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Review Article

Modulation of inflammatory signaling pathways by natural products in osteoarthritis: Mechanisms, challenges, and future directions

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Abstract

Osteoarthritis (OA) is a degenerative joint disease that is characterized by dysregulated inflammatory signaling that disrupts cartilage homeostasis and presents a significant therapeutic challenge. Although current treatments primarily focus on symptom management, this review explores the growing interest in anti-inflammatory natural products as potential disease-modifying therapies. This review aims to: identify key inflammatory pathways as promising drug targets, summarize recent findings on natural products that modulate these pathways, and discuss challenges and future directions. A comprehensive literature search was conducted using databases such as PubMed and Web of Science, focusing on studies published in the last decade. Central to OA pathogenesis is persistent inflammation resulting from cytokine /chemokine-driven catabolic signaling, which is exacerbated by the overactivation of NF-κB, MAPK, and PI3K/AKT pathways. Numerous plant-derived compounds exert inhibitory effects on these inflammatory cascades through mechanisms including NF-κB nuclear translocation suppression, MAPK phosphorylation blockade, and modulation of PI3K/AKT activity. However, clinical translation faces several complexities, such as bioavailability, precise targeting, and disease heterogeneity. Addressing these challenges using advanced technologies could enable the development of natural product-based OA therapeutics. Innovative research strategies are needed to fully leverage the therapeutic potential of these compounds in the management of OA.

Keywords: *Osteoarthritis, Inflammation, Natural product, Anti-inflammatory pathways, MAPK, NF- κB, PI3K/AKT*

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage breakdown, pain, stiffness, and loss of movement in affected joints [1]. OA is a significant global health burden affecting over 500 million individuals and is the primary cause of disability worldwide [2]. Despite its prevalence, current therapeutic approaches are limited to symptom management because no disease-modifying therapies have yet been clinically validated. This gap highlights the urgent need for disease-modifying treatments rather than merely systematic relief. The pathogenesis of OA is characterized by dysregulation of inflammatory pathways, which significantly

contribute to cartilage degradation. A critical aspect of this process is the disruption of homeostasis between catabolic proinflammatory signaling and anabolic anti-inflammatory repair mechanisms. Restoration of this equilibrium through modulation of inflammatory mediators is a promising therapeutic strategy [3].

Current pharmacological treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), focus on managing symptoms; however, they may lead to adverse effects during long-term use, including gastrointestinal complications and increased cardiovascular risk [4]. This limitation has sparked growing interest in natural products as potential multi-target anti-inflammatory agents. Natural compounds often exhibit a favorable safety profile and interact with multiple pathways simultaneously, thereby potentially offering more comprehensive therapeutic effects [5]. This review aims to identify potential anti-inflammatory molecular targets for innovative OA drug development, synthesize recent findings on promising natural products that modulate these key pathways, elucidate their molecular mechanisms, and examine challenges and future directions of natural product therapies for OA. By consolidating current studies on natural compounds that regulate inflammatory pathways in OA, this review aims to elucidate the complex inflammatory processes underlying OA and highlight potential anti-inflammatory therapeutic targets. The overarching goal is to contribute to the development of safer and more effective OA treatments and improve patient outcomes.

Key inflammatory signaling pathways in osteoarthritis pathogenesis

Osteoarthritis is characterized by dysregulation of inflammatory and catabolic signaling pathways that disrupt cartilage homeostasis [6]. The pathogenesis of this disease involves complex interactions between chondrocyte and extracellular matrix (ECM) components that normally maintain joint integrity. A shift in the balance favoring ECM degradation over synthesis significantly contributes to the initiation and progression of OA [7]. Mechanical stress plays a crucial role in initiating the inflammatory cascade in OA. When cartilage damage is caused by biomechanical factors, an inflammatory response is triggered, which activates immune cells and chondrocyte. This leads to increased production and release of matrix-degrading enzymes, particularly matrix metalloproteinases (MMPs). These enzymes break down structural components such as collagen and aggrecan, thereby jeopardizing the biological and biomechanical functions of the ECM [8].

