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Review

Research advances in the treatment of arthritis from natural products (2014–present)

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ABSTRACT

Arthritis, encompassing osteoarthritis (OA), rheumatoid arthritis (RA), and gouty arthritis (GA), is a prevalent inflammatory disease that significantly impacts quality of life. Natural products (NPs), derived from animals, plants, marine organisms, and microorganisms, have demonstrated beneficial effects in arthritis treatment both domestically and internationally. These natural compounds offer advantages in drug discovery due to their skeletal diversity, structural complexity, and multi-effect, multi-target, and low-toxicity properties compared to conventional small-molecule medicines. However, unclear mechanisms have hindered the development and clinical application of NPs. This review summarizes recent experimental studies from the past decade on natural medicine for arthritis treatment, emphasizing key NPs with therapeutic effects on OA, RA, and GA. It examines the effects and molecular mechanisms of NPs acting on different cells to treat arthritis. Furthermore, this review provides insights into the future prospects of NP research in this field, which is crucial for advancing NP-based arthritis treatments.

1. Introduction

Arthritis is an inflammatory syndrome characterized primarily by pain, swelling, and restricted mobility, significantly impacting patients' quality of life while imposing substantial economic and healthcare burdens on families and society. It has emerged as the most prevalent joint disease globally, affecting approximately 100 million people nationwide. Among the various forms, osteoarthritis (OA), rheumatoid arthritis (RA), and gouty arthritis (GA) are the most commonly encountered in clinical settings [1]. Currently, there is no definitive cure for arthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely utilized in managing these three types of arthritis due to their efficacy in pain relief and inflammation reduction. However, NSAIDs have been associated with adverse effects, including gastrointestinal irritation, cardiovascular dysfunction, and urinary system complications [2]. Glucocorticoids, another common treatment, are generally not the first choice due to significant side effects such as gastrointestinal reactions, osteoporosis, immunosuppression, and elevated blood pressure. Furthermore, chondroprotective agents for OA, disease-modifying anti-rheumatic drugs (DMARDs), biological agents and Janus kinase (JAK) inhibitors for RA, and urate-lowering drugs for GA all have limitations. Consequently, there is a pressing need to explore natural remedies that offer efficacy while minimizing adverse effects to address unmet clinical needs.

Traditional Chinese medicine (TCM) has withstood the test of practical application for millennia in treating major diseases. In recent years, the active natural products (NPs) derived from TCM have garnered attention for their potential in treating cancer[3], diabetes [4], Alzheimer's disease [5], and other ailments due to their multi-targeted, multi-pathway approach, low toxicity, and diverse biological activities. The numerous NPs obtained from TCM have demonstrated clinical efficacy in treating arthritis, highlighting the importance of exploring TCM-isolated NPs in arthritis treatment [6]. Sinomenine (SIN), a plant-derived alkaloid isolated from Caulis Sinomenii, has been approved by the State Food and Drug Administration of China for treating RA [7]. Additionally, several preclinical studies have shown the positive effects of numerous NPs in treating OA, RA, and GA [8]. For instance, Sakuranetin and Resveratrol have been found to inhibit inflammation and mitigate cartilage damage in OA treatment, while Genkwanin and Tetrandrine demonstrate anti-rheumatic action in RA treatment by inhibiting immune and inflammatory functions [8, 9]. Kaempferol and Berberine (BBR) can inhibit inflammation and mitigate cartilage damage in GA treatment through their anti-oxidative or anti-inflammatory activities [10]. However, the elucidation of the mechanism of action of NPs remains largely inadequate, which is a major factor limiting their development and clinical application. Given the widespread use and significant benefits of NPs in arthritis treatment, this review summarizes the target cells and underlying mechanisms of NPs, systematically discusses promising drug candidates targeting different cells, and examines the potential and challenges of NPs in future arthritis treatment.

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2. Classification and therapeutic drugs of arthritis

2.1. Pathogenesis and therapeutic drugs of OA

OA is a chronic progressive joint disease primarily characterized by cartilage degeneration and inflammatory response [11]. It is one of the most common causes of chronic disability in adults. The pathological features include thickening or fibrosis of the joint capsule, sclerosis or hyperplasia of the subchondral bone, wear, sclerosis or destruction of the articular cartilage, cystic changes of the bone [12], and localized inflammation. OA is considered a low-grade inflammatory disease predominantly mediated by autoimmune cells, particularly macrophages. Certain immune cells and cytokines play a crucial role in OA repair, with macrophages and natural killer cells contributing to the synovial inflammatory response, while T-cell immune responses facilitate osteoarthritic cartilage degradation and exacerbate the condition [13-16]. The primary objectives of OA treatment are symptom alleviation and enhancement of joint functionality. In addition to NSAIDs and glucocorticoid drugs, chondroprotective agents such as diacerein and glucosamine can be utilized in OA treatment to facilitate cartilage restoration. However, while chondroprotective agents demonstrate short-term effectiveness, they cannot prevent OA progression, necessitating long-term medication for patients with OA [17, 18].

2.2. Pathogenesis and therapeutic drugs of RA

RA is a chronic inflammatory autoimmune disease characterized by the immune system's attack on joint tissues, resulting in inflammation, pain, joint damage, and disability. The global prevalence of RA ranges from 0.5% to 1%, with an increasing prevalence in China [19]. RA development and progression involve a complex interplay between genetic predisposition and environmental factors. The RA microenvironment comprises activated immune cells and effector cells. Activated immune cells, including macrophages, neutrophils, and T cells, can induce RA. Effector cells, such as synoviocytes, osteoclasts, and chondrocytes, exacerbate RA when exposed to inflammatory stimuli. These functional cells exhibit upregulation of surface-specific receptor proteins and significant homing effects, secreting pro-inflammatory factors and interacting to promote RA progression [20]. Non-immune cells also contribute to RA pathogenesis. Fibroblast-like synoviocytes (FLS) are crucial components that maintain synovial homeostasis, mediate joint inflammation, and contribute to bone and cartilage destruction in RA. FLS exhibit invasive migratory characteristics, potentially leading to disease progression. Targeting RA fibroblast-like synoviocytes (RA-FLS) represents an ideal selective therapeutic approach, offering the potential to mitigate the disease without immunosuppressive consequences [21]. RA treatment focuses on controlling the disease's immunological progression. In addition to NSAIDs and glucocorticoids, DMARDs and biological agents with immunomodulatory effects are commonly used. However, most DMARDs have severe side effects, including gastrointestinal reactions, liver and kidney damage, and myelosuppression, requiring close monitoring during treatment. Biological agents are often expensive and may increase infection risk. Recently, small-molecule drugs, such as JAK inhibitors, have gained attention in RA treatment. JAK inhibitors effectively inhibit immune responses relying on the JAK-signal transducer and activator of transcription (STAT) pathway, showing therapeutic effects on various autoimmune diseases, including RA. Clinically, JAK inhibitors are used in RA patients who are unresponsive or intolerant to DMARD therapy. However, JAK inhibitors also have adverse effects, including pneumonia, upper respiratory tract infections, urinary tract infections, gastroenteritis, varicella-zoster virus reactivation, and increased cancer risk [22]. Although numerous drugs are available for RA treatment, challenges persist, including poor efficacy and significant side effects.

2.3. Pathogenesis and therapeutic drugs of GA

GA is one of the most prevalent inflammatory arthritis conditions caused by the deposition of monosodium urate (MSU) crystals in joint tissues due to persistent hyperuricemia [23, 24]. In recent years, the global incidence of GA has ranged from 1% to 6.8%, with China reporting an overall incidence of 1.1%. Notably, the incidence of GA in China has shown a significant increase [23]. Research has revealed that multiple immune cells and inflammatory factors contribute to gouty inflammation, and GA is closely associated with immune cell activation. GA is triggered by MSU crystals deposited in the joints, which activate macrophages, neutrophils, and monocytes to release cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, subsequently initiating the inflammatory cascade and gout onset [25, 26]. Controlling serum urate concentrations is crucial for GA prevention. Urate-lowering drugs to reverse hyperuricemia represent the fundamental approach for long-term effective management of GA. These drugs include allopurinol and febuxostat, which inhibit uric acid synthesis, and benzbromarone, which enhances uric acid excretion [25]. However, these medications have been linked to several adverse effects, including allergic skin reactions, abnormal liver function, leukopenia, thrombocytopenia, skin rashes, a sensation of fullness in the stomach, and diarrhea [27, 28].

3. Mechanism of OA treatment with NPs based on cells

3.1. Chondrocyte

Chondrocytes, the sole cellular components responsible for maintaining cartilage integrity through extracellular matrix (ECM) homeostasis, play a crucial role in the pathogenesis of OA (Fig. 1). These cells not only participate in the synthesis and degradation of the cartilage matrix but also contribute to inflammatory responses and immune regulation [29]. Research has identified numerous NPs that demonstrate therapeutic potential in OA by modulating immune regulation, inflammation, and chondrocyte metabolism [30].

Kaempferol, a flavonoid isolated from the leaves of *Ginkgo biloba* L., has been extensively studied for its anticancer, anti-inflammatory, and antibacterial properties [31]. Research examining the anti-inflammatory and anti-OA effects of kaempferol in rat articular chondrocytes stimulated with IL-1β demonstrated that kaempferol treatment concentration-dependently reduced the IL-1β-stimulated production of prostaglandin E2 (PGE2) and nitric oxide (NO), and downregulated the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in IL-1β-stimulated rat OA chondrocytes. Additionally, kaempferol inhibited IkBa degradation and nuclear factor κB (NF-κB) activation in rat chondrocytes stimulated with IL-1β [32, 33]. These findings suggest that kaempferol may serve as a novel therapeutic agent to prevent, halt, or slow the progression of OA. Baicalein, a flavonoid compound extracted from the TCM Scutellaria, exhibits various pharmacological activities, including antioxidant, anti-inflammatory, anti-tumor, antibacterial, anti-viral, and anti-allergic properties, and has been utilized clinically to treat acute and chronic inflammatory diseases [34, 35]. Baicalein is considered a potential therapeutic strategy for OA, as it demonstrated a chondroprotective effect and improved OA-related pain sensitivity by suppressing chondrocyte ferroptosis. Mechanistically, baicalein inhibited ferroptosis by enhancing the activity of AMPK/nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxy-

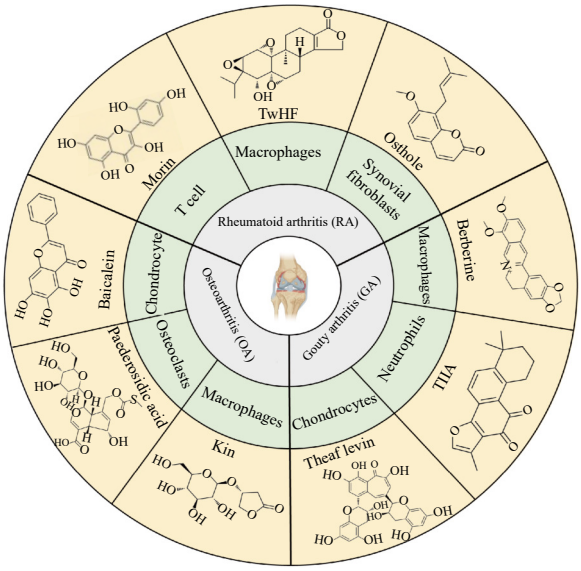

Fig. 1 Classification of arthritis and representative NPs.

