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ANTIARTHRITIC ACTIVITIES OF HERBAL ISOLATES

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ABSTRACT

A wide range of plant-derived compounds exhibiting therapeutic potential, including antimicrobial, anti-inflammatory, antiviral, antimalarial, antiarthritic (AA), hepatoprotective, and cardiotonic activities, have been documented in scientific literature. Medicinal plants are extensively utilized and are often considered safe and cost-effective substitutes for synthetic pharmaceuticals. However, due to insufficient regulation regarding their potency and purity, caution is necessary to ensure their safe application.

In this review, we aimed to consolidate various herbal constituents demonstrating antiarthritic properties, including alkaloids (montanine, 3-acetylaconitine, sanguinarine, jatrorrhizine hydrochloride, and piperine), terpenoids (eugenol, nimbolide, bartogenic acid, cannabidiol, and curcumin), and flavonoids (quercetin, resveratrol, kaempferol, chebulanin, ellagic acid, rosmarinic acid, gallic acid, chlorogenic acid, ferulic acid, and brazilin). These bioactive compounds exert their antiarthritic effects through diverse pharmacological mechanisms, such as suppression of cytokines, chemokines, and matrix metalloproteinases.

Additionally, experimental models used to evaluate antiarthritic activity, including adjuvant-induced arthritis in animal models, are discussed. Moreover, nanotechnology-based delivery systems for these bioactive compounds are highlighted, as they have demonstrated enhanced therapeutic effectiveness and improved bioavailability.

KEYWORDS: Arthritis; Herbal Solates; Arthritic Models; Alkaloids; Terpenoids; Flavonoids; Nanoparticles.

INTRODUCTION

Herbal products hold considerable significance in traditional systems of medicine. A vast number of plants and plant-derived formulations have been employed since ancient times.

Systems such as Ayurveda, Traditional Chinese Medicine (TCM), Traditional Korean Medicine (TKM), Kampo, and Unani utilize herbal remedies that have been practiced worldwide for several centuries or even millennia. These herbal products possess distinct advantages, including extensive clinical experience and remarkable diversity in chemical composition and biological activities.

Herbal medicines have emerged as crucial sources for the development of novel lead compounds and structural frameworks. They continue to play a vital role in addressing the growing demand for effective therapeutics and are expected to contribute significantly to drug discovery for the management of human diseases, particularly life-threatening conditions.

Arthritis is one of the most widespread and debilitating diseases worldwide, currently affecting approximately 350 million individuals. According to recent reports, nearly one in four adults in the United States suffers from arthritis accompanied by severe joint pain. Arthritis is characterized by the degeneration of cartilage, which normally cushions and protects the joints. It also triggers an inflammatory response along with proliferation of synovial cells. As a result, excessive accumulation of synovial fluid within the joints leads to thickening of synovial membranes, causing inflammation at joint sites. The progression of the disease often results in damage to articular cartilage and joint stiffness.

Commonly reported types of arthritis include ankylosing spondylitis, juvenile idiopathic arthritis, reactive arthritis, psoriatic arthritis, rheumatoid arthritis, septic arthritis, osteoarthritis, and gout (Figure 1).

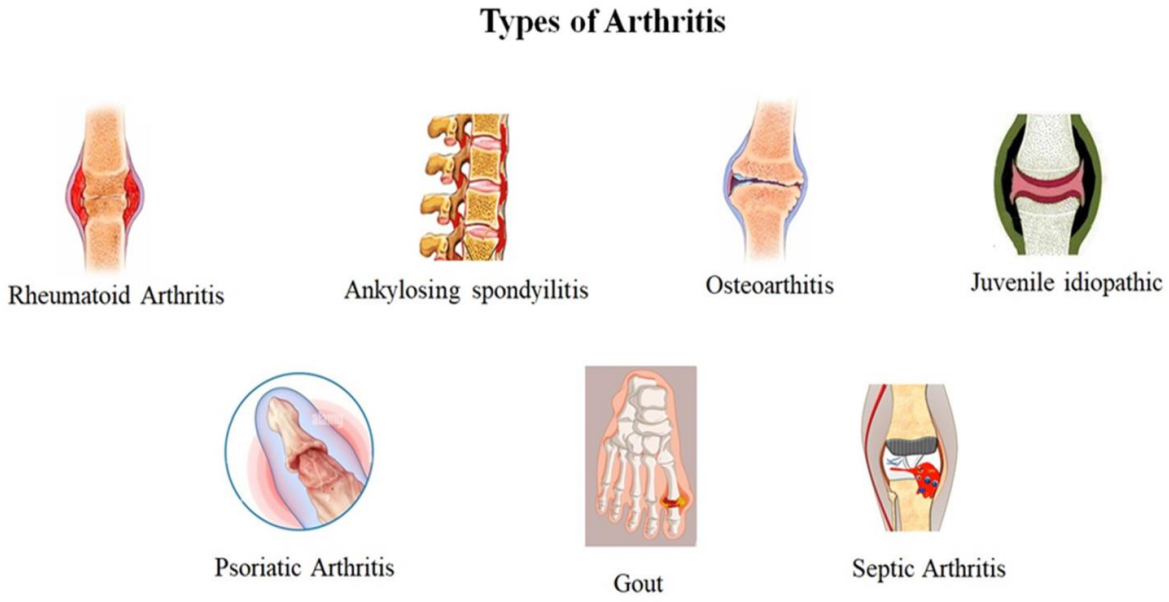

Figure 1. Common types of arthritis reported in the literatures.

Osteoarthritis (OA) is the most prevalent form of arthritis, affecting nearly 302 million individuals worldwide. The joints most commonly impacted by OA are the appendicular joints, particularly those of the knees, hips, and hands. Rheumatoid arthritis (RA) is another major form of arthritis that primarily affects synovial joints and typically presents as symmetrical joint involvement, leading to a significant socioeconomic burden. RA is a widely occurring disorder, affecting approximately 0.5–1% of the global population. Although the exact etiology of RA remains unclear, it is widely believed that autoimmune mechanisms play a central role in its development. Early diagnosis and prompt therapeutic intervention can help alleviate symptoms associated with RA.

