RESEARCH PAPER

EMERGING PHYTOTHERAPEUTIC STRATEGIES FOR THE MANAGEMENT OF ARTHRITIS: COMPREHENSIVE INSIGHTS INTO BIOACTIVE PHYTOCONSTITUENTS, MOLECULAR MECHANISMS, EXPERIMENTAL PHARMACOLOGY, AND FUTURE THERAPEUTIC PERSPECTIVES

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ABSTRACT:
Arthritis is one of the leading causes of chronic pain, disability, and reduced quality of life worldwide, affecting millions of individuals through progressive joint inflammation, cartilage degeneration, and bone destruction. Although conventional therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), biologics, and Janus kinase (JAK) inhibitors, effectively alleviate symptoms and delay disease progression, their long-term use is frequently associated with adverse effects, high treatment costs, and incomplete disease remission. Consequently, phytotherapy has emerged as a promising complementary and alternative therapeutic strategy owing to its multitarget pharmacological actions and comparatively favorable safety profile. This review comprehensively summarizes the current knowledge on the pathophysiology of arthritis, emphasizing inflammatory cytokines, oxidative stress, mitochondrial dysfunction, and major intracellular signaling pathways, including NF-κB, MAPK, JAK/STAT, PI3K/Akt, NLRP3 inflammasome, COX-2, and 5-lipoxygenase. Particular attention is given to bioactive phytoconstituents such as curcumin, resveratrol, quercetin, kaempferol, luteolin, apigenin, catechins, boswellic acids, thymoquinone, berberine, and other polyphenols, flavonoids, terpenoids, alkaloids, saponins, tannins, and glycosides. Furthermore, the review compiles experimental pharmacological evidence from *in vitro* and *in vivo* studies, summarizes medicinal plants with established anti-arthritic activity, and highlights their molecular targets and mechanisms of action. Emerging advances in nanotechnology-based phytopharmaceuticals, molecular docking, network pharmacology, omics technologies, and artificial intelligence are also discussed as future directions for improving the efficacy, bioavailability, and precision of plant-derived therapeutics. Collectively, the available evidence indicates that phytochemicals exert anti-inflammatory, antioxidant, immunomodulatory, and chondroprotective effects through simultaneous modulation of multiple molecular pathways. However, further standardization, pharmacokinetic evaluation, and well-designed multicenter clinical trials are required to facilitate their successful translation into evidence-based clinical practice. This review provides an integrated scientific framework for researchers and clinicians involved in the development of safer, multitarget, and effective phytotherapeutic interventions for arthritis management.

Keywords: Arthritis**,** Phytotherapy**,** Medicinal Plants**,** Phytoconstituents**,** Rheumatoid Arthritis**,** Osteoarthritis**,** NF-κB**,** Inflammation**,** Experimental Pharmacology**,** Molecular Targets.
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INTRODUCTION:

Arthritis comprises a heterogeneous group of chronic musculoskeletal disorders characterized by joint inflammation, pain, stiffness, progressive cartilage degeneration, and functional disability. More than 100 clinically distinct forms of arthritis have been identified, including osteoarthritis (OA), rheumatoid arthritis (RA), gout, psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and reactive arthritis. Although these disorders differ in etiology and pathogenesis, they collectively represent one of the

leading causes of chronic pain, physical disability, reduced quality of life, and healthcare utilization worldwide. The increasing prevalence of arthritis, coupled with population aging, obesity, sedentary lifestyles, and metabolic disorders, has transformed it into a major public health concern. Consequently, there is growing interest in identifying safer, more effective, and economically sustainable therapeutic interventions capable of controlling disease progression while minimizing treatment-related adverse effects.[1-6]

Global Burden of Arthritis

Arthritis has emerged as one of the most significant contributors to disability across the globe. According to the World Health Organization (WHO), musculoskeletal disorders affect approximately 1.71 billion people worldwide, making them the leading cause of disability measured by years lived with disability (YLDs). Osteoarthritis alone affected approximately 528 million individuals globally in 2019, representing an increase of more than 113% since 1990, and its prevalence is projected to continue rising because of increasing life expectancy, obesity, and physical inactivity. Approximately 73% of individuals with osteoarthritis are older than 55 years, while nearly 60% are women. The knee joint remains the most frequently affected anatomical site, followed by the hip and hand joints.[5-8]

