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Review

Prevention and treatment of knee osteoarthritis by natural products: potential mechanisms based on articular cartilage targets

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ABSTRACT

Knee osteoarthritis (KOA) is a prevalent chronic degenerative joint disorder characterized by an imbalance between articular cartilage degradation and synthesis, a central mechanism in KOA pathogenesis. Given the absence of disease-modifying therapies, there is a critical need to elucidate the underlying pathological processes, establish reliable biomarkers for early detection and prognosis, and identify safer, more effective therapeutic agents. In recent years, natural products have attracted considerable interest due to their low toxicity, cost-effectiveness, and distinct biological activities, demonstrating significant potential in KOA management. These compounds can impede KOA progression through multiple mechanisms, including promoting cartilage matrix synthesis, mitigating inflammation, reducing oxidative stress, suppressing chondrocyte apoptosis, and modulating autophagy, thereby supporting their translational application. This review summarizes biomarkers relevant to early diagnosis and phenotypic stratification in KOA, with a focus on elucidating the pharmacological actions and molecular mechanisms of natural products, such as flavonoids, alkaloids, saponins, terpenes, and traditional Chinese medicine (TCM) formulas, in KOA intervention, aiming to provide evidence-based strategies for improved disease management.

1. Introduction

Osteoarthritis affected 7.6% of the global population (approximately 595 million people) by the end of 2020, and this number is projected to increase by 60% to 100% by 2050 [1, 2]. Among the various forms of OA, knee osteoarthritis (KOA) is a common site [2]. KOA is a prevalent chronic disease and a major contributor to chronic joint pain, functional impairment, and reduced mobility [3]. It is characterized by the gradual loss of articular cartilage, synovial inflammation, osteophyte formation, and subchondral bone sclerosis [4]. The degeneration of articular cartilage is the primary issue in KOA and is considered a key driving factor of the disease [5].

Articular cartilage is a specialized connective tissue devoid of blood vessels, lymphatic vessels, and nerves, with its main source of nutrition derived from synovial fluid within the joint cavity and the blood supply from the subchondral bone. Consequently, its regenerative capacity is limited, which fundamentally contributes to the difficulty in curing KOA [6]. Currently, no effective cure exists for KOA. Therefore, treatment strategies have shifted toward early prevention, aiming to halt or delay disease progression before extensive structural damage occurs. Monitoring cartilage-related biomarkers can not only track KOA progression but also provide accurate and rapid prognostic insights [7].

Historically, the clinical management of KOA has focused on alleviating joint pain rather than modifying disease progression. Common clinical interventions include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, intra-articular corticosteroid injections (IACS), and intra-articular hyaluronic acid injections (IAHA) [8]. Long-term use of NSAIDs can lead to serious gastrointestinal adverse effects, while analgesics and IACS offer only temporary pain relief, and the efficacy of IAHA remains controversial [9]. The emergence of cell-based therapies and targeted small molecule agents, such as platelet-rich plasma, stem cell transplantation, nerve growth factor inhibitors, ion channel inhibitors, and calcitonin gene-related peptide antagonists, has advanced KOA treatment [10]. Although these approaches effectively alleviate symptoms, their high costs and recurrence rates remain significant challenges.

Natural products represent a diverse class of bioactive compounds derived from plant and animal extracts, as well as microorganisms. These substances exhibit a range of biological activities, including anti-inflammatory, anti-apoptotic, anti-oxidant, and proliferative effects [11]. In recent years, numerous studies have confirmed the anti-KOA potential of natural products such as oleanolic acid [12], luteolin [13], and astaxanthin [14]. Natural products primarily inhibit KOA progression by enhancing articular cartilage synthesis, modulating inflammatory responses, reducing oxidative stress, suppressing chondrocyte apoptosis, and regulating autophagy [15]. Given the lack of disease-modifying drugs for KOA, natural products hold promise as potential therapeutic candidates.

This review elucidates the cellular and molecular changes in articular cartilage under the pathophysiological conditions of KOA, thereby establishing a clear link between cartilage-related

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biomarkers and disease mechanisms. Subsequently, we present a retrospective analysis of *in vivo* and *in vitro* studies on natural products with anti-KOA activity. We systematically evaluate potential anti-KOA candidates to provide valuable insights for the development of therapeutic strategies and clinical applications.

2. Overview of articular cartilage

2.1. Composition of articular cartilage

Articular cartilage consists of sparse chondrocytes embedded within a dense extracellular matrix (ECM). Chondrocytes are primarily responsible for the synthesis and maintenance of the ECM and are also involved in cartilage repair and growth. The cartilage ECM provides a physical scaffold for chondrocytes and regulates numerous cellular processes, including proliferation, differentiation, migration, homeostasis, survival, and morphogenesis [16]. The cartilage ECM is composed mainly of water, type II collagen, and aggrecan [17]. Type II collagen forms a three-dimensional network interwoven with aggrecan, creating a complex fibrous structure. Minor collagens, such as types I, IV, and V, contribute to the stability of this network. Aggrecan is the predominant macromolecule in the ECM; it occupies the interstitial spaces within the collagen network and confers compressive resistance and hydration to the tissue. Under normal physiological conditions, the cartilage ECM maintains a steady-state metabolism, balancing anabolic and catabolic processes, which is essential for preserving cartilage integrity and function [16].

2.2. Changes of articular cartilage in KOA

KOA is characterized by an imbalance between joint repair and destruction. During disease progression, alterations in cartilage composition lead to loss of structural integrity [7]. In the early stages of KOA, the progressive loss of negatively charged glycosaminoglycans increases water content in the articular cartilage, resulting in ECM swelling [18]. At the same time, hypertrophic chondrocytes display increased synthetic activity, indicating an attempted repair response; however, this process also generates matrix degradation products and pro-inflammatory mediators, such as interleukin-1β (IL-1β) and IL-6 [19], which disrupt chondrocyte regulation. These mediators also act on adjacent synovium, triggering inflammatory and proliferative responses. Proliferating synovial cells release additional pro-inflammatory factors, leading to tissue swelling and neovascularization. These changes are accompanied by superficial fibrosis, manifesting as microscopic cracks on the cartilage surface [18]. As KOA advances, glycosaminoglycans are further depleted, the collagen network is disrupted, and the ECM deteriorates, resulting in deep cartilage fissures and stratification [20]. Subchondral bone vascular invasion and expansion of calcified cartilage occur beneath the articular surface, driven by inflammatory mediators [21]. In late-stage KOA, chondrocytes are predominantly clustered, apoptosis is evident, and calcified cartilage expands into the articular layer. The loss of articular cartilage leads to joint space narrowing and osteophyte formation at the joint margins (Fig. 1).

3. Cartilage-related biomarkers

The early stages of KOA are often radiographically undetectable. Therefore, enhancing diagnostic capabilities is essential to delay disease progression. Cartilage-derived biomarkers offer a promising approach by providing molecular insights into joint pathology during the asymptomatic early phases, potentially fulfilling clinical diagnostic needs (Fig. 2). In addition to enabling early detection of KOA, the identification of cartilage-related biomarkers aids in elucidating various pathological mechanisms, which may support the development of personalized treatment strategies.

3.1. Matrix metalloproteinase (MMP)

MMPs are a family of zinc-dependent proteolytic enzymes that cleave a wide range of ECM proteins. In the knee joint, they are produced mainly by chondrocytes and synovial cells. Evidence from animal models and chondrocytes isolated from KOA patients indicates that MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13 are the principal enzymes involved in ECM degradation [22]. In KOA, elevated MMP levels degrade aggrecan and type II collagen, increasing water content in the articular cartilage ECM and reducing tensile strength, ultimately leading to cartilage destruction [23].

3.2. A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)

ADAMTSs are secreted zinc-dependent endopeptidases. In the knee joint, ADAMTS-4 and ADAMTS-5 are the predominant isoforms, produced by chondrocytes, and primarily target proteoglycans within the articular cartilage ECM, mediating their cleavage [24]. Under normal physiological conditions, proteoglycan

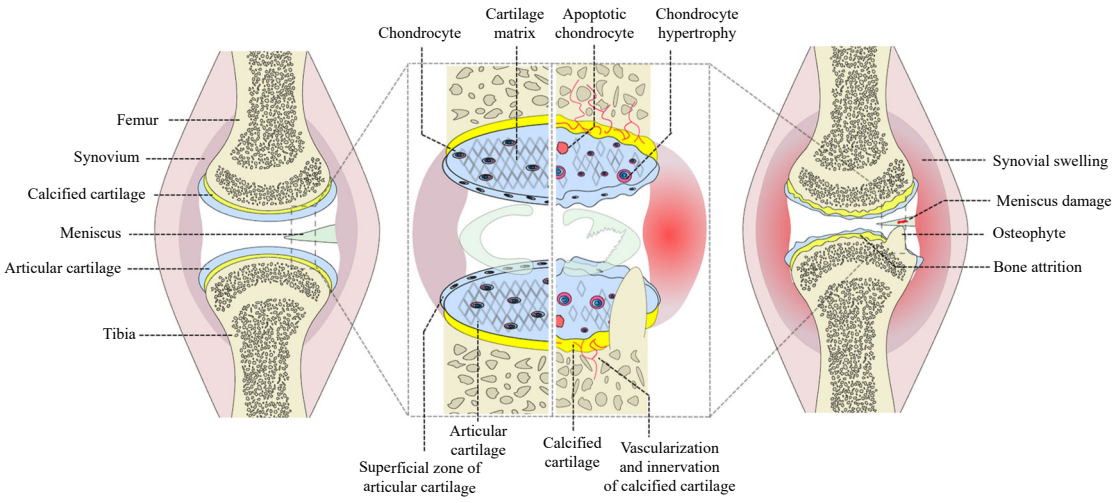

Fig. 1 Changes of cartilage in knee osteoarthritis (KOA).