genase-1(HO-1) signaling in IL-1β-exposed chondrocytes. Furthermore, Nrf2 increased expression of HO-1 to inhibit chondrocyte lipid reactive oxygen species (ROS). Collectively, these studies indicate that baicalein could be a promising therapeutic approach for OA [36]. Sakuranetin (SK) is a natural flavonoid principal derived from cherry, grass trees, shrubs, flowering plants, and some herbal drugs, possessing anti-inflammatory, antioxidant, and anti-fungal properties [37]. Research has shown that SK alleviated chondrocyte inflammation, rescued anabolism, and promoted chondrogenesis by suppressing the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/NF-κB signaling pathway. Moreover, SK reduced cartilage and subchondral bone degeneration *in vivo* [38]. These findings suggest that SK may be a promising agent for OA treatment. BBR is an isoquinoline derivative alkaloid primarily extracted from the plant *Coptis chinensis*, exhibiting antibacterial, anti-inflammatory, antioxidant, hypodiabetic, and hypolipidemic pharmacological effects [39, 40]. A molecular mechanism study on the effects of BBR on sodium nitroprusside (SNP)-stimulated chondrocyte proliferation *in vitro* and on articular cartilage in a rat model of OA revealed that BBR promotes SNP-stimulated chondrocyte proliferation by facilitating G_1/S phase transition and synthesis of proliferating cell nuclear antigen (PCNA) in cartilage through activation of the Wnt/β-catenin pathway, thereby inhibiting rat OA development[41]. Celastrol (CSL) is a pentacyclic triterpenoid extracted from the TCM *Tripterygium wilfordii* Hook. f., possessing anti-inflammatory, antioxidant, and immunosuppressive properties. Recent studies reported that CSL mitigated IL-1β-induced protease activation and enhanced cartilage ECM synthesis. Administration of CSL improved cartilage degeneration and reduced subchondral bone damage in OA mice. Further mechanistic studies revealed that inhibiting Nrf2 compromised the antioxidant function of CSL and exacerbated OA progression [42]. This study elucidates the role of CSL in OA treatment by activating Nrf2, offering a novel therapeutic approach for arthritis management. Despite its anti-inflammatory and immunosuppressive effects, the poor aqueous solubility, low bioavailability and toxicity of CSL limit its clinical application. To address these issues, researchers have developed various CSL nanoformulations to improve its bioavailability and reduce its toxicity, providing theoretical basis and technical support for studying the clinical application of CSL in OA treatment. Resveratrol (3,5,4′-trans-trihydroxystilbene) is a polyphenolic plant compound found abundantly in grape skins and wines, with diverse biochemical and physiological effects. Resveratrol, a non-flavonoid polyphenolic compound isolated from the roots of Veratrum grandiflorum, is beneficial in OA treatment due to its anti-inflammatory, antioxidant, and anti-apoptotic properties, as well as its ability to regulate the breakdown of cartilage, osteoblasts and synoviocytes. Research has shown that intra-articular injection of resveratrol can activate SIRT1, thereby inhibiting the expression of HIF-2α and catabolic factors, ultimately preventing cartilage destruction and effectively treating OA [43]. While current research indicates that resveratrol has shown potential therapeutic effects on OA in animal models and *in vitro* experiments, its clinical application still faces challenges of poor solubility and bio-permeability. Further research is needed to enhance its clinical application potential. Cyasterone is a NP mainly isolated from the Lamiaceae Martinov, known for its protective effects against various inflammatory diseases. A recent study has demonstrated that Cyasterone has the potential to alleviate OA symptoms by inhibiting IL-1β-mediated apoptosis and promoting the expression of collagen II and aggrecan. Additionally, it has been shown to suppress the production of inflammatory factors in rat chondrocytes. Further mechanistic studies have indicated that Cyasterone improves inflammation and degenerative progression of OA by mediating the NF-κB and mitogen-activated protein kinase (MAPK) pathways. These studies suggest that Cyasterone could be an effective drug for OA treatment [44].

3.2. Osteoclast

In the progression of OA, enhanced osteoclast activity contributes significantly to articular cartilage degeneration and bone destruction, playing a crucial role in disease advancement. Osteoclasts facilitate bone resorption by secreting acidic substances and enzymes that dissolve the bone matrix. The intricate interactions between osteoclasts and osteoblasts, hematopoietic and immune system cells, and even tumor cells are instrumental in regulating the bone microenvironment. Furthermore, osteoclasts are implicated in processes such as angiogenesis, innervation, and tumor metastasis, which may also significantly influence OA development [45]. In OA management, modulating osteoclast differentiation and activity has emerged as a potential therapeutic strategy, as it may regulate articular cartilage destruction, bone resorption, bone remodeling, and disease progression. A comprehensive investigation of osteoclast function and regulatory mechanisms can provide novel strategies and targets for OA treatment.

Paederosidic acid, a cyclenyl ether terpene extracted from *Paederia scandens* (Lour.) Merri., exhibits multiple biological activities, including anti-inflammatory, analgesic, and anti-tumor properties. It is utilized in the treatment of RA, pain, and inflammation of the liver and spleen. Research indicates that paederosidic acid demonstrates the potential in alleviating OA by targeting the $P2Y_{14}$ receptor ($P2Y_{14}R$). This mechanism inhibits osteoclast differentiation and dorsal root ganglion nerve damage, leading to significant improvements in cartilage degeneration and neuropathic pain in a monosodium iodoacetate-induced OA model [46].

Betulinic acid, a pentacyclic triterpenoid compound primarily derived from the bark of Betulaceae plants, exhibits a broad spectrum of biological activities, including anti-inflammatory, anti-tumor, antiviral, anti-malarial, anti-diabetic, and antioxidant effects [47]. Research has identified a betulinic acid derivative that can alleviate pain and improve cartilage damage and subchondral bone change in rats with MIA-induced OA model at a dose of 100 μg. Further mechanistic studies have revealed that this derivative can intervene in the activation of pivotal factors IκB/NF-κB and p38 kinase, preventing the subsequent induction of the key osteoclastogenesis regulator nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) and its target genes[48]. Consequently, this betulinic acid derivative may offer a novel approach for developing prospective drug candidates for OA treat-

ment. Xanthatin (XA), a sesquiterpene lactone isolated from *Xanthium strumarium* L., has demonstrated significant anti-tumor activity. Recent studies have shown that XA attenuates pro-inflammatory cytokine release, ECM catabolism, and receptor activator of nuclear factor-κB ligand (RANKL)-mediated osteoclast differentiation *in vitro*. Additionally, XA exhibited a protective effect on human cartilage tissues *in vivo* by inhibiting the STAT3/NF-κB signaling pathway, thus demonstrating therapeutic potential for OA [49,50] (Fig. 2). This suggests that XA may serve as a complementary or alternative therapy for the adjunctive treatment of OA. In summary, XA exhibits anti-inflammatory properties that can mitigate cartilage damage and ameliorate OA in mice or rats through distinct pathways of osteoclasts. Astragalin (AST), a natural flavonoid found in various traditional medicinal and edible plants such as Eucommia ulmoides and Cassia alata, possesses numerous pharmacological functions, including anti-inflammatory, antioxidant, neuroprotective, anti-diabetic, and anticancer properties. AST has been shown to attenuate RANKL osteoclast differentiation and protect against LPS-induced osteolysis in mouse models. Mechanistically, AST inhibits the expression of c-Fos, NFATc1, CTSK, and TRAP during osteoclastogenesis while suppressing RANKL-mediated ROS production by enhancing the expression of Nrf2-mediated ROS scavenging enzymes. Moreover, studies on cytotoxicity and apoptosis have demonstrated that AST does not produce cytotoxicity at 100 μmol·L^{-1}. Therefore, AST may represent a promising therapeutic agent for treating OA [51].

3.3. Macrophage

The relationship between macrophages and OA is intricate and multifaceted. In OA development, macrophages, as immune cells, play a pivotal role in joint inflammation and cartilage degeneration. These cells interact with chondrocytes by secreting inflammatory factors and matrix metalloproteinases, significantly regulating the inflammatory process of OA. Furthermore, the activation status of macrophages and the M1/M2 ratio strongly correlate with OA severity. Consequently, targeting macrophages presents a viable strategy for OA treatment.

The classic formula Si Miao Powder, documented in the book *Singing Convenience Reading* by Zhang Bingcheng, a Qing Dynasty physician, is a traditional remedy for impotence caused by dampness-heat downstream injection. This formula, known for its heat-clearing and dampness-eliminating properties, comprises four herbs: *Atractylodes lancea* (Thunb.) Dc., *Phellodendron amurense* Rom.Caill. Stapf. These herbs are believed to tonify the liver and kidneys, and strengthen tendons and bones. In TCM, Dipsaci Radix and Drynariae Rhizoma are frequently combined to treat osteoporosis, OA, and other orthopedic disorders. The Modified Si Miao Powder (MSMP) incorporates these two herbs into the original Si Miao Powder formula. Research has demonstrated that MSMP mitigated OA progression in mice and MSMP-containing serum modulated macrophage M1/M2 phenotype by inhibiting the NF-κB signaling pathway, providing experimental evidence and potential therapeutic targets for OA treatment [52]. Ji-Ming-Shan (JMS) is a traditional prescription consisting of seven herbs: Areca cathechu Burm.f., *Citrus reticulata* Blanco, *Chaenomeles speciosa* (Sweet) Nakai, *Euodia ruticarpa* (A. Juss.) Benth., *Perilla frutescens* (L.) Britton, *Zingiber officinale* Roscoe, *Platycodon grandifloras* (Jacq.) A.DC. This prescription is commonly used for treating rheumatism, tendon swelling, foot pain, beriberi, chronic nephritis, lower extremity edema, and gout, as well as for eliminating dampness and promoting diuresis. The 95% ethanol extract of Ji-Ming-Shan (JMS-95E) has been extensively studied in both *in vitro* and *in vivo* models to elucidate