Common treatment approaches for arthritis include non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen and aspirin, which exhibit rapid onset of action; corticosteroids (e.g., cortisone, dexamethasone); biological agents (e.g., etanercept and infliximab); and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and leflunomide. These therapies may be administered individually or in combination and represent the most commonly adopted treatment strategies for arthritis. However, DMARDs modulate the immune system and may consequently reduce the body's ability to combat infections. In addition, the high cost and potential adverse effects associated with synthetic drugs have limited their widespread use in arthritis management. As a result, herbal medicines are increasingly gaining attention as alternative therapeutic options due to their comparatively lower incidence of side effects.

2. Herbal Antiarthritic Drugs

Herbal products have been extensively utilized as therapeutic agents since ancient times. These natural substances exhibit extensive chemical diversity, pharmacological selectivity, and distinct molecular characteristics, making them promising candidates for the identification of novel lead compounds. A large number of plant-derived isolates with antiarthritic (AA) activity have been explored and documented. These bioactive compounds are broadly classified into alkaloids, glycosides, terpenoids, flavonoids, and other categories.

In recent years, several herbal constituents exhibiting anti-inflammatory-mediated antiarthritic effects have been isolated. These medicinal plants have been used either independently or in the form of extracts or purified compounds for the treatment of RA and OA. A plant isolate refers to a purified chemical compound obtained from a plant extract, possessing a well-defined structure responsible for specific biological activity, and serving as a foundation for the development of more potent therapeutic agents. Table 1 summarizes

various plant isolates along with their chemical structures and IUPAC nomenclature. These isolates exert their effects through multiple mechanisms, which are illustrated in Figure 2.

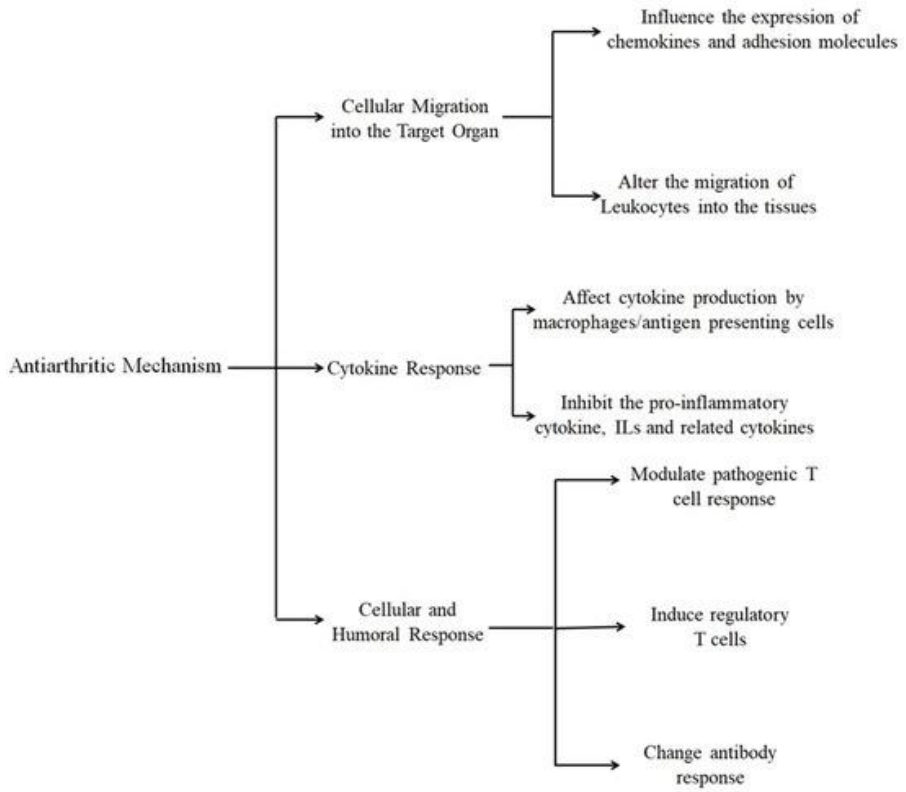

Figure 2. Mechanisms involved in the treatment of arthritis.

2.1. Alkaloids

2.1.1. Montanine

Plants belonging to the Amaryllidaceae family have a well-established history of use worldwide and are considered promising therapeutic agents for various human ailments. Members of this family have long been employed as alternative remedies, particularly in developing nations. Amaryllidaceae alkaloids are secondary metabolites derived from plants native to regions such as Argentina, Brazil, and Uruguay. Montanine shares structural resemblance with other Amaryllidaceae alkaloids, and its diverse pharmacological activities suggest its potential as an antiarthritic agent.

In recent years, montanine has attracted considerable scientific interest due to its potent anti-inflammatory properties. It has been isolated from the bulb of *Rhodophiala bifida* (Herb.) using maceration with 2% (v/v) sulfuric acid. Studies have demonstrated its significant antiarthritic activity through in vitro evaluation of lymphocyte proliferation and the invasiveness of fibroblast-like synoviocytes (FLS). Further investigations using antigen-

induced arthritis (AIA) in Balb/c mice and collagen-induced arthritis (CIA) in DBA/1J mice revealed that montanine administration reduced nociception and leukocyte migration in joints in the AIA model, while decreasing disease severity and joint damage in the CIA model. Histopathological findings indicated notable improvement in arthritic conditions. The observed effects were attributed to inhibition of lymphocyte proliferation and reduced FLS invasion. The median lethal dose (LD_{50}) of montanine was reported as 64.7 mg/kg in male mice, with observed adverse effects including altered motor activity, decreased respiratory rate, severe tremors, and clonic convulsions.

2.1.2. 3-Acetylaconitine

3-Acetylaconitine (AAc) is a nitrogen-containing alkaloid isolated from *Aconitum flavum* and *Aconitum pendulum* of the Ranunculaceae family. Tang et al. reported the isolation of AAc from the root of *Aconitum flavum* and evaluated its antiarthritic activity in experimental mouse and rat models.

An oral dose ranging from 0.3 to 0.5 mg/kg of AAc significantly reduced hind paw swelling in the formaldehyde-induced rat model and inhibited carrageenan-induced edema in adrenalectomized rats. Although AAc suppressed vascular permeability induced by acetic acid and histamine, it did not decrease adrenal ascorbic acid levels, indicating that its mechanism of action is independent of stimulation of the pituitary–adrenal axis.