A key pathological feature of OA is the establishment of a chronic inflammatory microenvironment that perpetuates cartilage degradation. Degraded matrix debris, dead chondrocyte, and chondrocyte-derived extracellular vesicles activate synovial macrophages that then release proinflammatory factors into the joint space. These factors include cytokines and chemokine, among other inflammatory mediators. Specific inflammatory cytokines and chemokine, such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), stimulate chondrocyte to upregulate the production of catabolic enzymes like MMPs and aggrecanase. These inflammatory mediators activate several signaling pathways, notably the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) cascades, which are critical in driving the inflammatory response and represent potential targets for therapeutic interventions. The activation of these pathways, coupled with increased oxidative stress, accelerates the breakdown of ECM components, particularly proteoglycans and type II collagen. Oxidative stress not only contributes to chondrocyte dysfunction and directly damages ECM components, further intensifying the degradation process [9].

A detrimental positive feedback cycle is created: cartilage degradation products intensify synovial inflammation, which enhances ECM catabolism, resulting in more debris-propagating joint inflammation. Infiltrating immune cells such as T and B cells secrete inflammatory factors that amplify this cycle. Although anti-inflammatory molecules counteract inflammation, pro-inflammatory stimuli overwhelm protective mechanisms in OA. As a result, chronic, unresolved inflammation damages the structural integrity of cartilage and inhibits anabolic repair by chondrocyte [10].

Disruption of chondrocyte homeostasis plays a crucial role in the initiation and propagation of inflammation in OA. Elevated levels of inflammatory mediators such as IL-1, IL-6, TNF-α, and cyclooxygenase-2 (COX-2) drive disease progression through multiple mechanisms. These effects include impairment of mitochondrial function, reduction of extracellular matrix synthesis, and increase in catabolic enzyme activation. Emerging concepts in the pathogenesis of OA highlight additional factors contributing to disease progression. For instance, the accumulation of senescent cells in articular

cartilage is implicated in the development of OA. These cells secrete proinflammatory factors, contributing to the chronic inflammatory state. Moreover, metabolic dysregulation, including alterations in glucose and lipid metabolism, has been recognized as a potential driver of OA, helping to expand understanding of the disease beyond mechanical wear and tear [11].

The interruption of this inflammatory feedback loop and its associated catabolic signaling pathways represents a potential therapeutic strategy for halting OA progression. This approach restores cartilage homeostasis by modulating the balance between anabolic and catabolic processes in the joint microenvironment. Consequently, treatments targeting inflammation, oxidative stress, and emerging factors like cellular senescence, may offer disease-modifying effects in OA management.

MAPK signaling pathway

The MAPK cascade critically regulates inflammatory signaling and downstream catabolic responses during OA progression [12]. The MAPK pathway comprises three main arms: p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK), each of which regulates specific inflammatory gene expression in osteoarthritic cartilage (Figure 1).

Key inflammatory mediators and biomechanical stressors activate the MAPK pathway. Specifically, cytokines such as IL-1, IL-6, and TNF-α play a crucial role in this activation process. These stimuli bind chondrocyte receptors and the phosphorylation of upstream MAP kinases. Subsequently, these kinases activate downstream MAPKs, including p38 and JNK, while phosphorylating key transcriptional regulators. This activation cascade stimulates the transcription of major inflammatory cytokines, notably IL-6, IL-8, and TNF-α. By stimulating these central inflammatory and catabolic pathways in osteoarthritic cartilage, the MAPK cascade critically controls joint destructive processes [13].

JNK plays a significant role in regulating chondrocyte apoptosis. The combined effects of inflammatory cytokines and cell death pathways contribute to the deterioration of cartilage integrity. The MAPK pathways, particularly p38 and JNK, enhance the production of matrix-degrading enzymes, including MMP-3 and MMP-13, which actively degrade the extracellular matrix. Concurrently, p38 and JNK activation leads to increased COX-2 expression, furthering catabolic processes in cartilage [14]. The ERK1/2 pathway also contributes to OA progression by altering chondrocyte differentiation and promoting MMP production [15]. Given these multiple detrimental effects, inhibition of excessive MAPK signaling may represent a potential strategy for mitigating the inflammatory cascade and preserving cartilage structure.

NF-κB signaling pathway

The NF-κB transcription factor pathway is a key regulator of inflammatory responses. The NF-κB signaling pathway comprises three primary protein groups: the NF-κB transcription factors (including p50, p52, p65, c-Rel, and RelB), the inhibitory IκB proteins, and the IKK kinase complex. In unstimulated cells, IκB proteins regulate NF-κB activity by retaining NF-κB dimers such as p65/p50 in the cytoplasm. Cellular stimuli activate IKK to phosphorylate IκB and target its degradation. This allows NF-κB to translocate to the nucleus and activate target genes [16].