Table 1. Global burden of arthritis and musculoskeletal disorders

Parameter	Current Estimate	Source
People living with musculoskeletal disorders	~1.71 billion	WHO
Global osteoarthritis cases (2019)	~528 million	WHO
Increase in osteoarthritis since 1990	>113%	WHO
Individuals with moderate to severe OA requiring rehabilitation	~344 million	WHO
Percentage of OA patients aged >55 years	~73%	WHO
Female proportion among OA patients	~60%	WHO
Most commonly affected joint	Knee	WHO

Epidemiology of Arthritis

The epidemiology of arthritis demonstrates marked variation according to age, sex, ethnicity, genetic predisposition, lifestyle, and geographic location. Osteoarthritis is predominantly an age-related degenerative disease, whereas rheumatoid arthritis is a systemic autoimmune disorder affecting approximately 0.5–1.0% of the adult population worldwide. Women exhibit a considerably higher prevalence of rheumatoid arthritis than men, with reported female-to-male ratios ranging from 2:1 to 3:1. Similarly, osteoarthritis occurs more frequently among postmenopausal women, suggesting an important influence of hormonal changes on disease susceptibility.[8-12]

In the United States, data reported by the Centers for Disease Control and Prevention (CDC) indicate that nearly one in five adults has physician-diagnosed arthritis. National Health Interview Survey data further demonstrated an age-adjusted arthritis prevalence of 18.9% among adults in 2022, with higher prevalence observed among women (21.5%) than men (16.1%). The prevalence increases markedly with advancing age, reaching more than half of adults aged 75 years and older. These epidemiological trends are mirrored across many developed and developing countries, where increasing longevity, obesity, and sedentary behavior continue to drive disease incidence.

Table 2. Major epidemiological characteristics of common arthritic disorders

Arthritis type	Approximate prevalence	Predominant age group	Female predominance	Principal pathological feature
Osteoarthritis	Most common form of arthritis	>50 years	Moderate	Cartilage degeneration
Rheumatoid arthritis	0.5–1.0% of adults	30–60 years	High	Autoimmune synovitis
Gout	Increasing worldwide	Middle-aged to elderly	Male predominance	Monosodium urate crystal deposition
Psoriati	0.1–1%	30–55	Similar	Immun

c arthritis		years	in both sexes	e-mediated joint inflammation
Ankylosing spondylitis	0.1–1.4%	Young adults	Male predominance	Axial skeletal inflammation

Economic Burden of Arthritis

Arthritis imposes a substantial socioeconomic burden on healthcare systems, employers, patients, and caregivers. The disease contributes to direct medical expenditures related to physician consultations, hospitalization, diagnostic imaging, laboratory investigations, pharmacotherapy, rehabilitation, and surgical interventions, including total joint replacement. Indirect costs arise from work absenteeism, reduced productivity, disability, premature retirement, and informal caregiving.[13-15] In the United States alone, arthritis accounts for annual healthcare expenditures and productivity losses exceeding US$300 billion, making it one of the most expensive chronic diseases. Similar economic trends have been reported across Europe and Asia, where increasing disease prevalence has resulted in escalating healthcare costs and significant pressure on national health systems. Importantly, the chronic and progressive nature of arthritis necessitates lifelong management, further amplifying its financial impact on individuals and society.

Current Treatment Limitations

Current pharmacological management primarily focuses on symptom control and slowing disease progression. Conventional treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), biologic agents targeting TNF-α, IL-6, and CD20, and Janus kinase (JAK) inhibitors. Although these agents have substantially improved patient outcomes, their long-term use is frequently associated with gastrointestinal complications, cardiovascular toxicity, hepatotoxicity, nephrotoxicity, immunosuppression, increased susceptibility to infections, osteoporosis, and high treatment costs.[16-17]

Need for Plant-Based Therapies

Medicinal plants have served as the foundation of traditional healthcare systems for centuries and continue to provide valuable therapeutic agents for inflammatory disorders. Numerous botanical species possess potent anti-inflammatory, antioxidant, immunomodulatory, analgesic, and chondroprotective activities attributable to their rich repertoire of secondary metabolites. Growing experimental and clinical evidence indicates that several medicinal plants, including Curcuma longa, *Boswellia serrata, Withania somnifera, Zingiber officinale, Tinospora cordifolia,* and *Nigella sativa*, significantly reduce inflammatory mediators, improve joint function, and attenuate cartilage degeneration. These findings support the integration of phytotherapy into contemporary arthritis management, either as complementary interventions or as leads for the development of novel disease-modifying therapeutics.[18-19]