2.1.3. Sanguinarine

Sanguinarine (SA) is a naturally occurring benzylisoquinoline alkaloid isolated from several plant species, including *Argemone mexicana*, *Bocconia frutescens*, *Chelidonium majus*, *Macleaya cordata*, and *Sanguinaria canadensis*. It is approved by the U.S. Food and Drug Administration and is known for its anti-inflammatory properties and ability to inhibit osteoclast formation.

Ma et al. isolated SA from the roots of *Sanguinaria canadensis* and investigated its therapeutic efficacy in osteoarthritis (OA) models. The findings demonstrated that SA suppressed the expression of catabolic proteases in in vitro, in vivo, and ex vivo systems. It inhibited activation of NF-κB and JNK signaling pathways, thereby reducing the production of catabolic mediators. Additionally, SA suppressed IL-1β-induced expression of matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) and inhibited ADAMTS-5 expression in chondrocytes. These results highlight the potential of SA as a therapeutic candidate for OA management.

2.1.4. Jatrorrhizine

Jatrorrhizine hydrochloride (JH) is a protoberberine alkaloid identified in several medicinal plants, including *Berberis aristata* and *Coptis chinensis*. Qiu et al. recently evaluated the antiarthritic potential of JH in a collagen-induced arthritis (CIA) rat model.

The results demonstrated that JH effectively reduced rheumatoid arthritis symptoms through anti-inflammatory effects and inhibition of bone destruction. In vitro studies further revealed suppression of inflammatory mediator production, along with inhibition of proliferation and migration of MH7A cells. JH was found to inhibit tumor necrosis factor-α (TNF-α)-induced activation of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, leading to reduced production of proinflammatory cytokines. These findings suggest that JH is a promising candidate for antiarthritic therapy.

2.1.5. Piperine

Piperine is an alkaloid obtained from black pepper (*Piper nigrum* L.), responsible for its characteristic pungency, and is commonly found in members of the Piperaceae family. *Piper nigrum* contains the highest concentration of piperine, typically ranging from 2% to 9%, and has been extensively used in Ayurvedic and Chinese medicinal systems.

Bang et al. (2009) reported the anti-inflammatory, analgesic, and antiarthritic activities of piperine. Its antiarthritic effects were evaluated using a collagen-induced arthritis model in vivo by measuring paw volume and weight distribution ratio. The results indicated a significant reduction in both parameters. Further analysis using ELISA and RT-PCR revealed that oral administration of piperine (20–100 mg/kg/day for 8 days) inhibited IL-6, MMP-13 expression, and prostaglandin E_2 (PGE_2) production. Although piperine did not directly inhibit NF-κB expression, it suppressed the migration of activator protein-1 (AP-1). Notably, a reduction in arthritic symptoms was observed by the fourth day of treatment, supporting its therapeutic potential in arthritis management.

2.1.6. Capsaicin

Capsaicin is a bioactive constituent of chili peppers belonging to the genus *Capsicum* and is synthesized as a secondary metabolite. It acts as a chemical irritant in mammals, including humans. Ahmed et al. investigated the effects of capsaicin on substance P (SP) and calcitonin gene-related peptide (CGRP) levels in the ankle joints and dorsal root ganglia (L2–L6) of adult female Lewis rats.

Subcutaneous administration of capsaicin at a dose of 200 mg/kg significantly decreased SP (19%) and CGRP (42%) levels in the dorsal root ganglia of adjuvant-induced arthritic rats. In the ankle joints, capsaicin reduced SP levels by 40%, accompanied by a comparable reduction in inflammatory response. Moreover, capsaicin treatment attenuated the elevated levels of sensory neuropeptides in both dorsal root ganglia and ankle joints. These findings indicate the potential utility of capsaicin in the management of arthritis.

2.1.7. Tubastrine

Tubastrine is an alkaloid isolated from the marine organism *Aplidium orthium* (Ascidiacea) and is known for its anti-inflammatory properties. It was extracted from frozen specimens using methanolic acid followed by chloroform extraction. Tubastrine demonstrated the ability to reduce superoxide generation in phorbol-12-myristate 13-acetate (PMA)-stimulated neutrophils in vitro.

In in vivo studies, tubastrine significantly decreased superoxide production in a gouty arthritis model. Additionally, it exhibited inhibitory effects on neutrophil infiltration, further supporting its anti-inflammatory and antiarthritic potential.

2.1.8. Orthidines

Orthidines (A–F) represent a class of marine-derived alkaloids isolated from the ascidian *Aplidium orthium*. Structurally, orthidines (A–D) are benzodioxane derivatives, orthidine E is a cyclobutane dimer of tubastrine, and orthidine F is a biosynthetically distinct dihomovanillamide derivative of spermine.

Pearce et al. isolated orthidines (A–F) from frozen samples of *Aplidium orthium* using methanolic acid and chloroform extraction, and evaluated their anti-inflammatory and antiarthritic activities in a gouty arthritis model. The compounds demonstrated dose-dependent inhibition of superoxide production in PMA-stimulated human neutrophils, with IC_{50} values ranging from 10 to 36 µM. This inhibitory effect was also observed in vivo, where orthidines reduced neutrophil-mediated superoxide production in a murine model of gouty inflammation.

2.2. Terpenoids

Terpenoids are a diverse class of plant secondary metabolites obtained from various plant parts, including stems, fruits, flowers, leaves, and roots. They are typically colorless, aromatic liquids with a high refractive index. Terpenoids possess significant pharmaceutical

importance due to their wide range of biological activities, including anti-inflammatory, antibacterial, antiviral, antioxidant, and anticancer effects.

Recent studies by Carvalho et al. identified 24 terpenoid compounds with significant efficacy in the treatment of inflammation and arthritis.

2.2.1. Eugenol

Eugenol is a main phenolic compound derived from clove buds (*Eugenia caryophyllata*), constituting approximately 80–90% of clove oil. Sharma et al. first reported its inhibitory effects on arthritic symptom.