In OA, NF-κB controls the expression of inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokine (IL-8), and catabolic mediators, such as MMPs. Biomechanical stressors, damage signals, and inflammatory stimuli induce the activation of chondrocyte receptors. This triggers kinase cascades that activate IKK to release NF-κB (Figure 1). The resulting cytokine production promotes inflammation and cartilage breakdown. Thus, the NF-κB pathway orchestrates the key inflammatory responses underlying the progression of OA [17]. Strategies that inhibit NF-κB signaling may suppress the cytokine/chemokine-driven amplification of joint inflammation and catabolism. Further research into therapies that safely normalize NF-κB hyperactivation will help identify disease-modifying OA treatments.

PI3K/AKT signaling pathway

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling cascade plays an important regulatory role in the inflammatory processes implicated in OA pathogenesis. PI3K, a ubiquitous catalytic enzyme, phosphorylates phosphatidylinositol lipids and generates second messengers that subsequently activate downstream AKT signaling. In OA, dysregulation of the PI3K/AKT pathway contributes to inflammatory cartilage degradation [17].

Activated AKT stimulates transcription factors, such as NF-κB and enhances the production of inflammatory mediators, such as cytokines (e.g.,

IL-6, IL-1), chemokine, COX-2, and MMPs (Figure 1). This catabolic signaling disrupts chondrocyte anabolism and matrix homeostasis. Conversely, PI3K/AKT inhibition reduces the expression of these inflammatory factors in chondrocyte while promoting protective mechanisms such as autophagy [18].

Beyond its functional role, the activity of the PI3K/AKT pathway is a potential biomarker of osteoarthritic inflammation and disease severity. Studies have demonstrated significantly elevated levels of phosphorylated AKT in both synovial fluid and cartilage tissue from osteoarthritic joints compared with healthy controls, indicating heightened activation of this pathway in disease [19]. This increased AKT phosphorylation is correlated with inflammatory activity and disease progression in OA. Consequently, monitoring the PI3K/AKT pathway activation is a valuable tool for assessing disease severity and evaluating therapeutic response in patients with OA. The PI3K/AKT cascade is a critical signaling node that regulates both inflammatory-driven catabolism and anabolic repair mechanisms in osteoarthritic cartilage. Modulation of this pathway presents a promising avenue for disease-modifying interventions, potentially reestablishing homeostatic balance and augmenting cellular repair processes in OA. Further research into targeted therapies that selectively modulate PI3K/AKT signaling in affected tissues may lead to more effective treatments for this debilitating joint disease.

Modulation of inflammatory pathways in osteoarthritis by natural products: mechanisms and therapeutic potentials

Emerging evidence has demonstrated the anti-inflammatory effects of numerous natural bioactive compounds in osteoarthritic models through diverse signaling mechanisms [20]. This review synthesized recent evidence regarding the molecular targets and signaling cascade mechanisms influenced by specific natural compounds that demonstrate potential in mitigating joint inflammation (Table 1). Elucidating these chondroprotective mechanisms is crucial for developing safe, multifaceted plant-derived therapies that can potentially halt cartilage deterioration underlying OA-related disability.

MAPK pathway

As shown in Table 1, various natural products exert anti-inflammatory effects on osteoarthritic chondrocyte by modulating MAPK signaling. Flavonoids such as liquiritigenin and wogonin suppress the phosphorylation of ERK, p38, and JNK [21,22]. Caffeic acid, quinone cryptotanshinone, and isorhapontigenin inhibit MAPK activation [23–25]. The terpenoid echinocystic acid and phenylpropanoid schisantherin A reduced the levels of phosphorylated ERK, p38, and JNK [26,27].