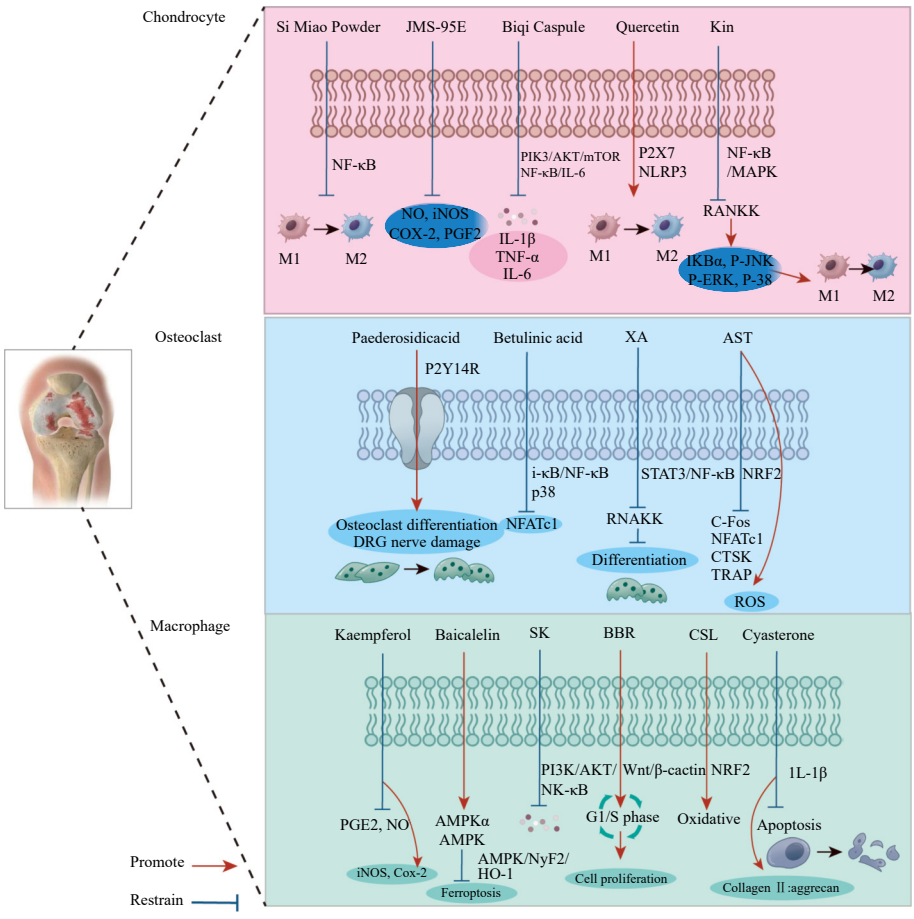

Fig. 2 The mechanism of OA treatment with NPs.

its anti-inflammatory activity. The study revealed that JMS-95E inhibited the inflammatory pathway, reducing the production or expression levels of NO, iNOS, COX-2, and PGE2 in macrophage cells. Cell viability assays indicated that the extract was not toxic at 200 μg·mL^{-1} concentration. Consequently, JMS-95E may be a potential OA treatment due to its multiple pharmacological targets, ability to reduce biochemical markers of inflammation, inhibition of xanthine oxidase, and promotion of recovery after acute inflammation [53]. Biqi Capsule (BQ, NMPA approval number: Z10910026), a TCM formula used clinically for arthritis treatment in China, has shown advantages in attenuating OA progression. BQ comprises 10 Chinese herbs, including *Strychnos nux-vomica* L., *Pheretima aspergillum* (E.Perrier), *Codonopsis pilosula* (Franch.) Nannf, *Poria cocos* (Schw.) Wolf, *Atractylodes macrocephala* Koidz., *Ligusticum chuanxiong* Hort., *Salvia miltiorrhiza*m Bunge, *Panax notoginseng* (Burk.) F.H.Chen, *Achyranthes bidentata* Bl., and *Glycyrrhiza uralensisisch* Fisch.. However, the bioactive components and pharmacological mechanisms underlying its anti-inflammatory and chondroprotective effects remain to be fully elucidated. An *in vivo* study using a papain-induced OA rat model investigated the pharmacological effects and underlying mechanisms of BQ against OA [54]. The results indicated that components such as Brucine, Liquiritin, Salvianolic Acid B, Glycyrrhizic Acid, Cryptotanshinone and Tanshinone IIA (TIIA) in BQ can modulate the NF-κB/IL-6 pathway in macrophages and synovial tissues to exert anti-inflammatory effects. This study provides empirical evidence and a theoretical foundation for the clinical application of BQ, demonstrating its potential as a promising therapeutic option for OA treatment.

Quercetin, a prevalent flavonoid compound found in various plants, demonstrates diverse biological activities, including cytoprotective, antithrombotic, antioxidant, and anticancer effects. Recent research has shown that quercetin exhibits chondroprotective effects in OA by inhibiting inflammation, reducing chondrocyte apoptosis, and inducing synovial macrophage polarization towards the M2 subtype. Further mechanistic investigations revealed that quercetin-induced suppression of transient receptor potential vanilloid (TRPV1) delays OA progression by shifting macrophage polarization from M1 to M2 subtypes through modulation of the purinergic ligand-gated ion channel 7 (P2X7)/nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) pathway. These findings highlight the potential significance of TRPV1 and P2X7 in quercetin's protective mechanisms against OA [55]. Kinsenoside (Kin), an active small-molecule component derived from the traditional Chinese medicinal herb *Apocynum venetum* L., is clinically used to treat liver disease, hyperglycemia, and cancers. A study demonstrated that Kin can influence macrophage polarization to inhibit OA progression. Specific mechanistic research revealed that Kin repolarizes M1 macrophages to M2 by targeting the NF-κB/MAPK pathway, inhibiting the phosphorylation of IκBα, phosphorylated (p)-c-Jun N-terminal kinase (JNK), p-extracellular signal-regulated kinase (ERK), and p-P38 in macrophages, thereby reducing the expression of related inflammatory cytokines. Additionally, Kin attenuates the infiltration of pro-inflammatory M1-type macrophages and articular cartilage degeneration [56]. In conclusion, this study aimed to identify a promising candidate targeting macrophage repolarization for effective OA treatment.

4. Mechanism of RA treatment with NPs based on cells

4.1. T cell

T cells, predominantly cluster of differentiation 4 ($CD4^+$) T cells, are the primary lymphocytes infiltrating rheumatoid joints. Extensive research indicates that abnormalities in peripheral blood lymphocytes, particularly the imbalance between T helper 17 (Th17) and regulatory T (Treg) cell subpopulations, play a crucial role in the onset of RA. Th17 cells secrete pro-inflammatory cytokines such as IL-17 and IL-21, which promote inflammatory responses in RA, leading to articular cartilage and bone destruction. Conversely, Treg cells maintain homeostasis and self-tolerance, inhibiting RA development. The Th17/Treg cell imbalance can trigger articular cartilage and bone destruction, thereby advancing RA progression. Notably, Treg cells from RA patients exhibit impaired function and altered phenotypes, demonstrating increased plasticity towards Th17 cells and reduced suppressive capacity. Consequently, modulating the differentiation and balance of Th17 and Treg cells in RA has emerged as a potential therapeutic approach [57].

Morin, a flavonoid extracted from mulberry plants, exhibits anticancer, antioxidant, and anti-inflammatory properties [58] (Fig. 3). Research indicates that Morin inhibits Th17 differentiation by blocking RORγt binding to the IL-17a gene's promoter and CNS2 region, alleviating CIA through limiting fatty acid synthesis following PPARγ activation. Tetrandrine, a bisbenzylisoquinoline alkaloid, demonstrates anti-tumor, anti-inflammatory, anti-hypertensive, and RA effects [59]. In RA treatment, it attenuates RA-FLS migration and invasion by activating PI3K/Akt and JNK pathways [60]. Another study suggests Tetrandrine, as an AhR ligand, modulates the Th17/Treg cell balance, exerting anti-arthritic effects [61]. SIN, an active alkaloid from TCM, is widely used in China for various rheumatic diseases, exhibiting anti-inflammatory, analgesic, and anti-tumor effects. SIN activates the PI3K/Akt/mTOR pathway, enhancing vasoactive intestinal polypeptide (VIP) generation in the gut. VIP subsequently enters systemic circulation, mitigating RA inflammatory response [62]. Furthermore, SIN-enriched beneficial bacteria *L. paracasei* and *L. casei* upregulate microbial tryptophan metabolites, activating AhR and regulating Th17/Treg cell balance in CIA rats [63]. Nuciferine, an alkaloid found in lotus leaf, demonstrates anti-inflammatory and anti-tumor effects. Research shows Nuciferine improves collagen-induced bone erosion, decreases pro-inflammatory cytokines and serum immunoglobulins, and restores Th17/Treg cell balance in CIA rat spleens, indicating potential therapeutic benefits for RA. The main component of Clematidis radix et Rhizoma is triterpenoid saponins [64]. Studies show that total Clematis triterpenoid saponins (CTSs) significantly ameliorate joint lesions, alleviate arthritis-related flora disorders, and interfere with metabolic pathways, including glycerophospholipid catabolism, sphingolipid metabolism, and arachidonic acid metabolism [65, 66]. Clematichinenoside AR (C-AR) is the most abundant CTS constituent [67]. Li et al. demonstrated that C-AR improves RA symptoms by increasing Treg cell proportion in AIA rats [68] and inhibits inflammation and fibrosis by preventing NLRP3 inflammasome activation [69].

4.2. Macrophage

Macrophages play a pivotal role in the pathogenesis of RA, contributing to various aspects of the disease, including the initiation and perpetuation of synovitis and the progression of joint damage. In RA, synovial macrophages exhibit beneficial effects through immunomodulation and enhanced phagocytic capacity, potentially aiding in the clearance of cartilage and bone debris, thus supporting joint function. During RA inflammation, M1 macrophages contribute to the destruction of articular cartilage and bone by secreting pro-inflammatory cytokines and chemokines. Conversely, M2 macrophages may promote the resolution of inflammation and tissue repair. An imbalance in the M1/M2 macrophage ratio in RA patients can exacerbate the inflammatory response. Modulating macrophage polarization may help restore immune balance and mitigate inflammatory responses, thereby improving the condition of RA patients.

Longteng Decoction (LTD), a Chinese herbal formula, comprises six key components: *Dioscorea nipponica* Makino, *Lonicera*

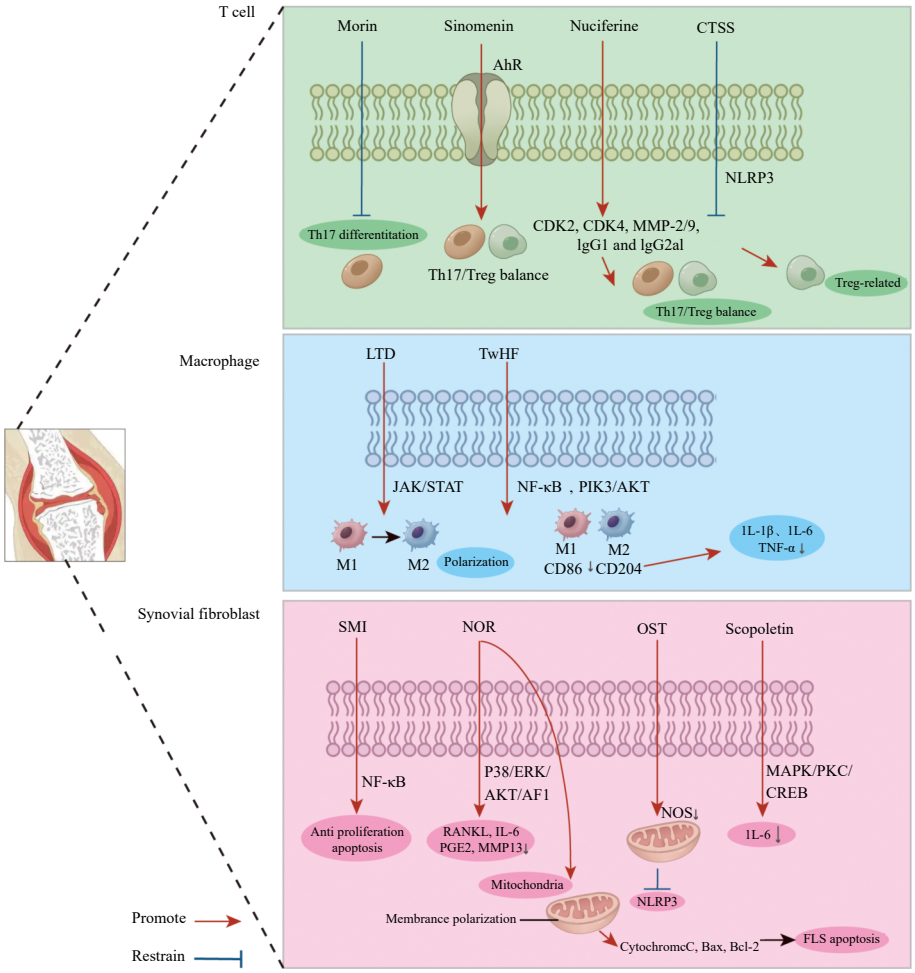

Fig. 3 The mechanism of RA treatment with NPs.