Subsequent research by Grespan et al. evaluated the antiarthritic activity of eugenol in a collagen-induced arthritis (CIA) mouse model. Arthritis was induced in male DBA1/J mice using bovine type II collagen (CII), followed by oral administration of eugenol (100 µg/mouse) from day 25 to day 40. The treatment significantly reduced cytokine levels, including TNF-α, transforming growth factor (TGF)-β, and interferon (IFN)-γ in ankle joints. Furthermore, eugenol inhibited mononuclear cell infiltration into the knee joints, demonstrating its anti-inflammatory and protective effects.

2.2.2. Nimbolide

Nimbolide is a triterpenoid compound isolated from the leaves and flowers of the neem plant (*Azadirachta indica*) and is widely used for treating various human disorders. This plant is known to contain numerous bioactive constituents with diverse pharmacological properties.

Cui et al. evaluated the antiarthritic activity of nimbolide in male albino rats using Freund's adjuvant-induced arthritis model. Oral administration of nimbolide (20 mg/kg/day) significantly reduced edema, paw swelling, organ indices, and arthritis scores, while improving body weight. Histopathological analysis demonstrated protective effects on joint tissues. Nimbolide exerted its anti-inflammatory action by decreasing proinflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-10. Additionally, it normalized elevated levels of inflammatory mediators, including iNOS, phosphorylated IκBα, NF-κB, COX-2, and IKKα.

2.2.3. Bartogenic Acid

Bartogenic acid (BA) is a bioactive compound isolated from the fruits of *Barringtonia racemosa* (Lecythidaceae). Patil et al. investigated its antiarthritic potential in experimental models.

BA, obtained from the methanolic fruit extract, demonstrated significant activity against complete Freund's adjuvant (CFA)-induced arthritis in rats. It reduced serum biomarkers such as rheumatoid factor and C-reactive protein and provided protection against both primary and secondary arthritic lesions at doses of 2, 5, and 10 mg/kg/day.

Additionally, BA normalized hematological parameters, including white blood cell count, hemoglobin levels, and erythrocyte sedimentation rate. The improvement in hemoglobin levels was attributed to enhanced erythropoietin-mediated bone marrow activity. Radiographic studies further confirmed its protective effect against joint damage.

2.2.4. Cannabidiol

Cannabidiol (CBD) is a terpenophenolic compound (meroterpenoid) derived from *Cannabis sativa* L., a member of the Cannabaceae family, which is cultivated globally. This plant contains a wide array of phytochemicals, including amides, amines, phytosterols, phenolics, carbohydrates, terpenes, and fatty acids, with CBD being a main active constituent.

Several studies have demonstrated that CBD exhibits anti-inflammatory effects by inhibiting T-lymphocyte proliferation, reducing nitric oxide production by macrophages, and suppressing antigen presentation. Malfait et al. reported the antiarthritic potential of CBD in murine collagen-induced arthritis models.

Arthritis was induced using bovine type II collagen in DBA/1 mice, followed by CBD treatment. Optimal therapeutic doses were identified as 5 mg/kg (intraperitoneal) or 25 mg/kg (oral). CBD treatment significantly reduced joint damage, decreased interferon-γ (IFN-γ) production, and suppressed antigen-specific immune responses. Ex vivo studies demonstrated reduced TNF-α release and decreased proliferation of synovial cells. Additionally, CBD showed dose-dependent inhibition of lymphocyte proliferation in vitro and reduced lipopolysaccharide-induced TNF levels in mice.

These findings highlight the immunosuppressive and anti-inflammatory properties of CBD, which contribute to its antiarthritic effects. Furthermore, a patent has been filed describing the therapeutic application of CBD in inflammatory diseases.

2.2.5. Curcumin

Curcumin is the principal bioactive constituent of *Curcuma longa* Linn (turmeric), a member of the Zingiberaceae family, predominantly cultivated in South Asia. *Curcuma longa* has been extensively utilized in traditional Indian Ayurvedic medicine as a common household

remedy, where its paste, often combined with slaked lime, is applied for the management of inflammation and wound healing.

Curcumin has attracted substantial scientific attention due to its diverse pharmacological properties and its ability to modulate multiple cellular signaling pathways. It has been reported to exhibit significant antiarthritic (AA) effects in both osteoarthritis (OA) and rheumatoid arthritis (RA) conditions.

Huang et al. investigated the anti-rheumatoid activity of curcumin in a collagen-induced arthritis (CIA) DBA/1J mouse model. Intraperitoneal administration of curcumin (50 mg/kg) resulted in a marked reduction in serum levels of B cell-activating factor (BAFF), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). Furthermore, Western blot analysis demonstrated suppression of IFN-γ-mediated STAT1 signaling in B lymphocytes, including inhibition of BAFF expression, STAT1 phosphorylation, and nuclear translocation following curcumin treatment.

Additionally, Kuncha et al. reported a synergistic effect of curcumin when combined with a low dose of prednisolone in a complete Freund's adjuvant (CFA)-induced arthritis rat model, enhancing its therapeutic efficacy.

Yu et al. further demonstrated the anti-neuroinflammatory effects of curcumin in lipoteichoic acid (LTA)-stimulated BV-2 microglial cells. The results indicated that curcumin inhibited the production of inflammatory mediators such as nitric oxide (NO), tumor necrosis factor-α (TNF-α), and prostaglandin E_2 (PGE_2), along with downregulation of COX-2 and inducible nitric oxide synthase (iNOS) expression. Curcumin also suppressed LTA-induced MAPK phosphorylation. Moreover, it modulated heme oxygenase-1 (HO-1) activity, thereby attenuating inflammatory mediator release and contributing to its protective role against neuroinflammation and neurodegenerative disorders.

2.3. Flavonoids

Flavonoids are naturally occurring polyphenolic compounds widely distributed in plants, including grains, fruits, flowers, vegetables, bark, stems, and roots. These compounds are well recognized for their anti-inflammatory properties and have been traditionally employed in the management of arthritis and related inflammatory disorders.

2.3.1. Quercetin (3,5,7,3′,4′-Pentahydroxyflavone)

Quercetin (QTN) is a flavonoid commonly found in dietary sources such as apples, buckwheat, onions, and citrus fruits. Yuan et al. recently investigated and elucidated the mechanisms underlying its antiarthritic activity.