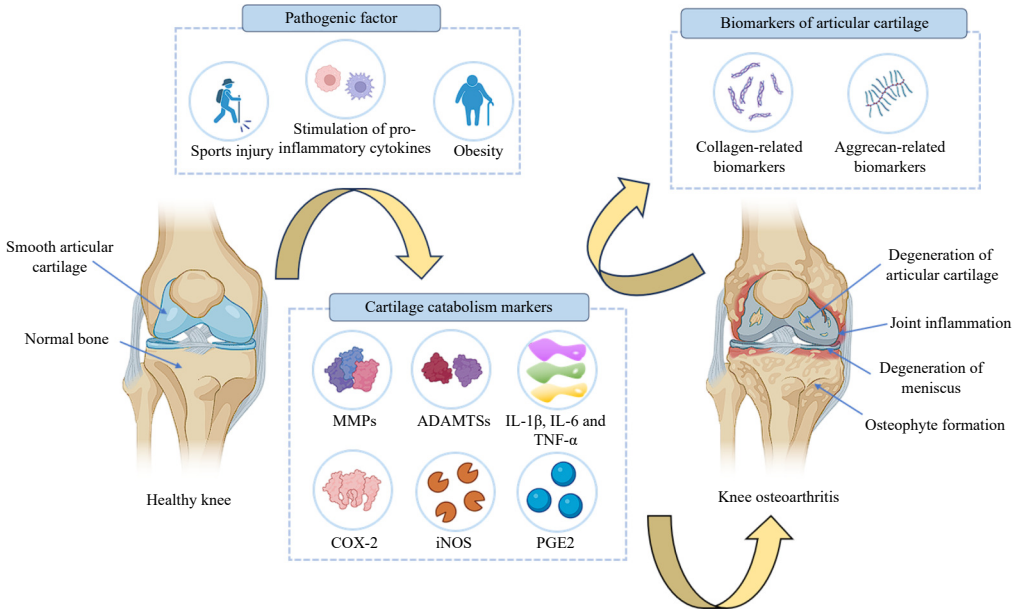

Fig. 2 The role of cartilage-related biomarkers in the progression of KOA.

synthesis and degradation are in dynamic equilibrium. However, under pathological conditions, overexpression of ADAMTS-4 and ADAMTS-5 accelerates aggrecan loss, leading to ECM swelling, increased susceptibility to mechanical stress, and further cartilage degradation.

3.3. Collagen-related biomarkers

The hallmark pathological feature of KOA is the destruction of articular cartilage. Collagen is a principal component of articular cartilage and constitutes the majority of the cartilage ECM. The fibrous network formed by collagen enhances tensile strength and elasticity, maintains structural integrity, and supports chondrocyte growth and proliferation, thereby promoting cartilage repair and regeneration and alleviating joint pain and inflammation. During the pathophysiological process of KOA, the collagen network is disrupted, and degradation fragments serve as biomarkers of ECM breakdown and disease progression [25]. Several collagen subtypes have been identified, with types I and II collagen being the most predominant and clinically relevant [26]. This section focuses on the roles of these collagens and their degradation products in KOA progression.

Type I collagen consists of three polypeptide chains: two α1 chains and one α2 chain, encoded by the *COL1A1* and *COL1A2* genes. It is the most abundant collagen in the body and is primarily distributed in bone, tendons, skin, ligaments, and blood vessel walls [27], but is generally absent in normal articular cartilage. In KOA, joint cartilage damage induced by inflammatory mediators and MMPs leads to the formation of fibrocartilage as a repair tissue, which fills damaged areas [28]. Type I collagen is typically undetectable in healthy articular cartilage but can be identified in damaged or diseased tissue [26]. C1M is a degradation fragment generated by MMP-mediated cleavage of type I collagen and serves as a biomarker of soft tissue destruction [17]. Studies in KOA indicate that C1M correlates with pain outcomes [29]. Van de Stadt et al. [30] reported an association between C1M and erosive hand osteoarthritis, and Kjelgaard-Petersen et al. confirmed C1M as a biomarker of *in vitro* synovitis [31]. Furthermore, C1M levels are positively correlated with IL-6 levels in KOA patients [32]. A recent study demonstrated that C1M is associated with OA phenotypes characterized by high remodeling, severe imaging damage, and elevated inflammation [33]. Collectively, the evidence suggests that C1M may serve as a novel biomarker for predicting KOA progression.

Type II collagen is a homotrimer composed of three α1 (II) chains encoded by the *COL2A1* gene and is predominantly synthesized by chondrocytes. It is a fibrillar collagen mainly distributed in cartilage, the vitreous body, and intervertebral discs. In articular cartilage, the ECM is largely composed of type II collagen, and its degradation is a key pathological hallmark of KOA [34]. Reduction and fragmentation of type II collagen are commonly observed in the articular cartilage of KOA patients [26]. Due to its abundance, type II collagen derivatives have been extensively studied as potential biomarkers for monitoring KOA progression and cartilage remodeling. C2M, a serum fragment generated by MMP-9 cleavage of type II collagen, reflects cartilage degeneration and is elevated in patients with mild and severe KOA compared to healthy individuals [35]. Type II collagen degradation (T2CM), comprising MMP-1, MMP-13, Coll2-1, and Coll2-1-NO2 fragments [36], is increased in end-stage KOA compared to moderate disease. Although research on T2CM is limited, it shows potential as a biomarker for disease progression. Serum type II collagen *C*-terminal propeptide (sPIICP) may serve as a biomarker for monitoring KOA progression. Clinical studies have shown that sPIICP levels are significantly reduced in advanced KOA and are strongly correlated with disease severity [37]. The C-telopeptide of type II collagen (CTX-II) is considered the most promising type II collagen biomarker, showing distinct levels between healthy individuals and KOA patients and reflecting disease progression [38]. Huang et al. [39] found higher CTX-II levels in KOA patients than in healthy controls, with levels increasing with disease severity. Selistre et al. [40] reported that elevated CTX-II levels correlate with greater pain severity and reduced physical function, while García-Alvarado et al. [41] demonstrated a positive correlation between CTX-II levels, pain severity, and radiographic grading.

3.4. Aggrecan-related biomarkers

Aggrecan is the principal proteoglycan in articular cartilage, forming hydrophilic macromolecular complexes with hyaluronic acid and link proteins, which enable cartilage to resist compressive loads and exhibit viscoelastic properties [23]. One of the earliest indicators of KOA is the loss of aggrecan from articular cartilage, which precedes structural degradation [42]. Aggrecan expression is relatively low in non-cartilaginous tissues, suggesting its specificity and potential as a key biomarker for KOA. ARGS are pro-

tein fragments generated by ADAMTS-4 and ADAMTS-5-mediated cleavage of aggrecan [35]. Early studies reported elevated ARGS levels in the synovial fluid of KOA patients and individuals with knee injuries. Hagemans et al. [43] found significantly higher serum ARGS levels in patients with anterior cruciate ligament tears compared to healthy controls, indicating that ARGS may reflect early joint pathology. Larsson et al. [44] demonstrated that ARGS in synovial fluid can differentiate radiographic KOA patients from those without radiographic changes and is negatively correlated with joint space width, suggesting a relationship with radiographic progression. In summary, aggrecan degradation occurs early in KOA, and ARGS can predict disease progression. Therefore, ARGS is a promising biomarker for early diagnosis of KOA.

4. Clinical management of KOA

Before knee arthroplasty becomes necessary in advanced KOA, common non-surgical treatments include NSAIDs, opioid analgesics, IACS, and IAHA [45].

Commonly used NSAIDs include ibuprofen, aspirin, diclofenac, ketoprofen, and indomethacin. They exert their anti-inflammatory and analgesic effects primarily by reversibly inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), thereby reducing prostaglandin E2 (PGE2) production [46]. PGE2 has vasodilatory effects, and prolonged NSAID use can elevate angiotensin levels, increasing the risk of cardiovascular and renal complications [47]. Inhibition of COX enzymes also reduces mucus production and gastric blood flow, leading to increased gastric acid secretion and potential adverse effects such as nausea, gastric or duodenal ulcers, and, in severe cases, gastrointestinal bleeding [48].

Common opioid analgesics include oxycodone, fentanyl, and tramadol. These agents alleviate pain by activating μ-opioid receptors and inhibiting cAMP production, thereby suppressing pain transmission. However, opioids carry a risk of dependence and can cause side effects such as nausea, dizziness, headache, and, in severe cases, respiratory depression [48].

Commonly used corticosteroids include methylprednisolone, triamcinolone, and betamethasone acetate. IACS exert immunosuppressive and anti-inflammatory effects by binding to nuclear steroid receptors, thereby reducing the production of inflammatory mediators such as IL-1, PGE2, leukotrienes, MMP-9, and MMP-11, which disrupt the inflammatory cascade [49]. IACS can provide short-term pain relief for one to eight weeks. However, prolonged use may lead to joint infection, cumulative chondrotoxicity, accelerated cartilage degeneration, subchondral dysfunction, and rapid KOA progression [50].

IAHA is a natural high-molecular-weight glycosaminoglycan present in synovial fluid and cartilage ECM, where it lubricates joints, absorbs mechanical shock, and increases synovial fluid viscosity. IAHA can inhibit MMPs, thereby protecting cartilage from degradation [51]. However, long-term injections may cause joint swelling [52]. Additionally, a meta-analysis showed that while IAHA provides slight pain relief compared to placebo, the difference does not reach the minimal clinically important difference and may significantly increase the risk of serious adverse events [9].