japonica Thunb., *Sinomenium acutum* (Thunb.) Rehd.et wils., *Paeonia lactiflora* Pall., *Artemisia annua* L., and *Trachelospermum jasminoides* (Lindl.) Lem.. Research has demonstrated LTD's efficacy in treating RA, showing its ability to reduce inflammatory joint swelling in CIA mice, inhibit synovial tissue inflammation infiltration, and mitigate cartilage damage. The primary mechanisms may involve regulating ILC2s and Th cell proliferation, modulating JAK/STAT signaling pathway activation, promoting M1-type macrophage transformation into anti-inflammatory M2 phenotype, suppressing pro-inflammatory factor secretion, and restoring RA tissue environment homeostasis [70]. Clinical studies have further indicated that LTD can decrease joint pain index and swelling degree, reduce morning stiffness duration, inhibit disease progression, lower erythrocyte sedimentation rate, and enhance patients' quality of life. Additionally, LTD can influence Th17 and Treg cell proliferation in peripheral blood and significantly improve hemorheology-related indicators [71]. These findings suggest that LTD may serve as a potential supplement or alternative to traditional RA treatments. *Tripterygium wilfordii* Hook F (TwHF), known as "Lei-gong-teng" in China, is a member of the Celastraceae family. It possesses properties for dispelling wind, eliminating dampness, promoting blood circulation, reducing swelling, alleviating pain, and killing worms. TwHF has been widely employed in treating systemic autoimmune diseases, including RA [72]. Studies have shown that TwHF significantly reduces joint pain, swelling, tenderness, morning stiffness, fatigue, and joint focus points in RA patients. Moreover, *in vivo* mechanistic studies revealed that TwHF treatment significantly decreased CD86 expression in M1 macrophages and increased CD204 expression in M2 macrophages, thereby reducing immune cell infiltration in RA synovial tissue. TwHF intervention also reduced joint symptoms, arthritis index, and toe swelling in AA rats [72]. Furthermore, TwHF has been investigated in clinical trials (NCT00062465), suggesting its potential as a herbal preparation for RA treatment.

4.3. FLS

Synovial fibroblasts (FLS) produce various inflammatory mediators, including TNF-α and IL-1β, which exacerbate synovial inflammation and joint destruction. FLS also regulate the activity of immune cells in the RA immune response. Additionally, they directly contribute to joint degradation. Consequently, therapeutic approaches targeting synovial fibroblasts may offer novel treatment options for RA patients.

Salvia miltiorrhiza (SM), a TCM, is widely utilized for treating and preventing age-related conditions, including cardiovascular and cerebrovascular diseases, as well as cancer [73]. SM has gained approval and usage in Japan, the United States, and several European countries. In China and other Asian nations, SM-derived medicines, such as drip-pill and injectable formulations (Salvia miltiorrhiza Injection, SMI), have been developed and clinically applied. SMI's active components include tanshinol, salvianolic acid B, tanshinone, dihydrotanshinone, ursolic acid, and cryptotanshinone. Research indicates that SMI can inhibit proliferation in RA FLS by inducing apoptotic signaling pathways, restoring normal apoptotic function, and promoting apoptosis [74]. These findings suggest potential therapeutic applications of

Salvia miltiorrhiza Injection in RA treatment. Norisoboldine (NOR), an isoquinoline alkaloid extracted from the traditional Chinese medicinal plant Ligusticum, demonstrates anti-inflammatory, anti-tumor, and fracture healing properties and is commonly used in RA treatment. NOR has been shown to alleviate joint injury by reducing the expression of RANKL, IL-6, PGE2, and matrix metalloproteinase 13 (MMP13) *via* the p38/ERK/AKT/AP-1 pathway [75]. Luo et al. found that NOR induced the loss of depolarized mitochondrial membrane potential, mediating cytochrome C release and Bax and Bcl-2 protein expression, ultimately promoting FLS apoptosis and interfering with RA [76]. Osthole, a coumarin derivative found in medicinal plants such as Cnidium monnieri and Angelica pubescens, can be obtained through extraction, separation, or total synthesis. Extensive research has demonstrated osthole's diverse biological activities, including anti-tumor, anti-inflammatory, neuroprotective, osteogenic, cardiovascular protective, antimicrobial, and antiparasitic effects. Studies have shown that osthole inhibits NLRP3 inflammasome activation by regulating mitochondrial homeostasis and function. Additionally, osthole promotes FLS apoptosis and reduces ROS production to treat RA [77]. Scopoletin, also known as 6-methoxy-7 hydroxycoumarin, is a naturally occurring coumarin found in many edible plants. It exhibits a wide range of pharmacological effects, including anti-inflammatory, antioxidant, anti-tumor, anti-diabetic, anti-hypertensive, hepatoprotective, and neuroprotective properties. Research has demonstrated its anti-RA effects through inhibition of IL-6 production in FLS *via* the MAPK/PKC/CREB pathway [78]. Collectively, these coumarin natural ingredients show promise as candidate drugs for RA treatment. Tetrandrine, a bisbenzylisoquinoline alkaloid, has demonstrated anti-tumor, anti-inflammatory, anti-hypertensive, and anti-RA effects. It has been used clinically to treat silicosis for over 50 years, exhibiting significant anti-fibrotic effects on the lungs. In RA treatment, tetrandrine has been shown to attenuate RA-FLS migration and invasion by activating the PI3K/Akt and JNK pathways [60].

5. Mechanism of GA treatment with NPs based on cells

5.1. Macrophage

Macrophages play a crucial role in the pathogenesis of GA. These immune cells recognize and phagocytose urate crystals, thereby promoting an inflammatory response and activating the NALP3 inflammasome. Macrophages exhibit high plasticity, capable of polarizing into diverse phenotypes in response to changes in their microenvironment. During the initiation of GA, macrophages can polarize into M1 phenotypes, which enhance the recruitment and activation of inflammatory cells by releasing pro-inflammatory cytokines. This process exacerbates the inflammatory response in GA, leading to inflammation and pain in the joints. Conversely, M2 macrophages secrete anti-inflammatory cytokines and growth factors, such as TGF-β and vascular endothelial growth factor, which contribute to reducing inflammatory responses and promoting tissue repair. Recent research indicates that certain NPs can exert therapeutic effects by indirectly influencing macrophage activity, either through inhibition of inflammatory mediator release or by modulation of macrophage immunophenotypes.

Simiao Pill, a classic TCM prescription for treating acute GA, primarily comprises *Atractylodes lancea* (Thunb.) Dc., *Phellodendron chinense* Schneid., *Achyranthes bidentata* Bl., and *Coixlacryma-jobiL.var.mayuen* (Roman.) Stapf. Research has demonstrated that Simiao pill can alleviate MSU-induced GA and inhibit HUA. Further investigation suggests that its anti-inflammatory mechanism may involve promoting M2 macrophage polarization through PI3K/Akt signaling [79] (Fig. 4). Dioscorea nipponica Makino, a perennial twining herb, has underground tubers widely utilized in traditional medicine. These tubers contain diosgenin, a significant NP with diverse pharmacological effects, including the treatment of coronary heart disease, anti-atherosclerosis, lipid-lowering, immune regulation, anti-tumor, and anti-inflammatory properties, which has been extensively applied in the clinical treatment of GA. Mechanistic studies indicate that the total saponin fraction from Dioscorea nipponica Makino reduces inflammation by modulating the NALP3 inflammasome, a crucial factor associated with GA pathogenesis. Additionally, Dioscorea nipponica Makino has been reported to decrease serum levels of IL-1β, TNF-α, LTB4, and PGE2 while increasing IL-4 and IL-10 through regulation of M1 and M2 macrophage proportions [80].

BQ, a therapeutic drug approved in China (Drug approval number: Z10910026), consists of *Salvia miltiorrhiza* Bge., *Strychnos nux-vomica* L., *Glycyrrhiza uralensis* Fisch., *Codonopsis pilosula* (Franch.) Nannf., and *Atractylodes macrocephala* Koidz.. BQ demonstrates anti-inflammatory, uric acid-lowering, and pain-relief properties. Brucine, a major active component of BQ, exhibits anti-inflammatory and analgesic effects, indicating potential for GA treatment. Mechanistic studies reveal that Brucine mitigates inflammation by inhibiting NLRP3/NF-κB pathway activation and downregulating inflammatory factor expression [81]. BBR, an alkaloid isolated from *Coptis chinensis* Franch., possesses anti-inflammatory properties. BBR is clinically recognized for its diverse effects, including anti-heart failure, anti-arrhythmic, cholesterol-lowering, and anti-tumor properties. Research demonstrates BBR's impact on MSU crystal-stimulated RAW 264.7 macrophages, affecting pro-inflammatory cytokines, intracellular ROS levels, inflammatory proteins, and the Nrf2 transcription factor. BBR also reduced midpaw volume, pain score, and joint elastase and pro-inflammatory cytokine levels in MSU crystal-induced rats, highlighting its potential in GA treatment. Alantolactone, an NLRP3 inhibitor derived from *Saussurea lappa*, shows promise in treating NLRP3-driven arthritis in gout. Studies characterize alantolactone as an effective and selective inhibitor of NLRP3 inflammasomes, reducing inflammatory cytokine release and preventing macrophage cell death [82]. These findings suggest potential clinical applications for alantolactone in GA treatment, though further studies are needed to validate its safety and efficacy in humans. Total glucosides of paeony (TGP), a bioactive compound extracted from paeony roots, have demonstrated anti-inflammatory and immune regulatory effects. Research indicates that TGP protects THP-1 macrophages from MSU-induced injury and inflammation by targeting the MALAT1/micro ribonucleic acid (miR)-876-5p/NLRP3 axis and TLR4/MyD88/NF-κB pathway, providing a foundation for TGP's application in GA treatment [83]. Taxifolin, a natural flavonoid compound found in various fruits, possesses diverse biochemical and pharmacological effects, including anti-inflammatory properties and protection against oxidative stress-induced apoptosis. Studies reveal taxifolin's ability to mitigate the inflammatory response in MSU crystal-induced acute gout models by reducing pro-inflammatory cytokine production, enhancing macrophage autophagy and phagocytosis, and inhibiting NLRP3 inflammasome activation [84].