Quercetin significantly reduced ankle swelling and arthritis severity scores in an adjuvant-induced arthritis mouse model. The study demonstrated that QTN promoted apoptosis of activated neutrophils and inhibited their infiltration into inflamed tissues. Additionally, it suppressed reactive oxygen species (ROS)-mediated formation of neutrophil extracellular traps (NETs) and auto phagic processes. These findings suggest that quercetin may serve as a promising therapeutic agent for RA by modulating neutron phil function.

Oral administration of QTN (30 mg/kg) resulted in a reduction of clinical symptoms in a chronic arthritis rat model. Gardi et al. further reported that QTN (150 mg/kg) significantly decreased levels of interleukin-1β (IL-1β) and monocyte chemo attractant protein-1 (MCP-1), while restoring antioxidant capacity in plasma in adjuvant-induced arthritic rats.

Gaikwad et al. demonstrated the anti-inflammatory activity of ethanolic extracts of *Madhuca indica* flowers in various experimental models, including formaldehyde-induced inflammation, carrageenan-induced edema, and cotton pellet granuloma in rats. The extract exhibited a dose-dependent anti-inflammatory effect, surpassing the standard drug diclofenac sodium in certain models. Further investigations by Tang et al. (2021) involved isolation of quercetin from methanolic leaf extracts of *Madhuca indica* and evaluation of its anti arthritic activity in Freund's complete adjuvant (FCA)-induced arthritis in Wistar rats. The results demonstrated significant reductions in paw swelling, joint diameter, and pain sensitivity following treatment with QTN (10 and 20 mg/kg). The mechanism involved suppression of inflammatory mediators such as IκBα, P2X receptors, COX-2, and NF-κB, along with reduction of oxidative and nitrosative stress and proinflammatory cytokines (TNF-α and interleukins).

Notably, quercetin was found to be more effective when administered alone compared to methotrexate or even in combination therapy, in reducing joint inflammation in experimental models. It provided enhanced protection against arthritis through downregulation of inflammatory mediators, including TNF-α, IL-1β, IL-17, and MCP-1.

2.3.2. Resveratrol

Resveratrol (Res), a naturally occurring flavonoid, is abundantly found in medicinal plants such as grape, cranberry, mulberry, pistachio, and peanut. The anti-arthritic (AA) potential of Res was assessed in a CFA-induced rat model by Chen et al. in 2013. Res was shown to suppress the mRNA expression of IL-1β and TNF-α, thereby reducing their overall levels following intragastric administration (10 mL/kg/day). Furthermore, Res activated

synoviocytes and enhanced the protein expression of phosphorylated ERK1/2 via protein kinase C (PKC) pathways.

It has also been documented that resveratrol inhibits the enzymatic activity of COX-1 and COX-2. In another study, Chen et al. evaluated its anti-arthritic effects in a CFA-induced arthritis rat model. The findings demonstrated a marked reduction in paw swelling along with decreased arthritis scores at doses of 10 or 50 mg/kg (i.g.). Additionally, Res inhibited the synthesis of inflammatory mediators such as COX-2 and PGE2, and improved histopathological features in arthritic rats.

Co-administration of Res with piperine significantly alleviated paw edema and improved histopathological alterations. This combination notably reduced serum levels of TNF-α, IL-1β, thiobarbituric acid reactive substances (TBARS), and nitrate/nitrite (NOx). Moreover, near-complete suppression of NF-κB p65 expression in synovial tissue was observed. The therapeutic outcomes were comparable to those of diclofenac treatment.

2.3.3. Kaempferol

Kaempferol (KAE), a naturally occurring flavonol, chemically identified as 3,4′,5,7-tetrahydroxyflavone, is present in several edible plants such as beans, tea, kale, broccoli, and spinach. KAE has traditionally been utilized for the management of inflammatory disorders. Studies indicate that KAE decreases COX-2 expression in RAW 264.7 cells and suppresses ROS generation by inhibiting iNOS and TNF-α protein expression. It also downregulates IL-4, C-reactive protein (CRP), and NF-κB expression in hepatic cells.

Yoon et al. reported that KAE exerts anti-arthritic activity by inhibiting the proliferation of both unstimulated and IL-1β-stimulated rheumatoid arthritis synovial fibroblasts (RASFs). Additionally, it suppresses the mRNA and protein expression of MMP-1, MMP-3, PGE2, and COX-2 induced by IL-1β.

2.3.4. Chebulanin

Chebulanin is a natural polyphenolic compound isolated from the fruits of *Terminalia chebula* Retzius (TC). This plant is extensively used in traditional Asian medicine for its antimicrobial, anti-inflammatory, antioxidant, and anti-arthritic properties. Zhao et al. evaluated the anti-arthritic potential of chebulanin in a collagen-induced arthritis (CIA) model using DBA/1 mice.

Chebulanin was extracted from dried fruits using a 70% acetone solution (1:10, w/v) at room temperature (23 ± 2 °C). The study assessed inflammatory cytokine expression through

immunohistochemical staining, along with histopathological analysis of joint tissues. Micro-CT imaging was employed to evaluate bone erosion and cartilage degradation.

The results demonstrated a dose-dependent reduction in the expression of IL-6, TNF-α, MMP-3, and COX-2 in joint tissues following oral administration (40, 80, or 160 mg/kg/day for 28 days). Histopathological observations revealed significant tissue recovery, while micro-CT findings confirmed decreased cartilage destruction and bone erosion. These findings highlight chebulanin as a promising therapeutic agent for rheumatoid arthritis (RA).

Additionally, Liu et al. confirmed its anti-arthritic effects via inhibition of NF-κB and MAPK signaling pathways in a CIA mouse model. Chebulanin significantly reduced arthritic scores, paw swelling, and levels of IL-6 and TNF-α after oral administration (80 mg/kg/day for 21 days). It also decreased phosphorylated signaling proteins including p-p38, c-JUN, p-p65, p-JNK, and p-IκBα, without affecting ERK levels.