Current clinical treatment approaches are often limited to targeting individual pathological processes and are frequently associated with varying degrees of adverse reactions. In contrast, natural products offer distinct therapeutic advantages due to their multi-target regulatory properties and lower risk of adverse effects. For example, Guizhi Decoction not only significantly reduces the levels of pro-inflammatory cytokines such as IL-1β and TNF-α, but also upregulates the expression of the cartilage-protective marker COL2A1 , thereby exerting a synergistic effect on both inflammation control and cartilage repair [53]. Moreover, natural products are typically derived from plants, fruits, and medicinal resources, offering improved safety profiles compared to synthetic drugs. Clinical studies have demonstrated that turmeric extract is comparable to ibuprofen in improving joint function and alleviating pain, yet exhibits superior safety and a significantly lower incidence of adverse reactions [54]. Given these advantages, the following sections will systematically review natural products with significant anti-KOA activity and their underlying mechanisms of action.

5. Current research status of natural products for the treatment of KOA

In recent decades, numerous natural products have been identified for their anti-KOA activity. These include various compound classes such as traditional Chinese medicine (TCM) formulas, flavonoids, alkaloids, and terpenes. A search of the ClinicalTrials database (https://clinicaltrials.gov/) using "osteoarthritis knee" as the disease keyword yielded 3880 results, of which 30 involved interventions with natural products (Table S1).

Existing clinical evidence indicates that turmeric extract and its active constituent curcumin demonstrate notable efficacy: they reduce serum levels of Coll2-1 and C-reactive protein [55], provide pain relief, and improve WOMAC scores to a degree comparable to ibuprofen, while significantly lowering the incidence of gastrointestinal adverse reactions [54]. However, the clinical benefits of certain natural products require further validation. For instance, colchicine can reduce inflammatory markers, but its long-term impact on joint function remains unclear [56]. Although Huoluo Xiaoling Dan exhibits good safety, its effects on pain and joint function improvement are not statistically significant [57]. *Rubus idaeus* extract shows analgesic potential, but larger-scale studies are needed to confirm its effects on joint function [58]. These findings highlight the importance of identifying molecular targets of natural products and conducting in-depth mechanistic studies as key directions for future research.

6. Natural products with anti-KOA activity

Many natural products have demonstrated anti-KOA activity in preclinical studies. Analysis of 30 registered clinical trials from the ClinicalTrials database reveals that TCM formulas, flavonoids, alkaloids, terpenes, and saponins collectively account for 50% (15/30) of the trials, while curcumin and resveratrol as single compounds represent 20% (6/30). The remaining trials involve probiotics, amino acids, and proteoglycans. Given their potential for clinical translation, this review focuses on natural products with high therapeutic potential. Fig. 3 summarizes several representative categories of natural products exhibiting anti-KOA activity.

7. TCM formula

According to TCM theory, the pathogenesis of KOA primarily involves four aspects: (1) TCM holds that "the liver governs tendons, and the kidney governs bones". Deficiency in liver and kidney function leads to insufficient nourishment of tendons and bones, accelerating joint degeneration and resulting in pain and restricted movement. (2) *Qi* and blood deficiency impair joint nourishment, disrupt local metabolism, exacerbate cartilage wear, and lead to symptoms such as morning stiffness and fatigue [59]. (3) Invasion of pathogenic wind, cold, and dampness obstructs meridians and disrupts *Qi* and blood circulation, resulting in joint pain, swelling, and stiffness [60]. (4) Chronic strain or trauma leads to blood stasis and meridian obstruction, causing joint swelling and pain [61]. Therefore, TCM formulas primarily treat KOA by nourishing the kidney and strengthening bones, reg-

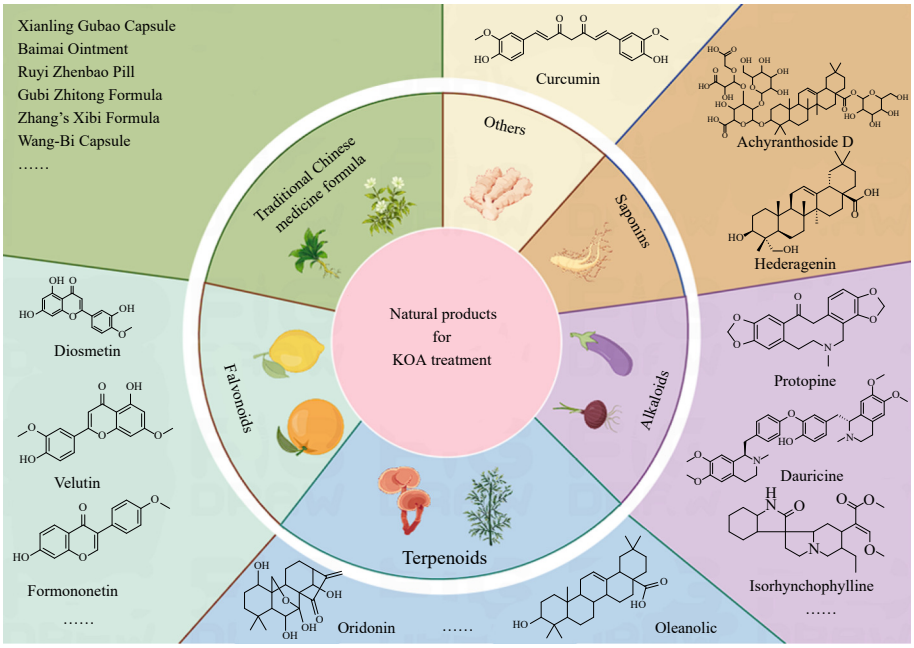

Fig. 3 Representative categories of natural products with anti-KOA activity.

ulating *Qi* and blood, expelling wind and dampness, and promoting blood circulation to resolve stasis. This section briefly introduces several TCM formulas with anti-KOA activity (Table 1) [62-69].

7.1. Xianling Gubao Capsules

Xianling Gubao Capsules are a well-known traditional Chinese herbal formula widely used in orthopedics and trauma medicine. From the perspective of TCM, they nourish the liver and kidneys, strengthen bones and tendons, dispel wind and dampness, eliminate stagnation, and resolve blood stasis. Thus, they are commonly used to treat orthopedic conditions such as osteoarthritis, fractures, and osteoporosis. Their primary function is to nourish the liver and kidneys while promoting blood circulation and strengthening muscles and bones, specifically targeting the liver and kidney deficiency type of KOA. A randomized controlled trial demonstrated that Xianling Gubao Capsules significantly improve clinical symptoms and joint function in KOA patients [70].

7.2. Baimai Ointment

Baimai Ointment is a representative topical formulation in Tibetan medicine, known for its warming and analgesic properties. It treats KOA by improving blood circulation and is particularly effective for the cold-damp obstruction and *Qi* stagnation with blood stasis types of KOA. *In vivo* experimental results indicate that Baimai Ointment reduces cartilage degeneration in KOA rats induced by destabilization of the medial meniscus (DMM), alleviates inflammation by downregulating pro-inflammatory cytokines (CXCL8, IL-1β, IL-6, and TNF-α) and VEGFA, and thereby preserves joint function [71].

7.3. Guizhi Decoction

Guizhi Decoction is a classic formula from ancient Chinese medicine. It harmonizes the nutritive and defensive *Qi* and warms the channels to dispel cold. This formula is primarily used for the cold-damp obstruction type of KOA and can improve joint dryness caused by disharmony of nutritive and defensive *Qi*. Multiple studies have shown that active components in Guizhi Decoction, such as licochalcone A and isoliquiritigenin, alleviate KOA through anti-inflammatory effects, inhibition of subchondral bone resorption, and suppression of angiogenesis [72, 73]. *In vitro* and *in vivo* experiments indicate that Guizhi Decoction downregulates inflammatory markers (TNF-α, IL-6, and IL-1β), upregulates COL2A1 and SOX9, and alleviates KOA by inhibiting the TNF signaling pathway [53].

7.4. Ruyi Zhenbao Pill

Ruyi Zhenbao Pill is a traditional Tibetan medicine with a history of over 1300 years. It contains more than 30 medicinal ingredients, including plant, animal, and mineral components. According to Tibetan medical theory, it clears heat, promotes dampness elimination, invigorates blood circulation, and unblocks meridians. It effectively treats KOA caused by wind-heat obstruction and meridian stagnation. Studies have found that Ruyi Zhenbao Pill exerts chondroprotective effects primarily by inhibiting inflammatory cytokines [inducible nitric oxide synthase (iNOS), COX-2, TNF-α, and IL-1β] and oxidative stress [74].

7.5. Gubi Zhitong formula

TCM holds that the Gubi Zhitong formula nourishes the kidneys and strengthens bones, nourishes and invigorates blood, and dispels wind while eliminating dampness. In the context of KOA, it addresses the root cause by nourishing the liver and kidneys while alleviating symptoms through promoting blood circulation and expelling pathogenic factors. This formula is suitable for treating the cold-damp obstruction and phlegm-blood stasis types of KOA. The Gubi Zhitong formula has demonstrated improvement in WOMAC scores in KOA patients, with a high efficacy rate of 98% and no significant adverse reactions [75]. A recent study reported that the formula exerts anti-KOA activity by reducing BINP3L expression, decreasing the colocalization of BNIP3L and LC3, inhibiting mitochondrial autophagy, and enhancing cartilage synthesis markers (COL2A1, SOX9, and aggrecan) [76].

8. Flavonoids

Flavonoids are a class of natural polyphenolic compounds with a core structure of 2-phenylchromone. In plants, flavonoids typically exist as glycosides, with sugars such as D-glucose or L-

Table 1 The effects of traditional Chinese medical formulas against KOA.