5.2. Neutrophil

Neutrophils, the primary leukocytes to arrive at inflammatory sites during acute GA, play a significant role in the pathogenesis of gout arthritis. These cells contribute to the disease progression through the formation of neutrophil extracellular traps (NETs), the release of pro-inflammatory cytokines and chemokines, and the exacerbation of the inflammatory response. Interestingly, NETs exhibit a dual function in GA. While they can promote inflammatory responses, they can also inhibit inflammation by forming aggregated NETs. Consequently, numerous NPs have

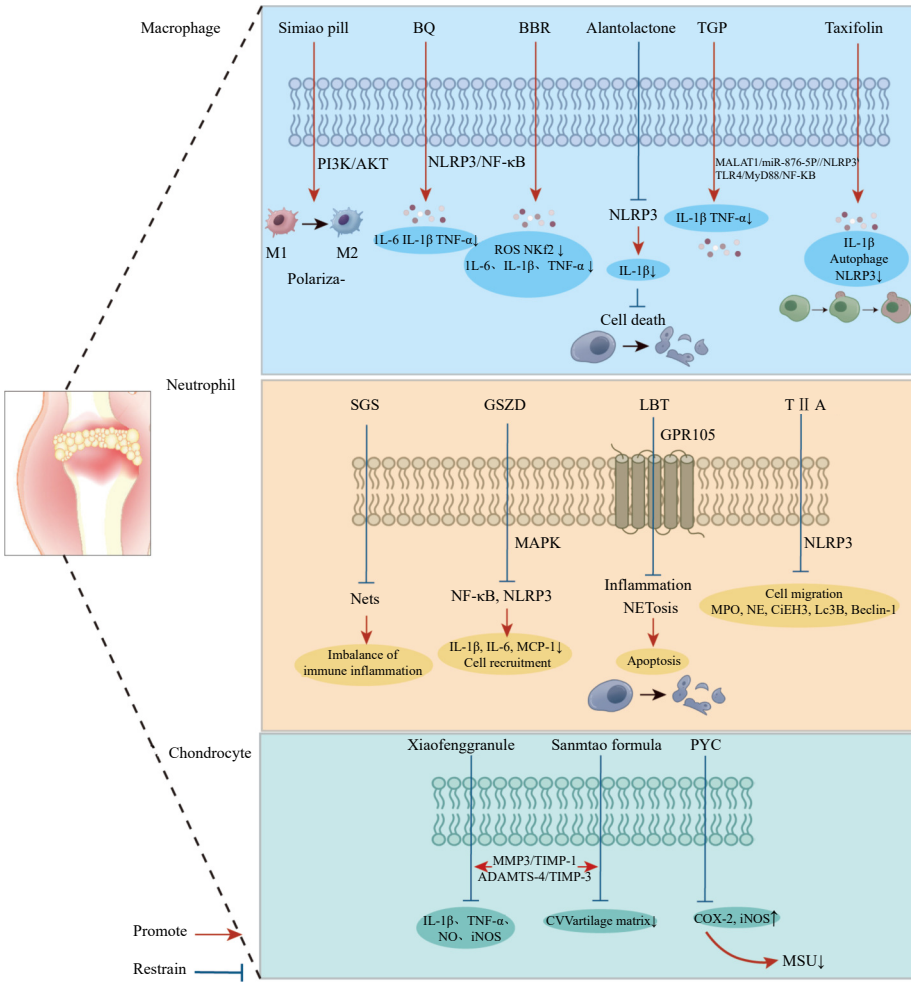

Fig. 4 The mechanism of GA treatment with NPs.

been found to alleviate GA symptoms by modulating NET formation.

Shirebi Granules (SGs, National Medical License No. Z20044062), derived from the classic prescription Simiaowan, comprise 12 Chinese herbs. *Atractylodes macrocephala* Koidz. and *Phellodendron chinense* Schneid. serve as the primary components, while *Forsythiae suspensa* (Thunb.) Vahl, *Dioscoreae oppositа* Thunb., *Coicis lacryma-jobi* L. var. *mayuen* (Roman.) Stapf, and *Stephaniae tetrandrae* S.Moorre function as ministerial drugs. *Morus alba* L., *Saposhnikovia divaricata* (Turcz.) Schischk., *Clematis chinensis* Osbeck., *Lonicera macranthoides* Hand.-Mazz, and *Cyathula officinalis* Kuan act as adjuvant drugs. This herbal combination aims to eliminate wind and dampness, clear heat, reduce swelling, clear collaterals, and alleviate pain. In 2020, the China National Medical Products Administration approved SGs for treating arthralgia accompanied by damp-heat syndrome. It is widely employed in the clinical treatment of rheumatism, OA, and gout [85]. A clinical study involving 402 participants demonstrated SGs' efficacy in reducing blood uric acid levels, joint pain, swelling, dysfunction, and fever in patients with acute GA. However, limited research on SGs' mechanisms restricts its widespread application. Recent studies suggest that SGs may effectively mitigate acute GA severity by suppressing NETs-promoted imbalance between immunity and inflammation. These findings not only expand SGs' potential clinical indications but also benefit acute GA therapy through clinical pharmacology in drug repurposing. TIIA, a primary active component in *Salvia miltiorrhiza*, exhibits anti-inflammatory, antioxidant, antibacterial, and anti-cardiovascular properties. A study examining the drug repurposing. TIIA's preventive and therapeutic effects on acute GA revealed that it can alleviate synovial hyperplasia and neutrophil infiltration, regulate cytokine and chemokine expressions, and inhibit NLRP3 activation in acute GA rats. Additionally, TIIA affected neutrophil migration, MPO, NE, and CitH3 expression, as well as LC3B and Beclin-1 protein expression [86]. These findings suggest that TIIA may serve as a potential therapeutic agent for acute GA.

Guizhi-Shaoyao-Zhimu Decoction (GSZD) is a TCM prescription comprising *Cinnamomum cassia* Presl, *Paeonia suffruticosa* Andr., *Glycyrrhiza uralensis* Fisch., *Ephedra sinica* Stapf, *Zingiber officinale* Rosc., *Atractylodes lancea* (Thunb.) Dc., *Atractylodes macrocephala* Koidz., *Paeonia lactiflora* Pall., *Aconitum carmichaelii* Debx.. It is commonly utilized in TCM for treating various forms of arthritis. *In vivo* studies demonstrate that GSZD significantly reduces neutrophil recruitment and levels of IL-1β, IL-6, and MCP-1 in peritoneal exudates of MIP mice. The anti-GA effect of GSZD is linked to the inhibition of NF-κB and NLRP3 inflammasome activation *via* the MAPK signaling pathway [87]. Lobetyolin (LBT), a bioactive compound isolated from *Codonopsis pilosula* (Franch.) Nannf., exhibits anti-inflammatory, antioxidant, and xanthine oxidase inhibitory properties [88]. While primarily studied for its anticancer properties, particularly its potential to inhibit tumor cell proliferation and induce apoptosis, LBT has recently been found to play a significant role in acute GA. Research indicates that LBT, as a potent G-protein coupled receptor 105 (GPR105) antagonist, can suppress MSU-induced acute GA by inhibiting neutrophil inflammatory activities. Studies reveal that LBT treatment in rats significantly reduces joint swelling and leukocyte levels. Furthermore, LBT inhibits neutrophil NETosis and promotes apoptosis recruitment. As a GPR105 antagonist, LBT shows promise as a potential therapeutic agent for acute

GA [89]. However, further investigation is necessary to elucidate the molecular-level interaction between GPR105 and LBT to verify its therapeutic potential.

5.3. Chondrocyte

Chondrocytes play a crucial role in the inflammatory response of GA, contributing to inflammation-mediated joint damage through the secretion of various inflammatory factors, including PGE2 and IL-6. Certain NPs significantly influence the pathogenesis of GA by modulating the inflammatory response of chondrocytes and mitigating cartilage damage.

Xiaofeng granule is a novel preparation primarily composed of *Phellodendron chinense* Schneid., *Atractylodes lancea* (Thunb.) Dc., *Coix lacryma-jobiL.var.mayuen* (Roman.) Stapf, *Achyranthes bidentata* Bl., *Ampelopsisjaponica* (Thunb.) Makino, and *Lonicera japonica* Thunb. Contemporary pharmacological studies have revealed that Xiaofeng granules contain numerous flavonoids and phenolic compounds with anti-GA properties. Research demonstrates that Xiaofeng granules significantly reduce swelling rates and mitigate joint pathological changes. Furthermore, both *in vivo* and *in vitro* studies indicate that it inhibits the activation of pro-inflammatory mediators in chondrocytes and regulates the balance between MMP-3/tissue inhibitor of metalloproteinase (TIMP)-1 and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 4 (ADAMTS-4)/TIMP-3 in chondrocytes [90]. The Sanmiao formula, renowned for its heat-clearing and dampening properties, comprises Phellodendron amurense, Atractylodes rhizome, and Achyranthes bidentata. Studies have shown that the Sanmiao formula ameliorates GA by suppressing inflammation and preventing the loss of cartilage matrix components. Mechanistic investigations reveal that the Sanmiao formula modulates the balance between MMP-3/TIMP-1 and ADAMTS-4/TIMP-3 in chondrocytes, thereby effectively inhibiting degradation of the cartilage matrix in GA and protecting chondrocytes [91].

Pycnogenol (PYC) is a standardized extract derived from the bark of the French maritime pine (*Pinus pinaster* Ait.). Its primary constituents include phenolic compounds such as catechin, epicatechin, taxifolin, procyanidins, proanthocyanidin, and various acids, including caffeic, ferulic, and p-hydroxybenzoic acid. Numerous *in vitro* and clinical studies suggest PYC's potential therapeutic value in treating various conditions, including cardiovascular disease and inflammatory disorders. PYC has demonstrated efficacy in alleviating symptoms in OA patients and has been proposed as an effective adjuvant treatment to facilitate the reduction of NSAID or COX-2 inhibitor therapy. Recent research has elucidated the mechanisms of PYC's effects on articular chondrocytes both *in vitro* and *in vivo*. The study found that PYC mitigated MSU-induced acute inflammation by inhibiting inflammatory cell infiltration and the expression of COX-2 and iNOS in synovial tissue and articular cartilage [92]. Collectively, these findings suggest that PYC may hold significant potential in the treatment of GA.