2.3.5. Ellagic Acid

Ellagic acid (EA) is a bioactive polyphenolic compound widely distributed in berries (strawberry, raspberry, cloudberry), almonds, grapes, walnuts, and pomegranates. Shruthi et al. isolated EA from the methanolic leaf extract of *Kirganelia reticulata* and evaluated its anti-arthritic activity using in vitro, in vivo, and in silico approaches.

In vitro studies revealed that EA exhibited significant inhibition of protein denaturation, membrane stabilization, and proteinase activity at a concentration of 250 µg/mL. In vivo studies using a formaldehyde-induced paw edema model demonstrated reduced cytokine production, leukotriene infiltration, and paw edema volume, along with protection of synovial membranes and cartilage at doses of 100 and 250 µg/mL.

The proposed mechanism involves inhibition of hypoxia-inducible factor (HIF-2α). Molecular docking studies showed that EA forms multiple hydrogen bonds within the active site of HIF-2α, effectively inhibiting its activity, even more efficiently than aspirin. Toxicity studies conducted as per OECD guideline 423 indicated no adverse effects up to 2500 mg/kg body weight.

Umar et al. further investigated the combined effect of methotrexate and EA in a CIA-Wistar rat model. The combination therapy significantly enhanced anti-arthritic and antioxidant effects, evidenced by reduced paw swelling, improved GSH and catalase levels, and decreased lipid peroxidation. It also suppressed pro-inflammatory cytokines and slowed disease progression.

2.3.6. Rosmarinic Acid

Rosmarinic acid is a polyphenolic compound present in herbs such as rosemary (*Rosmarinus officinalis*), mint (*Mentha arvensis*), sage (*Salvia officinalis*), and basil (*Ocimum basilicum*). It was first isolated in 1958 by Italian chemist Scarpatti from rosemary.

Wei et al. reported the anti-arthritic activity of rosmarinic acid isolated from methanolic leaf extract of *Rosmarinus officinalis* in a CFA-induced rat model. Oral administration at doses of 30 and 60 mg/kg significantly reduced paw swelling, inflammation, and joint stiffness. At 60 mg/kg, improvement in locomotor activity was observed between days 21 and 35. Additionally, rosmarinic acid decreased serum TNF-α levels in a dose-dependent manner. Acute toxicity studies (OECD 423) showed no toxic effects up to 2000 mg/kg body weight.

2.3.7. Gallic Acid

Gallic acid (GA) is a naturally occurring polyphenol found in gall nuts, oak bark, apple peels, sumac, grapes, and tea leaves, particularly green tea. Its anti-inflammatory, antimicrobial, anticancer, and pro-apoptotic activities are well established.

Shi et al. reported that tumor-like fibroblast-like synoviocytes (FLSs) migrate to cartilage and bone, contributing to pannus formation and increased secretion of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs). GA has been shown to inhibit these mediators.

Yoon et al. demonstrated that GA induces apoptosis in FLSs at concentrations ≥10 μM and modulates the expression of apoptosis-related proteins such as Bcl-2, Bax, p53, and pAkt. It also suppresses cytokines (IL-1, IL-6), chemokines (CCL-2/MCP-1, CCL-7/MCP-3), COX-2, and MMP-9 in a dose-dependent manner. These findings suggest that GA exerts therapeutic effects in RA through both anti-inflammatory and pro-apoptotic mechanisms.

Toxicity studies revealed an LD50 value greater than 2000 mg/kg in albino mice. Even at higher doses (900 mg/kg for 28 days), no significant alterations in behavior, morphology, or histopathological parameters were observed.

2.3.8. Chlorogenic Acid

Chlorogenic acid (CGA) is one of the most abundant phenolic acids, naturally present in tea and green coffee extracts. Chauhan et al. investigated the anti-arthritic (AA) potential of CGA in an adjuvant-induced arthritis model using male Wistar rats. At a dose of 40 mg/kg, CGA effectively regulated both total (CD3) and differentiated (CD4 and CD8) T-cell populations and significantly suppressed CD80/86 expression when compared to ibuprofen.

Flow cytometry analysis demonstrated that CGA inhibited Th1 cytokine production while enhancing Th2 cytokine levels. Fu et al. further reported that CGA attenuated the progression of arthritis and reduced serum levels of BAFF and TNF-α in a collagen-induced arthritis (CIA) mouse model. Mechanistic studies revealed that CGA suppressed TNF-α-induced BAFF expression and decreased the DNA-binding activity of NF-κB to the BAFF promoter region in MH7A cells. These findings highlight the therapeutic potential of CGA as an anti-arthritic agent. Toxicological studies indicated no abnormal behavior or mortality in animals treated with CGA up to a dose of 2000 mg/kg, confirming its safety at higher doses.

2.3.9. Ferulic Acid

Ferulic acid (FA) is a widely distributed phytochemical found in various plants, particularly in cereal grains such as rice and corn. FA exhibits potent free radical scavenging activity and enhances antioxidant defense mechanisms by modulating pathways involving NF-κB and COX-2, while also inhibiting iNOS expression.

These pharmacological properties prompted Zhu et al. to evaluate the therapeutic effects of FA in a CFA-induced arthritis rat model. The study also examined whether its efficacy is mediated through inhibition of the JAK/STAT signaling pathway. The results demonstrated that oral administration of FA (25 and 50 mg/kg) significantly reduced the arthritic index, erythrocyte sedimentation rate (ESR), and lymphocyte percentage in arthritic rats.

Additionally, FA treatment reversed elevated levels of rheumatoid factor (RF) and C-reactive protein (CRP), thereby restoring physiological balance. It also decreased the levels of pro-inflammatory mediators such as TNF-α, JAK2, TGF-β, STAT-3, and STAT-4. These findings suggest that FA exerts anti-arthritic effects primarily through inhibition of the JAK/STAT pathway. Toxicity studies revealed low toxicity, with an acute LD50 value of 3200 mg/kg in mice, and 2445 mg/kg and 2113 mg/kg in male and female rats, respectively.

2.3.10. Brazilin

Brazilin is a naturally occurring bioactive compound (red pigment) derived from the wood of plants such as *Caesalpinia violacea*, *Haematoxylum brasiletto*, *Paubrasilia echinata*, and the heartwood of *Caesalpinia sappan*. Jung et al. isolated brazilin from the ethyl acetate extract of *Caesalpinia sappan* heartwood and evaluated its anti-arthritic activity.