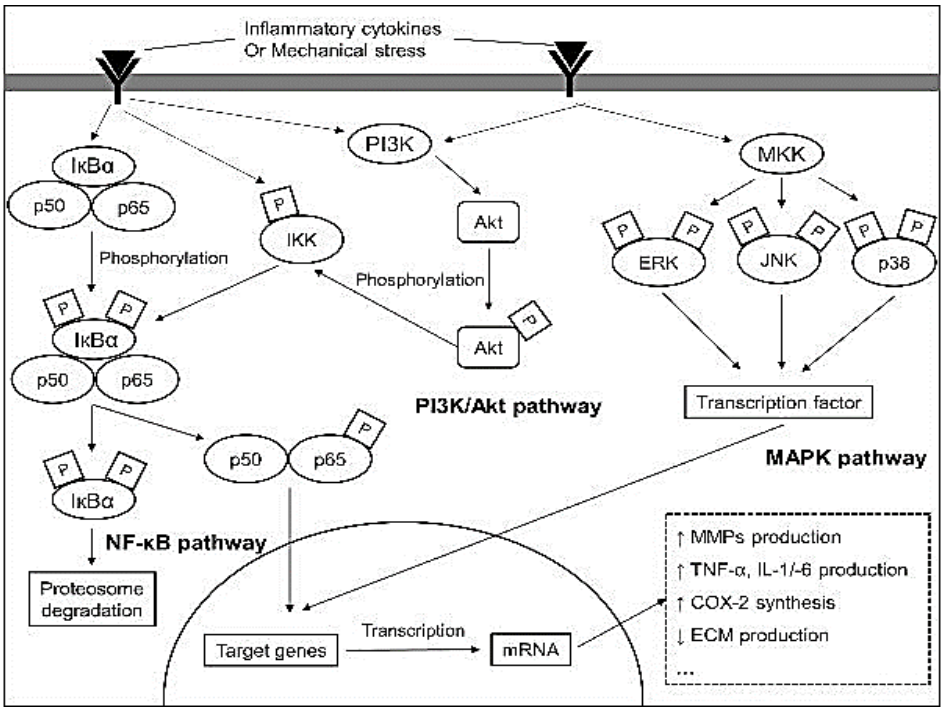

Figure 1: Intracellular inflammatory signaling cascades driving osteoarthritis progression

Table 1: Natural products modulate inflammatory pathways in osteoarthritic chondrocyte

Natural compound	Mechanism of action
Caffeic acid, cryptotanshinone, echinocystic acid, isorhapontigenin, liquiritigenin, schisantherin A, and wogonin	Inhibition of MAPK pathway activation
Asiatic acid, chrysin, sinapic acid, sinomenine, and *P. ginseng* saponin	Inhibition of IκB phosphorylation/NF-κB pathways
Eriodictyol, sinapic acid, oleuropein, polydatin, *A. bidentata* and *P. ginseng* saponin	Inhibition of IκB degradation/NF-κB pathways
Curcumin, danshensu, ginsenoside Ro, oleuropein, salvianolic acid B, and sinapic acid	Inhibition of the p65 phosphorylation/NF-κB pathways
α-mangostin, cryptotanshinone, curcumin, ligustilide, liquiritigenin, moracin, myricetin, myricitrin, peiminine, and piceatannol	Inhibition of the p65 nuclear translocation/NF-κB pathway
Artemisinin, astilbin, farrerol, leonurine, myricetin, oroxin B, and urolithin A	Inhibition of PI3K/Akt activation

Although these studies demonstrated inhibition of the MAPK pathway by diverse natural compounds, the specific mechanisms underlying this modulation remain unclear. Elucidating the targets and binding interactions involved in natural product-mediated MAPK regulation may reveal novel chondroprotective strategies.

NF-κB pathway

A diverse array of natural products modulates NF-κB activity, thereby influencing OA progression (Table 1).

Regulation of IκBα phosphorylation

Various natural plant-derived products effectively suppress NF-κB inflammatory signaling in chondrocyte by preventing cytokine-induced phosphorylation of the inhibitory protein IκBα. Diverse dietary compounds such as the pentacyclic triterpenoid asiatic acid from frankincense, chamomile flavonoid chrysin, *Panax ginseng* root saponins, the sinapic acid phenolic found in mustard and cruciferous vegetables, and ginger-derived alkaloid sinomenine, all share the capacity to block IκBα phosphorylation *in vitro* [28–32]. The maintenance of IκBα in its active state plays a crucial role in inhibiting the NF-κB pathway. This inhibition prevents NF-κB nuclear translocation and subsequent transcription of the catabolic and inflammatory mediators associated with cartilage degradation in OA. Specific compounds, notably sinapic acid, attenuate the expression of NF-κB target genes, such as MMPs, COX2, IL-6, and TNF-α, in IL-1β-activated chondrocyte through modulation of IκBα signaling [31].

Inhibition of IκBα degradation

Natural compounds also demonstrate the ability to modulate NF-κB signaling by preserving IκBα stability. *In vitro* studies have shown that sinapic acid inhibits IκBα degradation, thereby restricting NF-κB nuclear translocation and subsequent production of proinflammatory cytokines [31]. The mechanism of action is not limited to these compounds. Various plant extracts, including polydatin, *Achyranthes bidentata* saponins, and *Panax ginseng* saponins, have also exhibited the capacity to prevent IκBα breakdown, thus attenuating NF-κB-driven inflammation [30,33,34]. Similarly, the citrus flavonoid eriodictyol and olive phenolic oleuropein inhibited IκBα degradation and cytokine expression in chondrocyte cultures [35,36].