6. Discussion and Perspective

Arthritis is an inflammatory syndrome characterized primarily by acute or chronic joint pain, leading to programmed joint necrosis. It is closely associated with degenerative diseases, autoimmune disorders, and metabolic abnormalities, among other factors, and has a high incidence and disability rate. Research indicates that numerous NPs significantly inhibit inflammatory responses and can ameliorate various types of arthritis through anti-inflammatory, antioxidant, and immunoregulatory mechanisms. Therefore, reassessing the crucial role of NPs in drug development has significant implications for arthritis drug research and development. This article reviews the effects of NPs on regulating various cell types' functions and their molecular mechanisms in arthritis treatment. Studies have found that NPs exert anti-inflammatory effects in OA primarily by modulating chondrocyte inflammatory responses, osteoclast immunomodulatory functions, and macrophage polarization, thereby mitigating inflammatory responses and cartilage damage [29, 30, 45]. In RA, NPs mainly target T cells and macrophages, regulating the Th17/Treg cell balance and macrophage polarization. Additionally, some studies have shown that NPs can improve RA by regulating synovial fibroblast apoptosis [57]. In GA, NPs' mechanism of action involves regulating macrophage polarization, inhibiting NET formation, and suppressing pro-inflammatory mediator activation in chondrocytes [93, 94]. These effects collectively inhibit the inflammatory response, thereby further impeding GA onset and progression. OA, RA, and GA are three common inflammatory arthritis types with similar symptoms, such as pain, tenderness, swelling, and stiffness. However, their pathogenesis differ, and consequently, NPs play distinct roles in their treatment. For instance, Quercetin regulates pro-inflammatory factor levels, inhibits chondrocyte apoptosis, slows cartilage degeneration, and maintains articular cartilage ECM integrity. It can also inhibit NO production and iNOS expression in chondrocytes, exerting an anti-arthritic effect [55]. In RA treatment, Quercetin primarily exerts its anti-inflammatory effects by regulating the NF-κB pathway, inhibiting ERK phosphorylation, decreasing pro-inflammatory cytokine expression, inhibiting FLS migration and invasion, suppressing neutrophil activity, and blocking ROS production and autophagy by regulating the miR-146a/GATA6 axis [95]. In GA treatment, Quercetin can inhibit pro-inflammatory cytokine expression, reduce NO production, decrease malondialdehyde (MDA) levels (the end product of LPO), increase antioxidant enzyme activity, and effectively diminish uric acid levels [96]. In summary, Quercetin acts through multiple mechanisms in treating these three arthritis types. Importantly, compared to approved therapeutic drugs, the multi-targeting characteristic of NPs enables them to have two or more therapeutic mechanisms in arthritis treatment, maximizing therapeutic efficacy.

NPs exhibit a diverse range of structures and biological activities. For instance, apigenin, an edible flavonoid, demonstrates various pharmaceutical properties, including anti-inflammatory, antioxidant, antimicrobial, and anticancer effects [97]. Many NPs are characterized by low cytotoxicity and high safety indices. Cinnamic acid, for example, is a natural compound with low toxicity that has shown the ability to suppress systemic inflammation [98, 99]. NPs have been a significant source for drug discovery, with the utilization of NPs and their derivatives being one of the primary approaches in new drug research and development [100]. Between 1981 and 2020, 33.5% of approved small-molecule drugs in the anti-tumor field were NPs or NP derivatives. This proportion increased to 64.9% when including NP-simulated compounds and synthetic compounds with NP pharmacophores. In the treatment of arthritis, NPs have demonstrated promising applications and potential therapeutic value. Arthritis involves multiple processes, including signaling pathways, inflammatory responses, immune regulation, and oxidative stress, among others. These can be addressed by inhibiting inflammatory factor release, decreasing ECM catabolism, enhancing anti-inflammatory factor production, or reducing bone erosion.

Despite their potential, NPs face several challenges. The sourcing of NPs is often inconsistent, extraction costs are high, and some medicinal plants and fungi are at risk of extinction. Additionally, NPs frequently exhibit poor solubility, stability, and bioactivity, limiting their therapeutic potential and market viability [98, 101]. Nevertheless, the past decade has witnessed notable progress in preclinical studies of NPs. Future research directions should include further investigation of specific mechanisms of action, particularly at the molecular level. More extensive clinical

trials are necessary to validate the efficacy and safety of NPs in human subjects. Moreover, to address the limited bioavailability of NPs' active compounds, it is crucial to explore innovative delivery systems such as hydrogels and liposomes. Future studies could potentially focus on integrating biomaterials with NPs to enhance drug utilization and overall therapeutic effectiveness.

Natural-derived active molecules have demonstrated significant advancements in the research and development of novel anti-arthritis drugs over the past decade, presenting promising application prospects and development potential. However, the specific pharmacological mechanisms and drug targets of these compounds remain largely unknown. Further elucidation of these aspects requires an interdisciplinary approach, combining chemical biology, cell biology, molecular pharmacology, and related fields to unravel the underlying mechanisms.

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Declaration of competing interest

These authors have no conflict of interest to declare.

References

1 Huang X, Zhang W. Macrophage membrane-camouflaged biomimetic nanovesicles for targeted treatment of arthritis. *Ageing Res Rev*. 2024;95:102241. https://doi.org/10.1016/j.arr.2024.102241.
2 Wirth T, Lafforgue P, Pham T. NSAID: current limits to prescription. *Joint Bone Spine*. 2024;91(4):105685. https://doi.org/10.1016/j.jbspin.2023.105685.
3 Liu H, Huang M, Xin D, et al. Natural products with anti-tumorigenesis potential targeting macrophage. *Phytomedicine*. 2024;131:155794. https://doi.org/10.1016/j.phymed.2024.155794.
4 Benjamin MAZ, Mohd Mokhtar RA, Iqbal M, et al. Medicinal plants of Southeast Asia with anti-α-glucosidase activity as potential source for type-2 diabetes mellitus treatment. *J Ethnopharmacol*. 2024;330:118239 https://doi.org/10.1016/j.jep.2024.118239.
5 Mohamed Yusof NIS, Mohd Fauzi F. Nature's toolbox for Alzheimer's disease: a review on the potential of natural products as Alzheimer's disease drugs. *Neurochem Int*. 2024;176:105738. https://doi.org/10.1016/j.neuint.2024.105738.
6 Gandhi GR, Jothi G, Mohana T, et al. Anti-inflammatory natural products as potential therapeutic agents of rheumatoid arthritis: A systematic review. *Phytomedicine*. 2021;93:153766. https://doi.org/10.1016/j.phymed.2021.153766.
7 Xu W, Chen S, Wang X, et al. Effects of sinomenine on the proliferation, cytokine production, and regulatory T-cell frequency in peripheral blood mononuclear cells of rheumatoid arthritis patients. *Drug Dev Res*. 2020;82(2):251-258. https://doi.org/10.1002/ddr.21748.
8 Lv X, Wang X, Wang X, et al. Research progress in arthritis treatment with the active components of Herba siegesbeckiae. *Biomed Pharmacother*. 2023;169:115939 https://doi.org/10.1016/j.biopha.2023.115939.
9 Yuandani, Jantan I, Salim E, et al. Mechanistic insights into anti-inflammatory and immunosuppressive effects of plant secondary metabolites and their therapeutic potential for rheumatoid arthritis. *Phytother Res*. 2024;38(6):2931-2961. https://doi.org/10.1002/ptr.8147.
10 Wang S, Liu W, Wei B, et al. Traditional herbal medicine: therapeutic potential in acute gouty arthritis. *J Ethnopharmacol*. 2024;330:118182. https://doi.org/10.1016/j.jep.2024.118182.
11 Koike M, Nojiri H, Kanazawa H, et al. Correlation of the total superoxide dismutase activity between joint fluid and synovium in end-stage knee osteoarthritis. *Sci Rep*. 2024;14(1):12093. https://doi.org/10.1038/s41598-024-62614-x.
12 Vincent TL, Miller RE. Molecular pathogenesis of OA pain: past, present, and future. *Osteoarthritis Cartilage*. 2024;32(4):398-405. https://doi.org/10.1016/j.joca.2024.01.005.
13 Quicke JG, Conaghan PG, Corp N, et al. Osteoarthritis year in review 2021: epidemiology & therapy. *Osteoarthritis Cartilage*. 2022;30(2):196-206. https://doi.org/10.1016/j.joca.2021.10.003.
14 Weng Q, Chen Q, Jiang T, et al. Global burden of early-onset osteoarthritis, 1990–2019: results from the Global Burden of Disease Study 2019. *Ann Rheum Dis*. 2024;83(7):915-925. https://doi.org/10.1136/ard-2023-225324.
15 Xiao L, Lin S, Xu W, et al. Downregulation of Sox8 mediates monosodium urate crystal-induced autophagic impairment of cartilage in gout arthritis. *Cell Death Discov*. 2023;9(1):95. https://doi.org/10.1038/s41420-023-01388-z.
16 Takahashi I, Takeda K, Toyama T, et al. Histological and immunohistochemical analyses of articular cartilage during onset and progression of pre- and early-stage osteoarthritis in a rodent model. *Sci Rep*. 2024;14(1):10568. https://doi.org/10.1038/s41598-024-61502-8.
17 Starodubtseva IA, Vasilieva LV, Nikitin AV. The analysis of efficacy of the use of inhibitor interleukin-1 in the complex therapy of secondary osteoarthritis taking into account the dynamics of clinical and functional indicators. *Vestn Ross Akad Med Nauk*. 2016;71(2):141-147. https://doi.org/10.15690/vramn580.
18 Cen X, Liu Y, Wang S, et al. Glucosamine oral administration as an adjunct to hyaluronic acid injection in treating temporomandibular joint osteoarthritis. *Oral Dis*. 2017;24(3):404-411. https://doi.org/10.1111/odi.12760.
19 Drosos AA, Voulgari PV, Alamanos Y, et al. Epidemiology and risk factors for rheumatoid arthritis development. *Mediterr J Rheumatol*. 2023;34(4):404-413. https://doi.org/10.31138/mjr.301223.eaf.
20 Hong J, Luo F, Du X, et al. The immune cells in modulating osteoclast formation and bone metabolism. *Int Immunopharmacol*. 2024;133:112151. https://doi.org/10.1016/j.intimp.2024.112151.
21 Zheng Y, Wei K, Jiang P, et al. Macrophage polarization in rheumatoid arthritis: signaling pathways, metabolic reprogramming, and crosstalk with synovial fibroblasts. *Front Immunol*. 2024;15:1394108. https://doi.org/10.3389/fimmu.2024.1394108.
22 Favalli EG, Maioli G, Caporali R. Biologics or janus kinase inhibitors in rheumatoid arthritis patients who are insufficient responders to conventional anti-rheumatic drugs. *Drugs*. 2024;84(8):877-894. https://doi.org/10.1007/s40265-024-02059-8.
23 Ragab G, Elshahaly M, Bardin T. Gout: an old disease in new perspective – a review. *J Adv Res*. 2017;8(5):495-511. https://doi.org/10.1016/j.jare.2017.04.008.
24 Wang W, Liu C, Li H, et al. Discovery of novel and potent P2Y14R antagonists *via* structure-based virtual screening for the treatment of acute gouty arthritis. *J Adv Res*. 2020;23:133-142. https://doi.org/10.1016/j.jare.2020.02.007.
25 Liu YR, Wang JQ, Li J. Role of NLRP3 in the pathogenesis and treatment of gout arthritis. *Front Immunol*. 2023;14:1137822. https://doi.org/10.3389/fimmu.2023.1137822.
26 Zhao J, Wei K, Jiang P, et al. Inflammatory response to regulated cell death in gout and its functional implications. *Front Immunol*. 2022;13:888306. https://doi.org/10.3389/fimmu.2022.888306.
27 Yang CY, Chen CH, Deng ST, et al. Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med*. 2015;175(9):1550-7. https://doi.org/10.1001/jamainternmed.2015.3536.
28 Chung WH, Chang WC, Stocker SL, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis*. 2015;74(12):2157-2164. https://doi.org/10.1136/annrheumdis-2014-205577.
29 Ji Q, Zheng Y, Zhang G, et al. Single-cell RNA-seq analysis reveals the progression of human osteoarthritis. *Ann Rheum Dis*. 2019;78(1):100-110. https://doi.org/10.1136/annrheumdis-2017-212863.
30 Chen Y, Yu Y, Wen Y, et al. A high-resolution route map reveals distinct stages of chondrocyte dedifferentiation for cartilage regeneration. *Bone Res*. 2022;10(1):38. https://doi.org/10.1038/s41413-022-00209-w.
31 Alam W, Khan H, Shah MA, et al. Kaempferol as a dietary anti-inflammatory agent: current therapeutic standing. *Molecules*. 2020;25(18):4073. https://doi.org/10.3390/molecules25184073.
32 Zhuang Z, Ye G, Huang B. Kaempferol alleviates the interleukin-1β-induced inflammation in rat osteoarthritis chondrocytes *via* suppression of NF-κB. *Med Sci Monit*. 2017;23:3925-3931. https://doi.org/10.12659/MSM.902491.
33 Lee CY, Chang YC, Yang KC, et al. Development and functional evaluation of a hyaluronic acid coated nano-formulation with kaempferol as a novel intra-articular agent for Knee Osteoarthritis treatment. *Biomed Pharmacother*. 2024;175:116717. https://doi.org/10.1016/j.biopha.2024.116717.
34 Xu T, Ge X, Lu C, et al. Baicalein attenuates OVA-induced allergic airway inflammation through the inhibition of the NF-κB signaling pathway. *Aging (Albany NY)*. 2019;11(21):9310-9327. https://doi.org/10.18632/aging.102371.
35 Wang CZ, Zhang CF, Luo Y, et al. Baicalein, an enteric microbial metabolite, suppresses gut inflammation and cancer progression in Apc(Min/+) mice. *Clin Transl Oncol*. 2020;22(7):1013-1022. https://doi.org/10.1007/s12094-019-02225-5.
36 Wan Y, Shen K, Yu H, et al. Baicalein limits osteoarthritis development by inhibiting chondrocyte ferroptosis. *Free Radic Biol Med*. 2023;196:108-120. https://doi.org/10.1016/j.freeradbiomed.2023.01.006.
37 Toledo AC, Sakoda CP, Perini A, et al. Flavonone treatment reverses airway inflammation and remodelling in an asthma murine model. *Br J Pharmacol*. 2013;168(7):1736-1749. https://doi.org/10.1111/bph.12062.
38 Deng X, Qu Y, Li M, et al. Sakuranetin reduces inflammation and chondrocyte dysfunction in osteoarthritis by inhibiting the PI3K/AKT/NF-κB pathway. *Biomed Pharmacother*. 2024;171:116194. https://doi.org/10.1016/j.biopha.2024.116194.
39 Liu Y, Hua W, Li Y, et al. Berberine suppresses colon cancer cell proliferation by inhibiting the SCAP/SREBP-1 signaling pathway-mediated lipogenesis. *Biochem Pharmacol*. 2020;174:113776. https://doi.org/10.1016/j.bcp.2019.113776.
40 Xiao M, Men LN, Xu MG, et al. Berberine protects endothelial progenitor cell from damage of TNF-α *via* the PI3K/AKT/eNOS signaling pathway. *Eur J Pharmacol*. 2014;743:11-16. https://doi.org/10.1016/j.ejphar.2014.09.024.
41 Zhou Y, Tao H, Li Y, et al. Berberine promotes proliferation of sodium nitroprusside-stimulated rat chondrocytes and osteoarthritic rat cartilage *via* Wnt/β-catenin pathway. *Eur J Pharmacol*. 2016;789:109-118. https://