The compound was purified using high-performance liquid chromatography (HPLC) and structurally confirmed by mass spectrometry and ^1H/^13C NMR analysis. A type-II collagen-induced arthritis (CIA) mouse model was employed to assess its anti-rheumatoid

efficacy. Brazilin (10 mg/kg) and methotrexate (3 mg/kg) were administered intraperitoneally, and various inflammatory cytokines and oxidative stress markers were analyzed.

The results demonstrated a significant reduction in pro-inflammatory cytokines, paw edema, and arthritis index scores in treated mice. Additionally, bone mineral density was notably improved following treatment with both brazilin and methotrexate. Microstructural analysis revealed protection of joint architecture, enhanced bone formation, and reduced surface erosion. These findings indicate the protective and therapeutic potential of brazilin in rheumatoid arthritis.

2.4. Plant Sterols

Beta-Sitosterol

Beta-sitosterol is a plant-derived sterol commonly found in fruits, vegetables, nuts, and seeds. It is widely utilized for lowering cholesterol levels and alleviating symptoms of benign prostatic hyperplasia. Liu et al. investigated the immunomodulatory effects of β-sitosterol on macrophages and its potential application in rheumatoid arthritis (RA).

Administration of β-sitosterol (20 or 50 mg/kg, i.p.) enhanced immune modulation in CIA mouse models. Treatment of M1-polarized bone marrow-derived macrophages (BMDMs) with β-sitosterol significantly reduced the expression of CD86, IL-1β, iNOS, and MHC-II by 87.1%, 47.1%, 50.2%, and 31.3%, respectively.

In CIA mice, β-sitosterol suppressed the production of pro-inflammatory cytokines and reduced levels of collagen-specific antibodies (IgG and IgG1, but not IgG2c). These findings suggest that β-sitosterol possesses significant therapeutic potential in the management of rheumatoid arthritis.

3. Nano-Formulation of Isolated Compounds

Nanotechnology has emerged as a promising approach for the treatment of various severe diseases, aiming to enhance the efficacy and safety profile of therapeutic agents. Nanocarrier systems offer several advantages, including controlled and targeted drug delivery, which helps in minimizing adverse effects.

Recently, nanocarriers have gained considerable attention for the delivery of plant-derived extracts and isolated compounds. Numerous studies have reported enhanced anti-arthritic activity of herbal constituents when formulated using nanotechnology, primarily due to improved bioavailability and stability. Detailed information regarding plant isolates, their

nanoformulations, methods of preparation, and average particle size is summarized in Table 2.

Table 2. Plant isolates with their nano-formulation for antiarthritic or antioxidant activity.

Nanoformulation	Isolate Compound	Method of Preparation	Average Particle Size (nm)
Solid lipid nanoparticle	Piperine	Melt emulsification	128.80
Transferosome	Capsaicin	Conventional thin film hydration	94
Chitosan nanoparticles	Eugenol	Solvent dispersion method	30.8–37.95
Sodium alginate microcapsules	Cannabidiol	Ionic gelation	0.400 ± 0.050
Nanoemulsions	Curcumin	High-pressure homogenizing	150
Cadmium telluride quantum dots	Quercetin	*N*-acetyl-L-cysteine (nac) as stabilizer in aqueous solution	185
Nano-emulsion	Quercetin	Spontaneous emulsification techniques	136.8 ± 1.2
Mixed micellar nanosystem	Resveratrol	Thin film hydration method	52.97 ± 4.52
Eudragit nanoparticle	Kaempferol	Nanoprecipitation	87.8 ± 1.67
Ethosomes	Rosmarinic acid	Mechanical dispersion	138 ± 1.11
Liposomes	Rosmarinic acid	Dry film hydration	202 ± 1.12
Silica nanoparticles	Gallic acid	Covalent immobilization	8–30
Gold nanoparticles	Chlorogenic acid	Green synthesis	22.25 ± 4.78
Nanoemulsions	Ferulic acid	Spontaneous nano-emulsification	100–200
Solid lipid nanoparticles	β-sitosterol	Double emulsion solvent displacement	146.7

Table 2. Plant isolates with their nano-formulation for antiarthritic or antioxidant activity.

Piperine-loaded solid lipid nanoparticles (SLNs) were formulated using the melt emulsification technique and characterized for particle size (128.80 nm), entrapment efficiency (78.71%), and zeta potential (−23.34 mV). The developed SLNs were administered via oral and topical routes in CFA-induced arthritic rat models. Ex vivo permeation studies using Franz diffusion cells demonstrated that piperine from the SLN gel formulation effectively accumulated within the skin layers. A significant reduction in TNF-α levels was observed in the piperine-SLN-treated group compared to the arthritic control group, which may be attributed to the preferential localization of SLNs at inflamed sites, thereby reducing TNF-α secretion from activated macrophages. Histopathological evaluation revealed minimal inflammatory cell infiltration and reduced connective tissue proliferation in the SLN-treated group, whereas the control group exhibited moderate inflammatory infiltration and tissue proliferation.

Sarwa et al. (2013) developed capsaicin-loaded transferosomal vesicular systems for topical application in experimental arthritic rats. These transferosomes were prepared using the conventional thin-film hydration method and evaluated for physicochemical properties such as morphology, particle size distribution, zeta potential, elasticity, and viscosity. The optimized formulation exhibited nanoscale size (94 nm), adequate deformability, and a negative surface charge (−14.5 mV). Furthermore, the anti-arthritic efficacy of capsaicin-

loaded transferosomes was compared with a marketed formulation (Thermagel). The results indicated superior skin permeability and enhanced drug deposition at the target site for transferosomal formulations, resulting in improved anti-inflammatory and anti-arthritic activity compared to the conventional gel.

Jabbari et al. investigated the therapeutic potential of eugenol-encapsulated chitosan nanoparticles (Eug-CNPs) in a neonatal CIA rat model. These nanoparticles were prepared using the solvent dispersion method and evaluated for oxidative stress markers, including malondialdehyde (MDA) levels, FOXO3 protein expression (via Western blot), and gene expression of TGF-β and CCL2/MCP-1 (via RT-PCR), along with histopathological analysis of cartilage. The findings demonstrated that Eug-CNPs significantly reduced serum MDA levels and modulated FOXO3 protein expression compared to the control group. Additionally, Eug-CNPs downregulated TGF-β and MCP-1 gene expression, with a notable positive correlation between these markers. The formulation also alleviated joint inflammation, synovial hyperplasia, and cartilage degradation associated with rheumatoid arthritis.