Formulas	Models	Biological activities	Ref.
Wang-Bi Capsule	MIA-induced KOA in rats	Decrease TNF-α, IL-1β and p-AKT; Increase IL-10; Improve organizational morphology and ameliorate KOA.	62
	IL-1β induced RAW 264.7	Decrease NO and suppress inflammation.	
Zhang's Xibi Formula	DMM-induced KOA in mice	Decrease IL-17A, p53, MAPK14, and ERK1; Increase collagen II and improve organizational morphology; Delay the progression of KOA by regulating IL-17-mediated immune response.	63
Bushen Zhuangjin Decoction	ACLT-induced KOA in rats	Decrease MMPs, RANKL, TRACP, IL-1α, IL-5, IL-12, IL-17A, RANTES, TNF-α, M-CSF, and TrpA; Increase collagen II, IL-13, GABA, GSH, Kyn, and Met; Alleviate KOA inflammation and reduce pain by affecting neurotransmitters and neuropeptides.	64
Gujian Oral Liquid	DMM-induced KOA in mice	Decreases IL-1β, MMP-13, TNF-α, and p-p65; Increase collagen II; Protect against articular cartilage degeneration and inflammation.	65
	TNF-α induced chondrocytes	Decrease ADAMTS-5, MMP-13, TNF-α, and AKT1; Increase collagen II and aggrecan; - Ameliorate KOA by inhibiting TNF-α/NF-κB pathway.	
Biqi Capsule	Papain-induced KOA in rats	Decrease IL-6, IL-1β, TNF-α, PGE2, p-NF-κB; Improve organizational morphology; Exert anti-inflammatory and anti-cartilage damage.	66
Jinwu Jiangu Decoction	papain-induced KOA in rabbits	Decrease GSK-3β, Wnt5a, MMP-13, and cyclin 1; Increase APC and Axin; Improve organizational morphology.	67
Mixed Medicinal Herb Extract (NUC1)	TNF-α induced chondrocytes	Decrease MMP-1, MMP-3, and MMP-13; Inhibit the activity of MMP and prevent cartilage damage.	68
Tougu Xiaotong Capsule	ACLT-induced KOA in rats	Decrease ADAMTS-5, COL I, MMP-3, and MMP-13; Improve organizational morphology and delay cartilage degeneration.	69
	LPS-induced chondrocytes	Decrease IL-6, IL-1β, TNF-α, MMP-3, MMP-9, MMP-13, ADAMTS-4, ADAMTS-5, p-p38; and miR-34a; Increases miR-27b, miR-140, and miR-92a-3p; Inhibit p38 MAPK pathway-mediated inflammation to alleviate KOA.	

rhamnose attached. Some isoflavones share structural similarities with estrogen and can bind to estrogen receptors, thereby exhibiting estrogenic effects that promote bone and cartilage synthesis and metabolism. Flavonoids can be classified structurally into flavonols, isoflavones, chalcones, and others. This section focuses on the most promising flavonoid-based natural compounds for KOA treatment, including diosmetin, formononetin, luteolin, casticin, and acacetin, and elaborates on their specific mechanisms of action. The anti-KOA activities of other flavonoids are summarized in Table 2 [77-92].

8.1. Diosmetin

Diosmetin, a natural flavonoid derived from citrus and legume plants, as well as specific herbs such as *Rosa agrestis*, *Chrysanthemum morifolium*, and *Dianthus versolor*, exhibits various pharmacological effects, including anti-oxidant, anti-inflammatory, anti-apoptotic, and anti-cancer properties [93]. Several studies have confirmed its cartilage-protective benefits. Ding et al. [94] found that diosmetin (1.5 mg·kg^{-1}) effectively reduced subchondral bone loss in a DMM-induced KOA mouse model. Moreover, *in vitro* experiments demonstrated that diosmetin inhibits RANKL-induced osteoclast formation and bone resorption, thereby delaying articular cartilage degradation by reducing subchondral bone loss in KOA. Qian et al. [95] further reported that diosmetin (10 and 20 mol·L^{-1}) inhibits IL-1β-induced expression of pro-inflammatory cytokines and degradation of articular cartilage ECM markers (MMP-13 and ADAMTS-5) in chondrocytes, and exerts anti-inflammatory effects by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway to inactivate nuclear factor κB (NF-κB) signaling. The anti-KOA activity of diosmetin (10 mg·kg^{-1}) was also confirmed in a DMM-induced KOA rat model, where it effectively inhibited inflammation and improved cartilage degeneration [95].

8.2. Formononetin

Formononetin is an isoflavone derived from phytoestrogens, primarily sourced from soybeans and red clover. It exhibits various pharmacological activities, including anti-inflammatory and anti-oxidant effects. Several studies have confirmed its benefits in KOA. Jia et al. [96] reported that formononetin (25, 50, and 100 μmol·L^{-1}) inhibits the production of inflammatory mediators (iNOS and COX-2) and articular cartilage ECM degradation markers (MMP-3, MMP-13, and ADAMTS-5) in IL-1β-induced human chondrocytes. Further studies show that formononetin exerts anti-inflammatory activity by activating PTEN, inhibiting AKT, and consequently suppressing the nuclear translocation of p-NF-κB. Cho et al. [97] found that formononetin (50 μmol·L^{-1}) antagonizes IL-1β-induced depletion of proteoglycans in *ex vivo* articular cartilage, indicating its ability to prevent ECM swelling, maintain cartilage sensitivity to mechanical stress, and slow KOA progression. Additionally, formononetin exhibits bone-protective effects by inhibiting RANKL-induced osteoclast formation in bone marrow macrophages. It also exerts anti-inflammatory effects by inhibiting the phosphorylation of extracellular signal-regulated kinase (ERK) and JNK in the mitogen-activated protein kinase (MAPK) signaling pathway [98].

8.3. Luteolin

Luteolin, a natural flavonoid primarily found in peppers, Lonicera Japonica, and *Chrysanthemum morifolium*, exhibits various pharmacological activities, including anti-inflammatory, anti-tumor, and immune modulation. Luteolin (25, 50, 100 μmol·L^{-1}) inhibits the expression of pro-inflammatory cytokines (iNOS and COX-2) and cartilage catabolic markers (MMP-1, MMP-3, and MMP-13) in IL-1β-induced chondrocytes. Its anti-inflammatory effect is mediated by inhibition of NF-κB phosphorylation [99]. Another study showed that luteolin targets Raf1, acting as a Raf1 inhibitor, and alleviates reactive oxygen species (ROS) production by inhibiting the Raf1/MEK-1/ERK axis, thereby exerting anti-inflammatory and anti-oxidant effects [100]. Furthermore, luteolin (5, 10, 20 μmol·L^{-1}) promotes autophagy in chondrocytes by upregulating autophagy markers (Beclin-1 and LC-3), thereby maintaining cartilage cell metabolic homeostasis [13].

8.4. Casticin

Casticin is a flavonoid isolated from *Vitex trifolia*, exhibiting anti-inflammatory and anti-tumor activities. It exerts anti-KOA activity by inhibiting ROS-mediated activation of the NF-κB path-

Table 2 The effects of flavonoids against KOA.