doi.org/10.1016/j.ejphar.2016.07.027.
42 Liu M, Guo J, Zhao J, et al. Activation of NRF2 by celastrol increases antioxidant functions and prevents the progression of osteoarthritis in mice. *Chin J Nat Med*. 2024;22(2):137-145. https://doi.org/10.1016/S1875-5364(24)60586-8.
43 Li W, Cai L, Zhang Y, et al. Intra-articular resveratrol injection prevents osteoarthritis progression in a mouse model by activating SIRT1 and thereby silencing HIF-2α. *J Orthop Res*. 2015;33(7):1061-1070. https://doi.org/10.1002/jor.22859.
44 Teng L, Shen Y, Qu Y, et al. Cyasterone inhibits IL-1β-mediated apoptosis and inflammation *via* the NF-κB and MAPK signaling pathways in rat chondrocytes and ameliorates osteoarthritis *in vivo*. *Chin J Nat Med*. 2023;21(2):99-112. https://doi.org/10.1016/S1875-5364(23)60388-7.
45 Li Z, Huang Z, Bai L. Cell interplay in osteoarthritis. *Front Cell Dev Biol*. 2021;9:720477. https://doi.org/10.3389/fcell.2021.720477.
46 Li Y, Li Y, Zhu Y, et al. Structure-based virtual screening for discovery of paederosidic acid from Paederia scandens as novel P2Y(14)R antagonist. *Phytomedicine*. 2023;115:154851. https://doi.org/10.1016/j.phymed.2023.154851.
47 Saneja A, Arora D, Kumar R, et al. Therapeutic applications of betulinic acid nanoformulations. *Ann N Y Acad Sci*. 2018;1421(1):5-18. https://doi.org/10.1111/nyas.13570.
48 Wei J, Li Y, Liu Q, et al. Betulinic acid protects from bone loss in ovariectomized mice and suppresses RANKL-associated osteoclastogenesis by inhibiting the MAPK and NFATc1 pathways. *Front Pharmacol*. 2020;11:1025. https://doi.org/10.3389/fphar.2020.01025.
49 Freund RRA, Gobrecht P, Fischer D, et al. Advances in chemistry and bioactivity of parthenolide. *Nat Prod Rep*. 2020;37(4):541-565. https://doi.org/10.1039/C9NP00049F.
50 Xu Y, Chen Z, Lu X, et al. Targeted inhibition of STAT3 (Tyr705) by xanthatin alleviates osteoarthritis progression through the NF-κB signaling pathway. *Biomed Pharmacother*. 2024;174:116451. https://doi.org/10.1016/j.biopha.2024.116451.
51 Xing F, Geng L, Guan H, et al. Astragalin mitigates inflammatory osteolysis by negatively modulating osteoclastogenesis *via* ROS and MAPK signaling pathway. *Int Immunopharmacol*. 2022;112:109278. https://doi.org/10.1016/j.intimp.2022.109278.
52 He Q, Tian D, Wang Z, et al. Modified Si Miao Powder granules alleviates osteoarthritis progression by regulating M1/M2 polarization of macrophage through NF-κB signaling pathway. *Front Pharmacol*. 2024;15:1361561. https://doi.org/10.3389/fphar.2024.1361561.
53 Hsieh CY, Wang CC, Tayo LL, et al. *In vitro* and *in vivo* anti-osteoarthritis effects of tradition Chinese prescription Ji-Ming-San. *J Ethnopharmacol*. 2023;305:116084. https://doi.org/10.1016/j.jep.2022.116084.
54 Jia Z, Zhang J, Yang X, et al. Bioactive components and potential mechanisms of Biqi Capsule in the treatment of osteoarthritis: based on chondroprotective and anti-inflammatory activity. *Front Pharmacol*. 2024;15:1347970. https://doi.org/10.3389/fphar.2024.1347970.
55 Hu Y, Gui Z, Zhou Y, et al. Quercetin alleviates rat osteoarthritis by inhibiting inflammation and apoptosis of chondrocytes, modulating synovial macrophages polarization to M2 macrophages. *Free Radic Biol Med*. 2019;145:146-160. https://doi.org/10.1016/j.freeradbiomed.2019.09.024.
56 Zhou F, Mei J, Han X, et al. Kinsenoside attenuates osteoarthritis by repolarizing macrophages through inactivating NF-κB/MAPK signaling and protecting chondrocytes. *Acta Pharm Sin B*. 2019;9(5):973-985. https://doi.org/10.1016/j.apsb.2019.01.015.
57 Liu Q, Shen J, Wang J, et al. PR-957 retards rheumatoid arthritis progression and inflammation by inhibiting LMP7-mediated CD4+ T cell imbalance. *Int Immunopharmacol*. 2023;124:110860. https://doi.org/10.1016/j.intimp.2023.110860.
58 Balaga VKR, Pradhan A, Thapa R, et al. Morin: a comprehensive review on its versatile biological activity and associated therapeutic potential in treating cancers. *Pharmacol Res Mod Chin Med*. 2023;7:100264. https://doi.org/10.1016/j.prmcm.2023.100264.
59 Miao Y, Wu X, Xue X, et al. Morin, the PPARγ agonist, inhibits Th17 differentiation by limiting fatty acid synthesis in collagen-induced arthritis. *Cell Biol Toxicol*. 2023;39(4):1433-1452. https://doi.org/10.1007/s10565-022-09769-3.
60 Lv Q, Zhu XY, Xia YF, et al. Tetrandrine inhibits migration and invasion of rheumatoid arthritis fibroblast-like synoviocytes through down-regulating the expressions of Rac1, Cdc42, and RhoA GTPases and activation of the PI3K/Akt and JNK signaling pathways. *Chin J Nat Med*. 2015;13(11):831-841. https://doi.org/10.1016/S1875-5364(15)30087-X.
61 Yuan X, Tong B, Dou Y, et al. Tetrandrine ameliorates collagen-induced arthritis in mice by restoring the balance between Th17 and Treg cells *via* the aryl hydrocarbon receptor. *Biochem Pharmacol*. 2016;101:87-99. https://doi.org/10.1016/j.bcp.2015.11.025.
62 Yue M, Zhang X, Dou Y, et al. Gut-sourced vasoactive intestinal polypeptide induced by the activation of α7 nicotinic acetylcholine receptor substantially contributes to the anti-inflammatory effect of sinomenine in collagen-induced arthritis. *Front Pharmacol*. 2018;9:675. https://doi.org/10.3389/fphar.2018.00675.
63 Jiang ZM, Zeng SL, Huang TQ, et al. Sinomenine ameliorates rheumatoid arthritis by modulating tryptophan metabolism and activating aryl hydrocarbon receptor *via* gut microbiota regulation. *Sci Bull (Beijing)*. 2023;68(14):1540-1555. https://doi.org/10.1016/j.scib.2023.06.027.
64 Wang H, Geng X, Ai F, et al. Nuciferine alleviates collagen-induced arthritic in rats by inhibiting the proliferation and invasion of human arthritis-derived fibroblast-like synoviocytes and rectifying Th17/Treg imbalance. *Chin J Nat Med*. 2024;22(4):341-355. https://doi.org/10.1016/S1875-5364(24)60622-9.
65 Li R, Guo LX, Li Y, et al. Dose-response characteristics of Clematis triterpenoid saponins and clematichinenoside AR in rheumatoid arthritis rats by liquid chromatography/mass spectrometry-based serum and urine metabolomics. *J Pharm Biomed Anal*. 2017;136:81-91. https://doi.org/10.1016/j.jpba.2016.12.037.
66 Guo LX, Wang HY, Liu XD, et al. Saponins from *Clematis mandshurica* Rupr. regulates gut microbiota and its metabolites during alleviation of collagen-induced arthritis in rats. *Pharmacol Res*. 2019;149:104459. https://doi.org/10.1016/j.phrs.2019.104459.
67 Jiang SQ, Guo ZJ, Pan T, et al. The multi-omics and analysis to reveal thermal processing enhanced anti-rheumatoid arthritis efficacy of Radix Clematidis in rats. *J Pharm Biomed Anal*. 2022;215:114760. https://doi.org/10.1016/j.jpba.2022.114760.
68 Xiong Y, Ma Y, Han W, et al. Clematichinenoside AR induces immunosuppression involving Treg cells in Peyer's patches of rats with adjuvant induced arthritis. *J Ethnopharmacol*. 2014;155(2):1306-1314. https://doi.org/10.1016/j.jep.2014.07.028.
69 Li Y, Zheng JY, Liu JQ, et al. Succinate/NLRP3 inflammasome induces synovial fibroblast activation: therapeutical effects of clematichinenoside AR on arthritis. *Front Immunol*. 2016;7:532. https://doi.org/10.3389/fimmu.2016.00532.
70 Zhang H, Liu J, Zhang P, et al. Herbal formula Longteng Decoction promotes the regression of synovial inflammation in collagen-induced arthritis mice by regulating type 2 innate lymphocytes. *Front Pharmacol*. 2021;12:778845. https://doi.org/10.3389/fphar.2021.778845.
71 Tang Y, Liu Q, Feng Y, et al. Tripterygium ingredients for pathogenicity cells in rheumatoid arthritis. *Front Pharmacol*. 2020;11:583171. https://doi.org/10.3389/fphar.2020.583171.
72 Luo Y, Hou X, Xi A, et al. *Tripterygium wilfordii* Hook F combination therapy with methotrexate for rheumatoid arthritis: an updated meta-analysis. *J Ethnopharmacol*. 2023;307:116211. https://doi.org/10.1016/j.jep.2023.116211.
73 Zhang Y, Mao X, Li W, et al. *Tripterygium wilfordii*: an inspiring resource for rheumatoid arthritis treatment. *Med Res Rev*. 2020;41(3):1337-1374. https://doi.org/10.1002/med.21762.
74 Zhang L, Jiang S, Guan Z, et al. Effect of *Salvia miltiorrhiza* bunge extracts on improving the efficacy and reducing the toxicity of *Tripterygium wilfordii* polyglycosides in the treatment of rheumatoid arthritis. *J Ethnopharmacol*. 2023;317:116782. https://doi.org/10.1016/j.jep.2023.116782.
75 Wei ZF, Jiao XL, Wang T, et al. Norisoboldine alleviates joint destruction in rats with adjuvant-induced arthritis by reducing RANKL, IL-6, PGE(2), and MMP-13 expression. *Acta Pharmacol Sin*. 2013;34(3):403-413. https://doi.org/10.1038/aps.2012.187.
76 Luo Y, Wei Z, Chou G, et al. Norisoboldine induces apoptosis of fibroblast-like synoviocytes from adjuvant-induced arthritis rats. *Int Immunopharmacol*. 2014;20(1):110-116. https://doi.org/10.1016/j.intimp.2014.02.023.
77 Jiang X, Lu Z, Zhang Q, et al. Osthole: a potential AMPK agonist that inhibits NLRP3 inflammasome activation by regulating mitochondrial homeostasis for combating rheumatoid arthritis. *Phytomedicine*. 2023;110:154640. https://doi.org/10.1016/j.phymed.2022.154640.
78 Dou Y, Tong B, Wei Z, et al. Scopoletin suppresses IL-6 production from fibroblast-like synoviocytes of adjuvant arthritis rats induced by IL-1β stimulation. *Int Immunopharmacol*. 2013;17(4):1037-1043. https://doi.org/10.1016/j.intimp.2013.10.011.
79 Cao L, Zhao T, Xue Y, et al. The anti-inflammatory and uric acid lowering effects of Si-Miao-San on gout. *Front Immunol*. 2022;12:777522. https://doi.org/10.3389/fimmu.2021.777522.
80 Zhou Q, Sun HJ, Zhang XW. Total saponin fraction of dioscorea nipponica makino improves gouty arthritis symptoms in rats *via* M1/M2 polarization of monocytes and macrophages mediated by arachidonic acid signaling. *Chin J Integr Med*. 2023;29(11):1007-1017. https://doi.org/10.1007/s11655-022-3729-y.
81 Li G, Du S, Yan S, et al. Mechanism of Biqi Capsules in the treatment of gout based on network pharmacology and experimental verification. *J Ethnopharmacol*. 2025;337:118817. https://doi.org/10.1016/j.jep.2024.118817.
82 Dinesh P, Rasool M. Berberine, an isoquinoline alkaloid suppresses TXNIP mediated NLRP3 inflammasome activation in MSU crystal stimulated RAW 264.7 macrophages through the upregulation of Nrf2 transcription factor and alleviates MSU crystal induced inflammation in rats. *Int Immunopharmacol*. 2017;44:26-37. https://doi.org/10.1016/j.intimp.2016.12.031.
83 Meng Q, Meng W, Bian H, et al. Total glucosides of paeony protects THP-1 macrophages against monosodium urate-induced inflammation *via* MALAT1/miR-876-5p/NLRP3 signaling cascade in gouty arthritis. *Biomed Pharmacother*. 2021;138:111413. https://doi.org/10.1016/j.biopha.2021.111413.
84 Piao MH, Wang H, Jiang YJ, et al. Taxifolin blocks monosodium urate crystal-induced gouty inflammation by regulating phagocytosis and autophagy. *Inflammopharmacology*. 2022;30(4):1335-1349. https://doi.org/10.1007/s10787-022-01014-x.
85 Li X, Mao X, Jiang H, et al. Shirebi Granules ameliorate acute gouty arthritis by inhibiting NETs-induced imbalance between immunity and inflammation. *Chin Med*. 2024;19(1):105. https://doi.org/10.1186/s13020-024-00962-6.
86 Xu L, Liu X, Zhang Y, et al. Tanshinone IIA improves acute gouty arthritis in rats through regulating neutrophil activation and the NLRP3 inflammasome. *Dis Markers*. 2022;2022:1-12. https://doi.org/10.1155/2022/5851412.
87 Zhou GQ, Chen G, Yang J, et al. Guizhi-Shaoyao-Zhimu Decoction attenuates monosodium urate crystal-induced inflammation through inactivation of NF-κB and NLRP3 inflammasome. *J Ethnopharmacol*. 2022;283:114707. https://doi.org/10.1016/j.jep.2021.114707.