Quercetin (QTN) was encapsulated within cadmium telluride quantum dots (TGA-CdTe QDs) to enhance its anti-arthritic activity in an adjuvant-induced arthritis model in Wistar rats. Treatment with QTN-loaded QDs (QDs-QE) reduced lipid peroxidation and improved antioxidant enzyme activity, including superoxide dismutase (SOD). Additionally, reductions in catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx) levels in paw tissues were observed. Histopathological studies indicated cartilage regeneration following QDs-QE treatment. These findings suggest that QDs-QE possess significant therapeutic potential in rheumatoid conditions. Notably, the nanocarrier system enhanced anti-arthritic efficacy even at lower drug concentrations compared to free quercetin.

Gokhale et al. developed a quercetin-loaded nanoemulsion (QCT-NE) gel using a spontaneous emulsification technique for effective rheumatoid arthritis management. The formulation significantly inhibited TNF-α production in RAW 264.7 cells, reduced cartilage degradation, and delayed disease progression. The QCT-NE gel demonstrated a marked reduction in paw edema (51.13 ± 1.35 mm) compared to the control group (71.21 ± 0.33 mm), indicating its potential as a promising topical therapeutic system.

Zhang et al. (2020) formulated β-sitosterol-loaded SLNs using a double emulsion solvent displacement technique and evaluated their efficacy in CFA-induced arthritic rats. The formulation significantly decreased pro-inflammatory cytokines such as TNF-α, IL-2, IL-6, IL-16, and IL-17, while increasing anti-inflammatory cytokines IL-10 and TGF-β.

Additionally, reductions in paw edema, arthritic index, COX-2, PGE2, VEGF, and NF-κB levels were observed. These findings suggest that β-sitosterol-SLNs exert potent anti-arthritic effects via inhibition of NF-κB and activation of the HO-1/Nrf-2 signaling pathway.

A mixed micellar nano-system of resveratrol was developed using poloxamer 188 and poloxamer 407 via the thin-film hydration method for localized arthritis treatment. The optimized formulation demonstrated favorable physicochemical properties and was further coated with polylactic acid (PLA). The PLA-coated formulation exhibited superior anti-arthritic efficacy compared to uncoated micelles and drug suspension following intra-articular administration. The system effectively reduced cartilage damage and synovial inflammation, highlighting its potential for site-specific therapy.

Kaempferol, a potent antioxidant flavonoid, has limited clinical applicability due to poor aqueous solubility. To address this limitation, kaempferol-loaded Eudragit E100 nanoparticles (KAEN) were developed using a nanoprecipitation technique. The formulation enhanced drug dissolution through reduced particle size, improved encapsulation efficiency, amorphous transformation, and intermolecular interactions with excipients. Antioxidant assays confirmed that KAEN retained and even enhanced antioxidant activity compared to free kaempferol.

Yücel et al. formulated rosmarinic acid-loaded ethosomes (ETHs) and liposomes (LPs) and evaluated their transdermal delivery potential. Ethosomes exhibited superior skin permeation compared to liposomes and conventional solutions. Additionally, enhanced antioxidant activity and inhibition of collagenase and elastase enzymes were observed, indicating improved therapeutic performance.

Deligiannakis et al. developed antioxidant-functionalized silica nanoparticles (SiO_2 NPs) conjugated with gallic acid (GA), forming hybrid nano-antioxidants. These nanoparticles demonstrated enhanced radical scavenging activity compared to free GA, suggesting their applicability in oxidative stress-mediated arthritic conditions.

Chlorogenic acid-loaded gold nanoparticles (CGA-AuNPs) were synthesized using a green approach and evaluated for anti-inflammatory activity. The nanoparticles effectively inhibited pro-inflammatory cytokines and NF-κB-mediated pathways, demonstrating enhanced activity compared to free CGA. These findings support the potential of CGA-AuNPs as novel anti-arthritic agents.

Ferulic acid-loaded nanoemulsion (FA-NE) gel was developed using spontaneous emulsification to improve drug permeability and antioxidant efficacy. The formulation

exhibited sustained drug release, enhanced skin permeation, and superior protective effects against oxidative stress compared to conventional formulations.

Curcumin's therapeutic potential is limited by poor solubility and stability under physiological conditions. To overcome these challenges, nanoemulsions and polymeric micelles were developed to enhance its bioavailability. Zheng et al. prepared curcumin-loaded nanoemulsions (CM-Ns) using high-pressure homogenization. The formulation demonstrated improved pharmacokinetic parameters (AUC and Cmax) and significantly reduced TNF-α and IL-1β levels in synovial fluid and serum. These results indicate that CM-Ns provide an effective delivery system, enabling the transition of curcumin therapy from intravenous to oral administration.

4. CONCLUSIONS

Herbal isolates, commonly known as secondary metabolites, exhibit a wide spectrum of pharmacological activities and are extensively utilized worldwide as therapeutic agents or dietary supplements. Understanding the molecular structure of these bioactive compounds enables the design and synthesis of more effective and potent derivatives.

Various classes of plant-derived isolates, including alkaloids, terpenoids, flavonoids, and polyphenols, have been reported to demonstrate significant anti-arthritic (AA) activity. These compounds are relatively accessible from natural sources and display notable therapeutic efficacy. However, the extraction and purification of such isolates remain technically demanding and time-intensive processes, leading many researchers to rely on commercially available purified compounds for experimental studies.

In recent years, there has been a substantial increase in herbal-based formulations for arthritis management in the market. Nevertheless, most of these products contain crude extracts or combinations of plant materials rather than pure isolated compounds. Importantly, the therapeutic potential of these isolates can be further enhanced through nanoformulation approaches, which improve aqueous solubility, bioavailability, and enable targeted or site-specific drug delivery, thereby amplifying their anti-arthritic effectiveness.

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