Compounds	Models	Biological activities	Ref.
Velutin	DMM-induced KOA in mice	Increase collagen II and aggrecan; Improve organizational morphology.	77
	IL-1β-induced chondrocytes	Decrease TNF-α, MMP-3, ADAMTS5, COX-2 and p-p38; Increase collagen II; Regulate p38 pathway to protect against articular cartilage degeneration.	
Isobavachalcone	DMM-induced KOA in mice	Decrease MMP-13; Slow the course of KOA.	78
	IL-1β-induced chondrocytes	Decrease COX-2, iNOS, ADAMTS-5, and MMP-13; Downregulate p-NF-κB, p-PI3K, and p-AKT; Alleviate KOA *via* PI3K/AKT/NF-κB pathway.	
Naringenin	DMM-induced KOA in mice	Decrease IL-6, COX-2, and MMP-13; Increase collagen II; Improve KOA.	79
	IL-1β-induced chondrocytes	Decrease TNF-α, MMP-3, MMP-13, and ADAMTS-5; Downregulate p-NF-κB, TLR4, and TRAF6; Attenuate KOA *via* TLR4/TRAF6/NF-κB pathway.	
Procyanidin B2	DMM-induced KOA in rats	Decrease p-NF-κB; Increase collagen II and Nrf2; Attenuate the degeneration of articular cartilage.	80
	IL-1β-induced chondrocytes	Decrease MMP3, IL-8, Bax, Caspase-3, and p-NF-κB; Increase collagen II, aggrecan, Nrf2, and HO-1; Attenuate chondrocyte senescence *via* the Nrf2/NF-κB pathway and apoptosis *via* Nrf2/BAX/Bcl-2.	
Scutellarin	DMM-induced KOA in mice	Increase collagen II and aggrecan; Protect cartilage ECM and reduce osteophyte formation; Alleviate the cartilage degeneration.	81
	IL-1β-induced ATDC5 cells	Decrease MMP3, MMP13, ADAMTS4, and ADAMTS5; Downregulate p-NF-κB, p-ERK, p-JUK, and p-p38; Protect cartilage ECM *via* NF-κB/MAPK pathway.	
Baicalein	DMM-induced KOA in mice	Decrease MMP13, COLX, alox15, and ADAMTS-5; Increase Nrf2 and HO-1; Protect articular cartilage *via* AMPKα/Nrf2/HO-1 pathway.	82
	IL-1β-induced chondrocytes	Decrease MMP13, ADAMTS-5, and collagen I; Increase collagen II; Inhibit ferroptosis in chondrocytes *via* the AMPKα/Nrf2/HO-1 pathway.	
Hyperoside	DMM-induced KOA in mice	Suppresses cartilage degradation to a certain extent.	83
	IL-1β-induced chondrocytes	Decrease iNOS, COX-2, ADAMTS-5, MMP3, and MMP13; Downregulate Bax, p-NF-κB, p-PI3K, and p-AKT; Increase collagen II, aggrecan, SOX9, Bcl-2, and Nrf2; Inhibit inflammation and cartilage degradation via MAPK, PI3K/AKT/NF-κB, Nrf2/HO-1, NF-κB pathway crosstalk; Reduce chondrocyte apoptosis *via* Nrf2/ROS/BAX/Bcl-xl axis.	
Oroxin B	DMM-induced KOA in mice	Decrease MMP3; Increase collagen II and aggrecan; Protect articular cartilage in DMM rat.	84
	IL-1β-induced chondrocytes	Decrease MMP3, ADAMTS4, iNOS, TNF-α, and IL-1β; Increase collagen II and aggrecan; Reduce autophagy and alleviate KOA *via* PI3K/AKT/mTOR pathway.	
Silymarin	IL-1β-induced chondrocytes	Decrease MMP3, MMP9, IL-1β, TNF-α, Sirt-1, and TIMP-1; Increase collagen II and SOX9; Improve cartilage ECM homeostasis and alleviate KOA.	85
Alpinetin	DMM-induced KOA in rats	Inhibit the degradation of cartilage ECM.	86
	TNF-α-induced chondrocytes	Decrease ADAMTS-5, MMP-13, and p-ERK; Increase collagen II, Bcl-2, and CDK1; Interfere with the NF-κB/ERK1/2 pathway to alleviate KOA.	
Caviunin 7-*O*-[*β*-D-apiofuranosyl-(1−6)-*β*-D-glucopyranoside]	IL-1β-induced chondrocytes	Decrease MMP-1, MMP-3, MMP-13, and ROS; Increase collagen II, aggrecan, and SOX9; Improve IL-1β-induced chondrocytes and inhibit the further development of KOA.	87
Linarin	DMM-induced KOA in mice	Decrease iNOS; Reduce cartilage surface calcification.	88
	LPS-induced chondrocytes	Decrease COX-2, iNOS, TNF-α, NO, IL-6, PGE2, MMP-13, ADAMTS-5, and NF-κB; Increase collagen II and aggrecan; Prevent inflammatory *via* inhibiting TLR4 signaling pathway.	
Cynaroside	IL-1β-induced chondrocytes	Decrease TNF-α, MMPs, ADAMTS-4, p-p38, and p-p65; Increase collagen II and aggrecan; Protect chondrocytes *via* NF-κB and MAPK signaling pathway.	89
Myricitrin	DMM-induced KOA in mice	Prevent articular cartilage degeneration and osteophyte formation.	90
	IL-1β-induced chondrocytes	Decrease iNOS, COX-2, IL-6, TNF-α, PGE2, MMP-3, MMP-13, ADAMTS-5, p-p65, and p-p38; Increase collagen II; Alleviates KOA *via* inhibiting MAPK and NF-κB activation.	
Nepetin	DMM-induced KOA in mice	Prevent articular cartilage degeneration and alleviate KOA.	91
	IL-1β-induced chondrocytes	Decrease NO, iNOS, PGE2, COX-2, TNF-α, MMP3, MMP13, ADAMTS4, ADAMTS5, and p-p65; Increase aggrecan and collagen II; Protect chondrocyte *via* inhibiting the NF-κB pathway.	
Quercetin	Papain-induced KOA in mice	Decrease IL-1β, TNF-α, TLR4, and NF-κB; Alleviate the inflammatory damage of KOA and maintain the integrity of articular cartilage *via* inhibiting the TLR4/NF-κB signaling pathway.	92

way and reducing the release of inflammatory factors (IL-6, TNF-α, and PGE2) induced by IL-1β in ATDC5 cells, through anti-inflammatory and anti-oxidant effects [101]. Additionally, casticin reduces synovial hypoxia by downregulating hypoxia-inducible factor-1α (HIF-1α), effectively alleviating synovitis and synovial fibrosis. It also targets the NLR family pyrin domain containing 3 (NLRP3) inflammasome to inhibit the release of pro-inflammatory mediators, mitigate chondrocyte pyroptosis, and reduce KOA inflammation [102]. Moreover, casticin exhibits anti-apoptotic effects by reversing IL-1β-induced apoptosis in rat chondrocytes (5, 10, 20 μmol·L^{-1}). Its anti-apoptotic action is mediated by inhibiting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/HIF-1α signaling pathway, thereby reducing pro-inflammatory cytokine production [103].

8.5. Acacetin

Acacetin is a natural flavonoid compound primarily found in *Chrysanthemi Flos* and *Robinia pseudoacacia*, exhibiting various pharmacological activities, including anti-cancer, anti-inflammatory, and anti-oxidant effects. In IL-1β-induced chondrocytes, acacetin targets the NF-κB signaling pathway to inhibit the expression of cartilage ECM catabolic markers (MMP-1, MMP-3, MMP-13), demonstrating strong cartilage-protective effects [104]. Furthermore, through screening of lead compounds, acacetin has been identified as an inhibitor of STING. Overactive STING can activate the NF-κB signaling pathway, promote inflammatory mediator release, and induce cellular senescence and apoptosis. Xu et al. [105] reported that acacetin targets STING, inhibits its activation, and consequently suppresses the TBK1/NF-κB signaling pathway, thereby exerting anti-KOA activity.

8.6. Calycosin

Calycosin is a natural isoflavonoid primarily extracted from Astragali Radix. It exhibits various biological activities, including anti-inflammatory, anti-oxidant, and cardioprotective effects. Shi et al. [106] reported that calycosin (100, 200, 400 μmol·L^{-1}) significantly inhibits the expression of pro-inflammatory cytokines (iNOS and COX-2) and cartilage ECM catabolic markers (MMP-3 and MMP-13) in chondrocytes. In a DMM-induced KOA mouse model, calycosin (40 mg·kg^{-1}) also demonstrated anti-inflammatory and cartilage-protective effects. Mechanistic studies revealed that calycosin attenuates inflammation and apoptosis by inhibiting the activation of the PI3K/AKT and NF-κB signaling pathways. Su et al. [107] found that calycosin inhibits the COX-2/EGFR signaling pathway, contributing to its anti-inflammatory properties and promoting cartilage repair. Additionally, calycosin deactivates the PI3K/AKT/FoxO1 pathway, downregulating the expression of p-PI3K, p-AKT, and p-FoxO1 induced by IL-1β in chondrocytes, thereby preventing chondrocyte apoptosis and cartilage ECM degradation [108].

9. Terpenoids

Terpenoids are a class of natural products widely found in plants and represent the largest and most diverse group of plant-derived chemical substances. Based on their chemical structure, terpenoids are classified into monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes. Many terpenoids exhibit significant physiological activities, including anti-inflammatory, anti-oxidant, anti-microbial, anti-cancer, and immunomodulatory effects, and are widely used in pharmaceutical and chemical industries. Numerous terpenoids have demonstrated considerable potential for KOA treatment. This section focuses on the most promising terpenoid compounds for KOA, including oridonin, oleanolic acid, triptolide, and astaxanthin. Other terpenoid compounds with anti-KOA activity are summarized in Table 3 [109-120].

9.1. Oridonin

Oridonin is a diterpenoid isolated from *Rabdosia rubescens*, exhibiting anti-inflammatory, anti-tumor, anti-apoptotic, and anti-angiogenic pharmacological activities. Oridonin (10, 20, 30 μg·mL^{-1}) inhibits the production of cartilage ECM catabolic markers (MMP-1, MMP-3, and MMP-13) in IL-1β-induced human chondrocytes, demonstrating anti-KOA activity. Additionally, oridonin is a PPAR-γ agonist, and its anti-inflammatory effects are blocked by the PPAR-γ inhibitor GW9662. It exerts anti-KOA activity by activating PPAR-γ to inhibit NF-κB activation and reduce inflammatory cytokine secretion [121]. Furthermore, oridonin is an inhibitor of NLRP3; it directly binds to the NACHT domain of NLRP3, blocking the interaction between NLRP3 and NEK7, thereby inhibiting NLRP3 inflammasome activation and assembly [122].

9.2. Oleanolic

Oleanolic is a pentacyclic triterpenoid primarily derived from the fruits of *Ligustrum lucidum*. Several studies have confirmed its therapeutic effects in KOA. Salman et al. [123] showed that intra-articular administration of oleanolic acid in KOA rats improved motor coordination, alleviated pain, and reduced joint inflammation, as demonstrated by behavioral and electrophysiological evaluations. Yu et al. [12] further reported that oleanolic acid (50 mg·kg^{-1}) suppressed the expression of cartilage catabolic markers (MMP-3 and MMP-13) and pro-inflammatory mediators (IL-1β, TNF-α, iNOS, and COX-2) in MIA-induced KOA rat cartilage tissues. Mechanistically, oleanolic acid targets SIRT3 to inhibit NF-κB activation, thereby exerting anti-inflammatory and antioxidant effects [124]. In addition to modulating inflammation and oxidative stress, oleanolic acid also protects the cartilage ECM. It interacts with β-catenin, activates the Hippo/YAP pathway, and inhibits the nuclear translocation of both β-catenin and YAP, which helps prevent ECM degradation. Notably, knockdown of β-catenin abolishes the chondroprotective effect of oleanolic acid on the cartilage ECM, indicating that its protective action is β-catenin-dependent [125].

9.3. Triptolide

Triptolide is an epoxy diterpenoid lactone compound primarily derived from the roots, leaves, flowers, and fruits of *Tripterygium wilfordii*. It exhibits various biological activities, including anti-inflammatory, anti-tumor, and immune-regulating properties. An *in vivo* study showed that triptolide (2.5, 5, 10, and 20 μg·mL^{-1}) suppressed the expression of pro-inflammatory cytokines (COX-2 and IL-6) and cartilage catabolic markers (MMP-3 and MMP-13) in IL-1β-induced KOA rats, thereby alleviating tissue damage [126]. Further mechanistic studies revealed that triptolide exerts anti-inflammatory effects by inhibiting the NF-κB signaling pathway, reducing pro-inflammatory cytokine production [127]. Additionally, triptolide targets the NLRP3 inflammasome and inhibits the activation of cleaved-caspase-1, thereby exerting anti-inflammatory effects [128].