88 Yoon IS, Cho SS. Effects of lobetyolin on xanthine oxidase activity *in vitro* and *in vivo*: weak and mixed inhibition. *Nat Prod Res*. 2019;35(10):1667-1670. https://doi.org/10.1080/14786419.2019.1622108.
89 Liu C, Zhou M, Jiang W, et al. GPR105-targeted therapy promotes gout resolution as a switch between NETosis and apoptosis of neutrophils. *Front Immunol*. 2022;13:870183. https://doi.org/10.3389/fimmu.2022.870183.
90 Shi L, Zhao F, Zhu F, et al. Traditional Chinese medicine formula "Xiaofeng Granules" suppressed gouty arthritis animal models and inhibited the proteoglycan degradation on chondrocytes induced by monosodium urate. *J Ethnopharmacol*. 2016;191:254-263. https://doi.org/10.1016/j.jep.2016.06.008.
91 Zhu F, Yin L, Ji L, et al. Suppressive effect of Sanmiao Formula on experimental gouty arthritis by inhibiting cartilage matrix degradation: an *in vivo* and *in vitro* study. *Int Immunopharmacol*. 2016;30:36-42. https://doi.org/10.1016/j.intimp.2015.11.010.
92 Peng Y, Lee C, Wang C, et al. Pycnogenol attenuates the inflammatory and nitrosative stress on joint inflammation induced by urate crystals. *Free Radic Biol Med*. 2012;52(4):765-774. https://doi.org/10.1016/j.freeradbiomed.2011.12.003.
93 Deng P, Wang S, Sun X, et al. Global trends in research of gouty arthritis over past decade: a bibliometric analysis. *Front Immunol*. 2022;13:910400. https://doi.org/10.3389/fimmu.2022.910400.
94 Tan H, Zhang S, Zhang Z, et al. Neutrophil extracellular traps promote M1 macrophage polarization in gouty inflammation *via* targeting hexokinase-2. *Free Radic Biol Med*. 2024;224:540-553. https://doi.org/10.1016/j.freeradbiomed.2024.09.009.
95 Atta A, Salem MM, El-Said KS, et al. Mechanistic role of quercetin as inhibitor for adenosine deaminase enzyme in rheumatoid arthritis: systematic review. *Cell Mol Biol Lett*. 2024;29(1):14. https://doi.org/10.1186/s11658-024-00531-7.
96 Feng W, Zhong XQ, Zheng XX, et al. Study on the effect and mechanism of quercetin in treating gout arthritis. *Int Immunopharmacol*. 2022;111:109112. https://doi.org/10.1016/j.intimp.2022.109112.
97 Lotfi MS, Rassouli FB. Natural flavonoid apigenin, an effective agent against nervous system cancers. *Mol Neurobiol*. 2024;61(8):5572-5583. https://doi.org/10.1007/s12035-024-03917-y.
98 Zhu Y, Ouyang Z, Du H, et al. New opportunities and challenges of natural products research: when target identification meets single-cell multiomics. *Acta Pharm Sin B*. 2022;12(11):4011-4039. https://doi.org/10.1016/j.apsb.2022.08.022.
99 Liu Y, Zhao B, He P, et al. Cinnamic acid: a low-toxicity natural bidentate ligand for uranium decorporation. *Inorg Chem*. 2024;63(16):7464-7472. https://doi.org/10.1021/acs.inorgchem.4c00610.
100 Luo Z, Yin F, Wang X, et al. Progress in approved drugs from natural product resources. *Chin J Nat Med*. 2024;22(3):195-211. https://doi.org/10.1016/S1875-5364(24)60582-0.
101 Atanasov AG, Zotchev SB, Dirsch VM, et al. Natural products in drug discovery: advances and opportunities. *Nat Rev Drug Discov*. 2021;20(3):200-216. https://doi.org/10.1038/s41573-020-00114-z.

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