 mg twice/day for 28 days) and Prostaphane (200 μ M once/day for 30 days), which are employed in clinical trials in subarachnoid haemorrhage and prostate cancer patients, respectively (Zolnourian et al., 2020; Dinkova-Kostova and Copple, 2023).

A series of synthetic oleanane triterpenoids has been explored due to their broad applications in preventing and treating chronic diseases. Several potential signaling pathways, such as Keap1/NRF2, PPAR γ , JAK/STAT, and PI3K/AKT, have been implicated in the molecular mechanisms of oleanane triterpenoids in mediating their biological actions (Liby and Sporn, 2012). For example, synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9 (11)-dien-28-oic acid

(CDDO) has been reported to directly interact with the thiol groups of Keap1 and activate the NRF2/ARE signaling pathway (Dinkova-Kostova et al., 2005). Omaveloxolone (RTA408, 55) is a semisynthetic triterpenoid derived from oleanolic acid and has been considered one of the most potent activators of the NRF2/ARE signaling pathway. RTA408 has been demonstrated to inhibit radiation-induced oxidative stress by disrupting the interaction between Keap1 and NRF2 (Goldman et al., 2015). RTA408 is also effective against inflammation by suppressing the NF- κ B signaling pathway (Zhang et al., 2021). RTA408 has been reported to promote chondrocyte proliferation, suppress inflammation and oxidative stress, inhibit chondrocyte apoptosis, and ameliorate ECM degradation by activating the NRF2/ARE signaling and inhibiting the NF- κ B pathway in IL-1 β -treated chondrocytes. In addition, RTA408 significantly enhances the levels of collagen II and aggrecan, decreases the scores of Osteoarthritis Research Society International (OARSI) and modified Mankin, and improves the microarchitecture of subchondral bone. In addition, RTA408 at doses of 200 μ g/kg and 500 μ g/kg has been proven to be safe after 8 weeks of treatment in rats (Jiang et al., 2022). The safety of RTA408 (2.5 mg once/day for 28 days/cycle, up to 12 cycles) has been reported in a phase-I clinical trial in patients with metastatic non-small-cell lung cancer or melanoma, and similar assays of RTA408 (150 mg once/day for 48 weeks) in a phase-II clinical trial in Friedreich ataxia (Lynch et al., 2019; Madsen et al., 2020).

Dimethyl fumarate (DMF, Tecfidera, 56), a methyl ester of fumaric acid, is currently the only agent in clinical practice as a NRF2 activator. Notably, DMF increases the activity of mitochondrial tricarboxylic acid (TCA) cycle and the production of ATP. Additionally, DMF and its metabolite monomethyl fumarate have good bioavailability (Sheikh et al., 2013) and exhibit beneficial effects against inflammation and oxidative stress (Kourakis et al., 2020). Mechanically, DMF may stimulate the NRF2/ARE signaling pathway and interact with the anti-inflammatory hydroxycarboxylic acid receptor 2 (HCAR2) (Chen H. et al., 2014). DMF has been approved by FDA as a medication for the therapeutic management of multiple sclerosis. In TNF α -treated human primary chondrocytes, DMF the doses of 1, 5, and 10 μ M may inhibit the expression of MMP-1/-3/-13 by down-regulating the JAK/STAT3 signaling pathway, ameliorating the degradation of collagen II, and protecting joint cartilage (Li et al., 2014). ERK1, but not ERK2, plays a critical role in the expression of collagen II and aggrecan by mediating the TGF β 1/Smad3/TIMP-3 axis (Zhu et al., 2017). It has been reported that mice with ERK1 deficiency are susceptible to age-associated OA, due to decreased activity of NRF2. DMF exhibits protective effects against OA in ERK1-knockout mice by stimulating the expression of NRF2 (Chen J. et al., 2022).

Many clinical trials for NRF2 activators, such as plant extracts, dietary supplements, and pure compounds, have been performed and can be found on [Clinicaltrials.gov](https://clinicaltrials.gov). The drug development of NRF2 activators has been advanced. Upregulation of the NRF2/ARE signaling pathway may provide beneficial effects in adverse environments. It should be noted that over-activation of the NRF2/ARE signaling pathway also has some potential negative effects. Various challenges, such as target specificity, pharmacodynamic responses, short-term and long-term safety considerations, and the variation of NRF2 activity, may adversely affect the expression of NRF2 (Dinkova-

Kostova and Copple, 2023). For example, protein-protein interaction (PPI) inhibitors are designed to target Keap1. However, NRF2 is not the only binding partner of Keap1. Inhibition of Keap1 also induces the expression of p62, which may further increase the activation of NRF2. The biological consequences are still needed for detailed investigation (Saito et al., 2016). In addition, NRF2 may promote the expression of the multidrug-resistant protein 3 (MRP3), which acts to export various cytostatic drugs (Slocum and Kensler, 2011; Marchan and Bolt, 2013). ROS at low concentrations can be healthy, and the NRF2/ARE signaling should be functioning properly. For example, ROS are essential to regulate insulin signal transduction and glucose-mediated insulin secretion in pancreatic β cells. It can be postulated that over-activation of the NRF2/ARE signaling pathway may be associated with insulin resistance and dysregulated lipid accumulation. In addition, some oxidative modifications of proteins are important for the processes of ubiquitination and protein degradation (Chen J. et al., 2014; Smith et al., 2016). Insulin may increase the production of collagen II and proteoglycan and decrease the breakdown of cartilage (Bradley, 2021). Thus, there is a risk that over-activation of the NRF2/ARE signaling pathway may worsen the pathological changes of OA. Thus, it should be careful to administer some dietary supplements, such as green tea extract and purified EGCG, which may produce over-activation of the NRF2/ARE signaling pathway (Huang et al., 2015).

Conclusion

In this review article, we comprehensively discuss the chondroprotective effects of natural compounds by activating the NRF2/ARE signaling pathway (Figure 2). These effective compounds mainly involve polyphenols, terpenoids, and alkaloids, and they inhibit inflammatory responses, ECM degradation, and chondrocyte apoptosis in OA cartilage. Activation of the NRF2/ARE signaling shows great potential for the therapeutic management of OA. However, we did not discuss the pharmacological properties of these compounds. The information about how these compounds activate the expression of NRF2 is relatively limited. The structure-activity relationship of polyphenols

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(flavonoids) or terpenoids in activating the NRF2 signaling pathway should be elucidated. The delivery of natural effective compounds to the damaged joint cartilage has become a major therapeutic limitation. In addition, randomized clinical trials of natural compounds against OA development are still required to fully elucidate the chondroprotective effects of natural compounds. These critical limitations should be scientifically addressed in future research.

Author contributions

YX: Conceptualization, Methodology. ZW, ZY, LL, and YX: Data curation, Writing-original draft preparation, Data curation, Validation, Writing-reviewing and Editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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