9.4. Astaxanthin

Astaxanthin is a ketocarotenoid found in marine organisms, primarily extracted from crustaceans and algae. It possesses strong anti-oxidant properties, effectively scavenging free radicals and preventing lipid peroxidation, making it a potent ROS scavenger. It also exhibits anti-tumor, immune-boosting, and bone repair-promoting activities. *In vitro* studies have shown that astaxanthin (10 μmol·L^{-1}) significantly reduces the expression of

Table 3 The effects of terpenoids against KOA.

Compounds	Models	Biological activities	Ref.
Tormentic acid	IL-1β-induced chondrocytes	Decrease MMP-3, MMP-13, iNOS, NO, PGE2, and p-p65; Alleviate KOA *via* inhibiting NF-*κ*B signaling pathway.	109
Astaxanthin	DMM-induced KOA in rats	Increase collagen II and GPX4; Inhibit cartilage degradation and chondrocyte ferroptosis; Delay the progression of KOA.	110
	IL-1β-induced chondrocytes	Decrease iNOS, COX-2, MMP-13, ROS, and p53; Increase collagen II, SLC7A11, GPX4, and ferritin; Improve ferroptosis of chondrocytes *via* regulating P53/SLC7A11/GPX4 pathway.	
Geniposidic acid	DMM-induced KOA in mice	Decrease MMP-1, MMP-3, iNOS, and COX-2; Increase GPX4 and ferritin.	111
	IL-1β-induced chondrocytes	Decrease MMP-1, MMP-3, PGE2, MDA, and p-p65; Increase GPX4, ferritin, GSH, and Nrf2; Inhibit inflammation and ferroptosis to alleviate the progression of KOA.	
Betulinic acid	DMM-induced KOA in mice	Decrease COMP, MMP-13, and COLX; Increase collagen II and aggrecan; Reduce cartilage ECM degradation.	112
	LPS-induced BMDM	Decrease IL-18, p20, p17, and GSDMD; Alleviate inflammation *via* inhibiting the activation of NLRP3.	
Geniposide	MIA-induced KOA in mice	Decrease MMP-13; Increase collagen II and improve articular cartilage.	113
	IL-1β-induced chondrocytes	Decrease p62, MMP-13, p-mTOR, and p-AMPK; Increase collagen II, LC3-II, and GLP-1R; Protect KOA cartilage and chondrocytes *via* activating the GLP-1R/AMPK/mTOR signaling pathway.	
Ergolide	DMM-induced KOA in rats	Decrease p-p65, p-p38 and MMP-13; Increase collagen II and inhibit cartilage degradation.	114
	IL-1β-induced chondrocytes	Decrease iNOS, MMP-13, ADAMTS-5, p-p65, and p-p38; Increase collagen II and aggrecan; Protect chondrocytes *via* inhibiting NF-*κ*B and P38/MAPK.	
Artemisinin	DMM-induced KOA in rats	Decrease MMP-3; Increase ATG5, activate autophagy, and alleviate KOA.	115
	IL-1β-induced chondrocytes	Decrease IL-6, IL-1β, TNF-α, MMPs, ADAMTS-5, TNFSF11, p-PI3K, p-AKT, and p-mTOR; Increase ATG-5, ATG-7, and LC-3; Alleviate KOA *via* inhibiting PI3K/AKT/mTOR pathway.	
Ginkgolide C	MIA-induced KOA in rats	Decrease IL-1β, IL-18, COX-2, INOS, IL-6, IL-10, MMP-13, ADAMTS-4, NLRP3, and MDA; Increase collagen II and Nrf2; Alleviate KOA by inhibiting activation of NLRP3.	116
	H_2O_2-induced ATDC5 cells	Decrease MMP-3, MMP-13, ADAMTS-4, Drp1, Fis1, NLRP3, ASC, caspase 1, and GSDMD-N; Increase collagen II, Mfn2, Nrf2, and keap1; Alleviate KOA by inhibiting NLRP3 inflammasome.	
Gardenoside	ACLT-induced KOA in rats	Improve organizational morphology; Increase aggrecan, and alleviate KOA.	117
	IL-1β-induced chondrocytes	Decrease IL-6, MMP-3, MMP-13, ADAMTS-5, and p-p65; Increase collagen II, aggrecan, and p-I*κ*B-α; Suppress cartilage ECM degradation by inhibiting the NF-*κ*B signaling pathway.	
Harpagide	ACLT-induced KOA in rats	Decrease IL-6, MMP-13 and PFKP; Improve organizational morphology and prevent articular cartilage degeneration.	118
	TNF-α-induced chondrocytes	Decrease IL-6, MMP-13, COX-2, p-IRE1α, and GRP78; Increase COL2A1, aggrecan, Bcl-2, CDK1, and p-AMKPα; Inhibits inflammatory response by the glycolytic pathways.	
Glaucocalyxin A	DMM-induced KOA in mice	Decrease p-p65 and MMP-13; Increase COL2A1; Improve organizational morphology.	119
	IL-1β-induced ATDC5 cells	Decrease MMP-13, p-p38, p-ERK, p-JUK, p-p65, and iNOS; Increase COL2A1 and SOX9; Delay the progress of KOA by inhibiting NF-*κ*B and MAPK signaling pathways.	
Kirenol	DMM-induced KOA in mice	Decrease MMP-13; Increase collagen II; Improve organizational morphology and alleviate KOA.	120
	IL-1β-induced chondrocytes	Decrease iNOS, COX-2, PGE2, IL-6, TNF-α, MMP-13, ADAMTS-5, p65, p-PI3K, and p-AKT; Increase collagen II and aggrecan; Alleviate IL-1β-induced inflammatory response by inhibiting PI3K/AKT/NF-*κ*B pathway.	

pro-inflammatory cytokines (iNOS and COX-2) and cartilage catabolic MMP-13 in IL-1β-induced chondrocytes. Furthermore, *in vivo* studies have confirmed that astaxanthin (20 $mg \cdot kg^{-1}$) protects cartilage. Mechanistic studies suggest that astaxanthin exerts anti-KOA activity by regulating the p53/SLC7A11/GPX4 signaling pathway, thereby inhibiting chondrocyte ferroptosis [110]. Astaxanthin also acts as an agonist of SIRT1, upregulating SIRT1 to alleviate inflammation and promote cartilage formation, and its cartilage-protective effect is reversed by the SIRT1 inhibitor Ex527 [14]. Moreover, astaxanthin activates Nrf2, promoting its nuclear translocation to regulate downstream protective factors, preventing cartilage ECM degradation and exerting anti-KOA effects [129].

In a 12-week randomized controlled trial involving 100 patients with mild KOA, supplementation with krill oil, astaxanthin, and lower molecular weight hyaluronic acid significantly improved WOMAC (P = 0.0489) and pain scores (P = 0.026 35) compared to the placebo group. Notably, the incidence of adverse reactions was significantly higher in the placebo group (P = 0.0455), indicating that astaxanthin not only demonstrates excellent anti-inflammatory and analgesic effects but also exhibits good tolerability, effectively alleviating clinical symptoms in patients with mild KOA [130].

10. Alkaloids

Alkaloids are a class of nitrogen-containing organic compounds found in plants, known for their significant biological activities and as important active ingredients in TCM. Based on structural features, alkaloids are classified into pyrrolizidine alkaloids, isoquinoline alkaloids, and imidazole alkaloids. They are primarily distributed in higher plants, especially in families such as Berberidaceae, Liliaceae, Fabaceae, Ranunculaceae, and Solanaceae. These compounds exert biological effects through interactions with biomolecules such as proteins, nucleic acids, and biological membranes, thereby altering their structure and func-

tion and influencing physiological processes and metabolic pathways. However, some alkaloids may present toxicological risks. Therefore, when considering alkaloids as potential therapeutic agents for KOA, careful dosage management is essential to balance efficacy and safety. This section focuses on the most promising alkaloids for KOA treatment, including protopine, dauricine, isorhynchophylline, oxymatrine, and sinomenine, while discussing their safety profiles and mechanisms of action. Other alkaloids with anti-KOA activity are summarized in Table 4 [131-140].

10.1. Protopine

Protopine is an isoquinoline alkaloid with anti-inflammatory and anti-oxidant activities, primarily derived from herbs such as *Corydalis* spp. and *Chelidonium majus*. Chen et al. [141] reported that protopine (10 or 20 μg·mL^{-1}) inhibited the expression of COX-2, MMP-3, MMP-13, and PTGS2 in tert-butyl hydroperoxide (TBHP)-induced chondrocytes, while upregulating cartilage synthesis markers such as collagen II. This demonstrates its effectiveness in alleviating TBHP-induced catabolism and inflammation in chondrocytes and inhibiting their degeneration. *In vivo* experiments revealed that protopine enhanced the expression of COL2A1, GPX4, and Nrf2 in the articular cartilage of anterior cruciate ligament transaction (ACLT)-induced KOA mice. This suggests that protopine may protect articular cartilage by activating the Nrf2 pathway, regulating chondrocyte redox homeostasis, and inhibiting chondrocyte ferroptosis and inflammation [141]. Notably, protopine exhibits no significant cytotoxicity toward chondrocytes at concentrations below 20 μg·mL^{-1}, highlighting its favorable safety profile as a potential therapeutic agent for KOA [141].