Regulation of NF-κB p65 subunit activity and localization

Several natural products exert chondroprotective effects by modulating the activity of the NF-κB subunit p65. Specifically, these compounds interfere with the phosphorylation of p65, a critical step in NF-κB activation. *In vitro* studies have shown that curcumin, oleuropein, ginsenoside Ro, and sinapic acid inhibit inflammatory stimuli-induced p65 phosphorylation [31,36–38]. This inhibition restricts p65 nuclear translocation and subsequent transcriptional activity. Additionally, other plant-derived phenolic compounds, including danshensu and salvianolic acid B, have exhibited similar effects in osteoarthritic cartilage models, reducing p65 phosphorylation [39,40]. Inhibition of p65 phosphorylation is also associated with decreased expression of NF-κB-regulated inflammatory cytokines, such as IL-6 and TNF-α, in chondrocyte.

Moreover, natural products inhibit NF-κB transcriptional activity by preventing nuclear translocation of the p65 subunit. Compounds such as α-mangostin, moracin, and piceatannol reduce p65 nuclear levels in cytokine-stimulated chondrocyte. This reduction in nuclear p65 is correlated with a decrease in the expression and production of inflammatory mediators [41–43]. Curcumin directly binds to p65, thereby blocking its nuclear import [37]. A diverse array of natural products, including cryptotanshinone, ligustilide,

liquiritigenin, myricetin, myricitrin, and peiminine, have demonstrated the ability to inhibit p65 nuclear translocation in osteoarthritic models, thereby attenuating downstream inflammatory processes [21,24,44–47].

Collectively, these findings highlight the central role of modulation of the NF-κB pathway as a key mechanism underlying the anti-inflammatory properties of nutraceuticals for the management of OA. The development of optimized natural formulations that target NF-κB signaling at multiple molecular checkpoints could enable a more potent and specific blockade of cartilage-induced inflammation.

PI3K/AKT Pathway

Natural products exert anti-inflammatory effects by modulating PI3K/AKT activity in OA (Table 1). Flavonoids such as farrerol and myricetin suppress PI3K/AKT phosphorylation, thereby reducing downstream inflammation [45]. Similarly, phenolic compounds such as astilbin, leonurine, oroxin B, and urolithin A inhibit PI3K and/or AKT activation [48,19,49,50]. The terpenoid artemisinin also limits osteoarthritic inflammation by blocking cytokine-induced stimulation of the PI3K/AKT/mTOR pathway. These findings highlight a diverse array of natural compounds that can influence this signaling cascade.

Although the current evidence supporting the modulation of PI3K/AKT signaling by natural products in OA is promising, further mechanistic studies are needed. A deeper understanding of these interactions could lead to the development of more effective and targeted natural therapies for managing OA-related inflammation and joint damage.

CHALLENGES AND FUTURE PERSPECTIVES

Despite promising preclinical evidence supporting the use of natural products for OA treatment, there is an urgent need for new therapeutic options. Current first-line pharmacological treatments, such as NSAIDs, steroids, and opioids, have significant limitations, including increased health risks associated with long-term use and the possibility of dependence [51,52]. Clinical studies have demonstrated that natural products offer potential benefits in OA treatment with a favorable safety profile and fewer reported adverse effects compared to conventional therapies. These compounds have unique advantages, including high structural diversity and multi-target mechanisms of action [53]. However, translating these preclinical findings into practical clinical solutions is difficult. The development of natural products for OA treatment faces significant challenges, including enhancing the bioavailability of often poorly soluble compounds, unraveling complex multi-target mechanisms, conducting robust clinical trials to establish efficacy and dosing, and thoroughly evaluating long-term safety profiles and potential drug interactions.

Emerging biotechnologies offer promising opportunities to overcome these obstacles (Figure 2). For instance, integrating natural products with rehabilitation protocols in combinatorial therapeutic approaches has been demonstrated to provide superior symptom relief compared with single-modality treatments [54]. In addition, enhancing the therapeutic potential of natural compounds involves addressing their bioavailability and delivery challenges. Chemical modifications have shown promise in improving the solubility, stability, and bioactivity of compounds such as curcumin and arctigenin [55,56]. Concurrently, advanced biomaterials, including hydrogels and microspheres, offer innovative solutions for sustained and localized drug release, potentially reducing the dosing frequency [57,58]. These developments represent a significant frontier in maximizing the efficacy of natural product-based interventions.