10.2. Dauricine

Dauricine is an isoquinoline alkaloid isolated from *Menispermum dauricum*. Xia et al. [142] reported that dauricine (1, 2.5, 5 μmol·L^{-1}) inhibits the expression of inflammatory markers (iNOS and COX-2) and cartilage degradation markers (ADAMTS-5, MMP-3, and MMP-13) in IL-1β-induced chondrocytes, while upregulating cartilage synthesis markers (collagen II and aggrecan), thereby confirming its protective effects on chondrocytes exposed to IL-1β. *In vivo* experiments revealed that dauricine (2.5 and 5 mg·kg^{-1}) reduced osteophyte formation induced by ACLT-DMM in mice, protected the ECM of articular cartilage, and slowed cartilage degeneration. The mechanism involves blocking Ca^{2+} influx by inhibiting TRPV5, calmodulin, and CaMK-II, while preventing activation of the NF-κB pathway, thereby exerting anti-inflammatory and chondroprotective effects. Moreover, dauricine exhibits bone-protective effects by modulating the ROS/NF-κB/NFATc1 pathway to inhibit RANKL-induced osteoclastogenesis, maintain subchondral bone homeostasis, and alleviate KOA [143].

Table 4 The effects of alkaloids against KOA.

Compounds	Models	Biological activities	Ref.
Cepharanthine	DMM-induced KOA in mice	Decrease MMP3, ADAMTS5, and MMP13; Increase collagen II and improve organizational morphology.	131
	IL-1β/TNF-α induced chondrocytes	Decrease MMP3, iNOS, p-p65, p-p38, p-ERK, and p-JUK; Increase collagen II, aggrecan, SOX9, Atg7, and LC3 II; Ameliorate KOA by inhibiting the MAPK/NF-κB pathway.	
Koumine	papain-induced KOA in rats	Decrease IL-1β, IL-6, MMP13, and ADAMTS5; Increases LC3B, PINK1, and collagen II; Improve organizational morphology.	132
	IL-1β-induced chondrocytes	Decrease MMP13, ADAMTS5, IL-1β, LC3, and p62; Increase collagen II, DRP1, and PINK1; Ameliorate ECM degradation in KOA cartilage through activation of PINK1/Parkin-mediated; Mitochondrial autophagy.	
Chelidonine	ACLT-induced KOA in rats	Decrease IL-12, IFN-γ, IL-1β, IL-6, and TNF-α; Improve organizational morphology.	133
	IL-1β induced chondrocytes	Decrease IL-12, IL-6, TNF-α, p65 and MMP3; Increase collagen II and aggrecan; Ameliorate chondrocyte inflammation and matrix catabolism.	
Vindoline	DMM-induced KOA in mice	Decrease MMP13, p-p65, and p-ERK; Increase aggrecan, and improve organizational morphology.	134
	IL-1β-induced ATDC5 cells	Decrease MMP13, ADAMTS5, p-p65, and p-ERK; Increase aggrecan, collagen II, and SOX9; Alleviate KOA by suppressing the NF-κB and ERK pathway.	
Sipeimine	DMM-induced KOA in mice	Decrease MMP-13, NLRP3, and p-PI3K; Increase collagen II; Improve organizational morphology.	135
	LPS-induced chondrocytes	Decrease COX-2, iNOS, MMP-13, ADAMTS5, p-p65, NLRP3, GSDMD, ASC, cleaved-caspase 1, and p-PI3K; Increase collagen II and aggrecan; Ameliorate KOA by inhibiting the PI3K/AKT/NF-κB pathway.	
Daurisoline	H_2O_2-induced chondrocytes	Decrease Bax, cleaved-caspase 3, LC3 II, and MMP-13; Increase Bcl-2, p-PI3K, p-mTOR, and collagen II; Inhibit autophagy by activating the PI3K/Akt/mTOR pathway.	136
α-Solanine	DMM-induced KOA in mice	Decrease MMP-3, MMP-13, COL10, IL-1β, GSDMD, caspase-1, p-p65, CD31, and Netrin-1; Increase collagen II; Improve KOA by suppressing NF-κB signaling pathway.	137
Abrine	ACLT-induced KOA in mice	Decrease IFN-γ, Bax, cleaved-caspase 3, CTX-II, and COMP; Improve organizational morphology.	138
	IL-1β-induced C28/I2	Decrease IL-6, IFN-γ, IL-12, TNF-α, Bax, cleaved-caspase 3, PIM2, VEGF, p-VEGFR2, and p-eNOS; Inhibit the apoptosis of chondrocytes *via* PIM2/VEGF pathway.	
Corynoline	DMM-induced KOA in mice	Increase collagen II and Nrf2; Improve organizational morphology.	139
	IL-1β induced chondrocytes	Decrease MMP-3, MMP-13, ADAMTS-5, iNOS, COX-2, TNF-α, IL-6, PGE2, ROS, and p-p65; Increase aggrecan, Nrf2, and HO-1; Ameliorate KOA *via* Nrf2/NF-κB pathway.	
Dehydrocorydaline	ACLT-induced KOA in rats	Decrease p-JAK1 and p-STAT3; Improve organizational morphology.	140
	TNF-α-induced chondrocytes	Decrease MMP-13, COX-2, p-JAK1, and p-STAT3; Increase aggrecan and collagen II; Accelerate cell proliferation and ECM synthesis by targeting COX-2 through JAK1-STAT3 signaling pathway.	

Additionally, at concentrations below 10 μmol·L^{-1}, no proliferative toxicity to chondrocytes was observed, indicating good safety [142].

10.3. Isorhynchophylline

Isorhynchophylline is a hydroxylated indole alkaloid extracted from the TCM *Uncaria rhynchophylla*, clinically used for cardiovascular and central nervous system diseases. It exhibits various biological activities, including anti-inflammatory and anti-oxidant effects. Research by Li et al. [144] demonstrated that isorhynchophylline inhibits the expression of inflammatory markers (iNOS, COX-2, IL-6, TNF-α, and NLRP3) and cartilage degradation markers (ADAMTS-5 and MMP-13) induced by IL-1β in chondrocytes, while upregulating cartilage synthesis markers (collagen II and aggrecan), inhibiting NF-κB activation, suppressing downstream pro-inflammatory mediators, and improving inflammation in KOA. Moreover, *in vivo* studies have confirmed its anti-KOA effects. Jiang et al. [145] established a DMM-induced KOA rat model and found that isorhynchophylline reduced joint space narrowing and ameliorated cartilage damage. Further mechanistic studies revealed that isorhynchophylline alleviates inflammation by blocking the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway, upregulating ATG5, Beclin 1, and LC3, and activating chondrocyte autophagy [145].

10.4. Oxymatrine

Oxymatrine is a tetracyclic quinoline alkaloid, primarily isolated from *Sophorae Flavescentis*, and has anti-inflammatory, antioxidant, and anti-fibrotic effects. Oxymatrine (10, 20, and 50 μmol·L^{-1}) reduces the production of inflammatory cytokines (COX-2, iNOS, TNF-α, and IL-1β) and cartilage ECM degradation markers (ADAMTS-5 and MMP-13) induced by IL-1β in chondrocytes. It also improves articular cartilage degeneration in DMM-induced KOA mice. Its anti-KOA effects involve multiple mechanisms. Zhou et al. [146] reported that oxymatrine targets Nrf2, disrupts the Keap1-Nrf2 interaction, induces Nrf2 translocation to the nucleus, promotes the release of HO-1 and NQO1, and exerts anti-inflammatory and anti-oxidant effects by inhibiting downstream NF-κB signaling. Jiang et al. [147] found that oxymatrine inhibits NF-κB and MAPK signaling cascades, suppresses cartilage ECM degradation, and reduces RANKL-induced osteoclastogenesis, exerting anti-KOA effects. Lu et al. [148] confirmed that oxymatrine inhibits ROS production, upregulates LC3 II/LC3 I, inhibits the AKT/mTOR pathway, activates autophagy, reduces chondrocyte apoptosis, and protects the articular cartilage ECM. Moreover, oxymatrine shows no significant cytotoxicity at 100 μmol·L^{-1}, making it a promising adjunctive treatment for KOA.

10.5. Sinomenine

Sinomenine is a morphinan alkaloid, primarily isolated from the TCM *Sinomenium acutum*. It exhibits various pharmacological activities, including anti-inflammatory, anti-oxidant, and analgesic effects. Sinomenine (6.25, 12.5, and 25 μmol·L^{-1}) downregulates the expression of pro-inflammatory cytokines (iNOS, COX-2, NO, PGE2, and TNF-α) and inhibits the production of cartilage ECM degradation markers (MMP-3, MMP-13, and ADAMTS-5) in IL-1β-induced chondrocytes. It targets Nrf2, upregulates HO-1, and blocks the NF-κB pathway to improve the imbalance of inflammation and ECM metabolism [149]. Additionally, sinomenine targets miR-223-3p, inhibiting NLRP3-mediated inflammatory responses by overexpressing miR-223-3p, thereby blocking KOA progression [150]. *In vitro* studies indicate that sinomenine shows no significant cytotoxicity at concentrations below 25 μmol·L^{-1} in mouse chondrocytes, suggesting good safety [149].

11. Saponins

Saponins are a class of glycosides with triterpenoid or steroidal aglycones, widely distributed in the plant kingdom. Based on structure, saponins are categorized into steroidal saponins and triterpenoid saponins. Many active ingredients in TCM contain saponins, such as Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, and Anemarrhenae Rhizoma. Saponins exhibit various biological activities, including anti-inflammatory, anti-tumor, and anti-viral effects.