Further investigation at the earliest stages of the disease is crucial because natural compounds with cartilage-regenerating capacity may be most effective before irreversible damage occurs [59]. To fully exploit the therapeutic potential of natural products, well-designed and rigorous clinical trials are required. In addition, improving patient stratification through emerging “omics” technologies and developing biomarkers that reflect the specific mechanisms influenced by these compounds are vital areas of focus [60].

Overall, managing the intricate nature of OA poses complex challenges, but overcoming these obstacles can translate promising natural compounds into viable clinical solutions. The development of effective and economical treatments for OA, a widely disabling condition, can be accelerated through several key advancements. Enhancing understanding of the pharmacological actions, safety profiles, and bioavailability of natural products is crucial. Equally important is the optimization of efficacy through advanced research methods. These combined efforts could significantly contribute to the progression of natural products from promising compounds to viable therapeutic options for OA management.

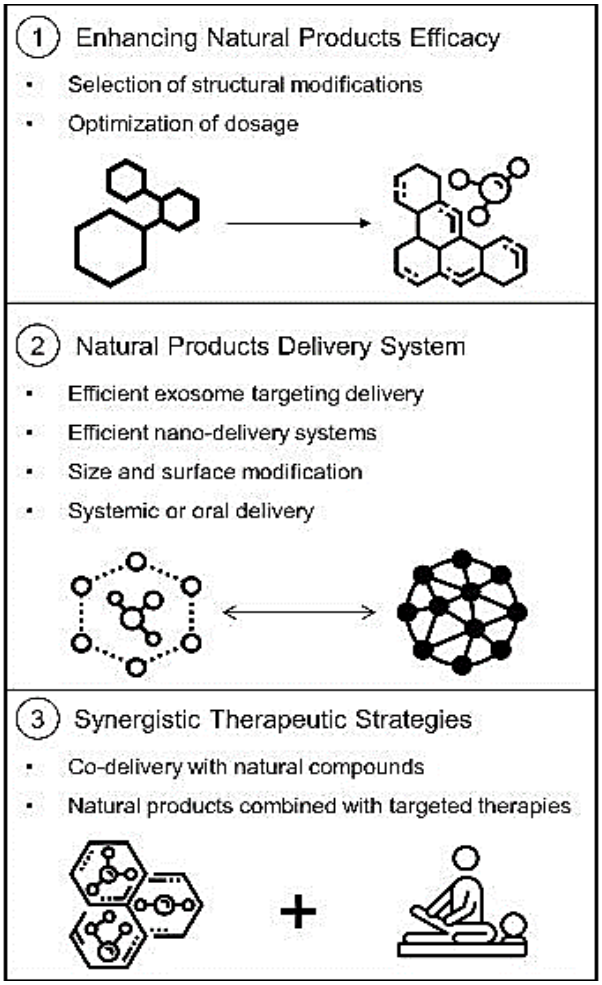

Figure 2: Novel application of natural products in osteoarthritis therapy

CONCLUSION

Preclinical evidence indicates that small-molecule natural products of botanical origin have promising potential in OA therapy. *In vitro* and animal studies have revealed the diverse anti-inflammatory effects of these agents by targeting key OA signaling pathways. However, translating these bioactive molecules into clinical therapies remains challenging because of the multifaceted complexity of the disease in humans.

Despite these obstacles, the multimodal and multitargeted actions of natural products provide a distinct advantage over current single-target drug approaches, making them remarkably well-suited to address the complex pathophysiology of OA. By overcoming these challenges through cutting-edge methodologies, it is possible to exploit the immense opportunity to transform promising natural compounds into effective and economical clinical solutions for this highly disabling condition.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors made substantial contributions to this review article. They collectively participated in conceptualizing the review's scope and structure, conducting comprehensive literature searches, and analyzing and interpreting the gathered information. The authors collaboratively drafted, revised, and critically reviewed the manuscript, ensuring that all key aspects of the topic were thoroughly addressed. Each author provided critical intellectual input throughout the writing process and approved the final version for publication. The decision regarding the target journal for submission was reached through consensus among all authors. In addition, the authors declare that this work was performed by the authors named in this article, and all liabilities of claims relating to the content of this article will be borne by them.

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