11.1. Achyranthoside D

Achyranthoside D is a triterpenoid saponin extracted from *Achyranthes bidentata*. It has been reported to alleviate intervertebral disc degeneration and exert chondroprotective effects by activating the PI3K/AKT/mTOR pathway and enhancing autophagy [151]. Xie et al. [152] reported that achyranthoside D reduces serum cartilage metabolism markers (CTX-II and COMP), downregulates cartilage degradation markers (MMP-3, MMP-13, and ADAMTS-5) in cartilage tissue, upregulates cartilage-specific markers (collagen II and aggrecan), prevents ECM degradation, and maintains cartilage homeostasis. Achyranthoside D targets and regulates Wnt3a, and by inhibiting the Wnt signaling pathway, it leads to NLRP3 inflammasome inactivation, ultimately inhibiting cartilage damage and alleviating KOA [152].

11.2. Hederagenin

Hederagenin is a pentacyclic triterpenoid saponin found in various medicinal plants, such as Dipsaci Radix, Pulsatillae Radix, and Lonicerae Japonicae. It exhibits multiple pharmacological activities, including anti-inflammatory, anti-lipid peroxidation, and anti-cancer effects [153]. Hederagenin effectively mitigates KOA progression in MIA-induced rat models. Its mechanism involves crosstalk between multiple signaling pathways, resulting in chondroprotective and anti-inflammatory effects. Specifically, hederagenin, in a concentration-dependent manner, inhibits IL-1β-induced increases in p-Janus kinase 2 (JAK2) and p-signal transducer and activator of transcription 3 (STAT3) levels and suppresses p-ERK expression, indicating that its anti-KOA effect is mediated through crosstalk between the JAK2/STAT3 and MAPK signaling pathways. Further studies revealed that hederagenin activates the Keap1-Nrf2 pathway, promoting Nrf2 translocation from the cytoplasm to the nucleus and upregulating HO-1 expression. By targeting the Keap1-Nrf2/HO-1/ROS/associated X protein (Bax)/B-cell lymphoma-2 (Bcl-2) axis, it exerts dual anti-apoptotic and anti-oxidant effects, alleviating KOA inflammation and cartilage degradation [154]. However, its clinical application is limited by poor solubility and low bioavailability. Despite these challenges, hederagenin demonstrates significant bioactivity and holds potential as a therapeutic agent for KOA.

11.3. Timosaponin B-II

Timosaponin B-II is one of the main bioactive components extracted from *Rhizoma Anemarrhenae*. Multiple studies have shown that timosaponin B-II exerts anti-inflammatory, anti-oxidant, and osteogenic effects, such as scavenging free radicals, inhibiting inflammatory factor secretion, and promoting osteoblast differentiation to prevent bone loss [155]. Timosaponin B-II also suppresses IL-1β-induced inflammatory responses in chondrocytes and reduces ROS production. Its mechanism involves downregulating p-ERK1/2, p-p38, p-JNK, and p-p65, inhibiting the nuclear translocation of p65, and suppressing the MAPK and NF-κB signaling pathways to mitigate inflammation and prevent cartilage ECM degradation [156].

12. Other natural products

12.1. Curcumin

Curcumin is a polyphenolic pigment extracted from the rhizomes of Zingiberaceae plants such as Curcumae Longae and Curcumae Rhizoma. It is a natural antioxidant widely used in TCM to alleviate inflammation and treat degenerative diseases. Numerous studies have confirmed its efficacy in KOA, with major effects including promotion of collagen synthesis, inhibition of pro-inflammatory cytokine secretion, protection against oxidative stress, and prevention of chondrocyte apoptosis [157, 158]. The therapeutic mechanisms of curcumin in KOA involve multiple signaling pathways. Curcumin upregulates PINK1, p62, Beclin1, and LC3B, thereby activating adenosine 5'-monophosphate-activated protein kinase (AMPK)/PINK1/Parkin-mediated mitophagy to protect chondrocytes [159]. It inhibits p-p38, MSK1, and MEKK3 to modulate the p38 MAPK pathway, suppressing chondrocyte apoptosis and attenuating KOA progression [160]. Curcumin also downregulates NF-κB and p-JNK, thus blocking the NF-κB/JNK signaling pathway, reducing osteoclast differentiation in subchondral bone and alleviating joint damage [161]. Clinical trials have demonstrated that curcumin effectively reduces knee pain in KOA patients [162], with analgesic efficacy comparable to diclofenac but with better gastrointestinal tolerance [163]. Therefore, curcumin is a promising adjunctive treatment for KOA and an alternative for patients intolerant to NSAID side effects.

12.2. Resveratrol

Resveratrol is a non-flavonoid polyphenolic compound exhibiting various pharmacological activities. Numerous studies indicate that resveratrol may exert anti-inflammatory, anti-oxidant, anti-apoptotic, and autophagy-promoting effects, maintain cartilage homeostasis, prevent subchondral bone angiogenesis, and delay KOA progression. Xiong et al. [164] reported that resveratrol inhibits cartilage thickening and expression of COLX and MMP-13, delays aggrecan loss, suppresses osteoclast differentiation *via* the OPG/RANKL/RANK pathway, and downregulates VEGFA to prevent angiogenesis, thereby eliminating pathological coupling between osteogenesis and angiogenesis and delaying KOA progression. Wei et al. [165] found that resveratrol inhibits inflammatory markers (IL-1β, IL-6, TNF-α, and IL-18) in KOA rats, improving inflammatory injury through modulation of NF-κB and HO-1/Nrf2 signaling pathways. Wang et al. [166] demonstrated that resveratrol delays KOA progression by reducing aggrecan loss, decreasing chondrocyte apoptosis, and lowering NO levels in synovial fluid. Qin et al. [167] reported that resveratrol upregulates HIF-1α and HIF-2α, regulates the AMPK/mTOR signaling pathway, improves cartilage degeneration, and promotes chondrocyte autophagy. Multiple clinical trials have confirmed resveratrol's efficacy. In a 3-month randomized double-blind study involving 110 participants, resveratrol (500 mg·d^{-1}) combined with meloxicam significantly improved pain and joint function compared to placebo, with resveratrol demonstrating superior safety and efficacy as an adjunct therapy [168]. Another 14-week randomized double-blind trial in 80 healthy postmenopausal women showed that resveratrol (75 mg twice daily) alleviated chronic pain associated with age-related KOA and improved quality of life [169].

13. Perspectives and conclusions

Understanding the pathogenesis of KOA is essential for developing effective therapeutic strategies. A central feature of KOA onset is the imbalance between articular cartilage degradation and repair, primarily characterized by the accumulation of abnormal proteins, progressive loss of collagen, disruption of the ECM and collagen fiber network, and excessive production of pro-inflammatory cytokines and cartilage matrix degradation products [19-21]. Given the limited regenerative capacity of articular cartilage and the scarcity of disease-modifying treatments, KOA is often chronic and difficult to cure, with advanced stages typically requiring surgical intervention for symptom relief. Identifying reliable biomarkers could enable earlier diagnosis and more accurate prediction of disease progression. For instance, elevated serum levels of MMP-3 [170, 171] and ADAMTS-4 [172], as well as increased MMP-1 in synovial fluid [173, 174], have demonstrated predictive value for early KOA. Although C1M has been associated with KOA phenotypes such as radiographic damage [33], inflammation [32], and pain [175], its specific role across different stages of KOA progression remains to be fully elucidated. As a major structural component of the articular cartilage matrix, type II collagen and its metabolic fragments are particularly valuable for monitoring disease dynamics. Clinical studies have confirmed that circulating levels of C2M [35] and CTX-II [39, 40] are significantly elevated in KOA patients, suggesting their utility as potential biomarkers for disease staging. Similarly, ARGS, a fragment derived from aggrecan cleavage, reflects early aggrecan loss and may serve as a discriminative marker to distinguish early-stage KOA patients from healthy individuals [43]. Key matrix-degrading enzymes, including MMP-3, MMP-13, and ADAMTS-5, have emerged as promising therapeutic targets. Screening bioactive natural compounds that modulate these biomarkers may provide a scientific foundation for novel disease-modifying agents.

In recent years, advances in phytochemistry and pharmacological research on TCM have increasingly validated the therapeutic potential of natural products in KOA management [11]. Compared to synthetic drugs, these compounds, mainly derived from fruits, vegetables, and medicinal plants, exhibit multi-target regulatory effects and favorable safety profiles, offering distinct advantages in addressing the multifactorial nature of KOA pathogenesis.

Despite significant progress, several limitations remain. The chemical diversity and structural complexity of natural products often result in pleiotropic actions, leading to intricate mechanisms of action that are not yet fully understood. Currently, most studies focus on downstream signaling pathways, such as the inhibition of NF-κB and MAPK signaling cascades [176]. However, research on the direct binding interactions between natural compounds and their molecular targets remains limited, which constrains the rational development and optimization of these agents [177].

Furthermore, oral administration of natural products frequently encounters challenges related to poor stability and low bioavailability. Future research could leverage modern technologies, including nanotechnology and targeted delivery systems, to enhance pharmacokinetic properties and therapeutic efficacy. For example, curcumin has demonstrated anti-KOA activity in *in vivo*, *in vitro*, and clinical studies, yet its clinical utility is limited by poor aqueous solubility, chemical instability, and suboptimal pharmacokinetics, resulting in low systemic bioavailability [178]. A recent study reported a core-brush nanoplatform that loaded curcumin onto SiO_2@PP; intra-articular injection of SiO_2@PP-Cur significantly attenuated cartilage matrix degradation in MIA-induced KOA rats, promoted macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, and effectively alleviated joint inflammation and remodeled the damaged joint microenvironment [179].

These advancements underscore the promise of natural products as viable candidates for KOA therapy. Integrating biotechnological innovations with multidisciplinary research approaches brings us closer to developing more effective, safer, and targeted treatments for this debilitating condition.

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Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

These authors have no conflict of interest to declare.

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