OVERVIEW OF ARTHRITIS[20-28]

Arthritis is a collective term encompassing more than one hundred musculoskeletal disorders characterized by varying degrees of joint inflammation, cartilage degeneration, pain, stiffness, and progressive impairment of physical function. These disorders differ in etiology, immunopathogenesis, clinical presentation, and disease progression, yet they share common pathological features including chronic inflammation, extracellular matrix degradation, oxidative stress, and abnormal immune responses. Arthritis represents one of the leading causes of disability worldwide and significantly compromises mobility, work productivity, and quality of life. The disease burden continues to increase due to population aging, obesity, sedentary lifestyles, metabolic disorders, and improved life expectancy. Understanding the different forms of arthritis and their underlying pathological mechanisms is essential for the development of effective therapeutic interventions, particularly those targeting multiple molecular pathways through phytotherapeutic approaches. Although numerous forms of arthritis have been identified, five major types account for the majority of clinical cases, namely rheumatoid arthritis, osteoarthritis, gout, psoriatic arthritis, and ankylosing spondylitis. Each disorder possesses distinct pathogenic mechanisms while sharing several overlapping inflammatory and degenerative pathways.

Classification of Arthritis

Arthritic disorders are broadly classified according to their etiological origin, immunological characteristics, metabolic involvement, and anatomical distribution. Degenerative arthritis primarily results from progressive deterioration of articular cartilage, whereas inflammatory arthritis develops due to persistent immune-mediated inflammation of synovial tissues. Crystal-induced arthritis occurs following deposition of monosodium urate or calcium pyrophosphate crystals within joints, while spondyloarthropathies mainly affect the axial skeleton and entheses. Despite these classifications, increasing evidence indicates substantial overlap among inflammatory signaling pathways, oxidative stress mechanisms,

and cartilage-destructive processes across different arthritic conditions.

Table 3. Classification of Major Types of Arthritis

Arthritis Type	Etiology	Primary Target Tissue	Major Clinical Features	Principal Pathogenic Mechanism
Rheumatoid Arthritis	Autoimmune	Synovial membrane	Symmetrical polyarthritis, joint swelling	Autoimmune inflammation
Osteoarthritis	Degenerative	Articular cartilage	Joint pain, stiffness, reduced mobility	Cartilage degeneration
Gout	Metabolic	Synovium and cartilage	Acute inflammatory attacks	Monosodium urate crystal deposition
Psoriatic Arthritis	Autoimmune	Synovium and entheses	Arthritis associated with psoriasis	Immune dysregulation
Ankylosing Spondylitis	Autoimmune	Axial skeleton	Back pain, spinal stiffness	Enthesitis and new bone formation

PATHOPHYSIOLOGY OF ARTHRITIS[29-32]

Despite considerable heterogeneity among arthritic disorders, several pathological events are common to nearly all forms of arthritis. Persistent inflammation within synovial tissues, oxidative stress, immune dysregulation, extracellular matrix degradation, angiogenesis, and progressive destruction of cartilage and bone collectively contribute to disease initiation and progression. These interconnected mechanisms establish a self-perpetuating inflammatory cycle that ultimately leads to chronic pain, structural joint damage, and irreversible functional impairment.

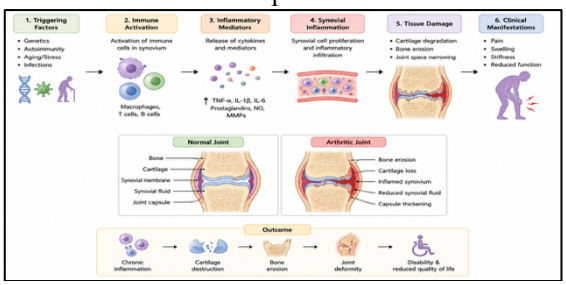

Figure 1. Pathophysiology of arthritis

MOLECULAR MECHANISMS OF ARTHRITIS[33-38]

Arthritis is a multifactorial disorder resulting from the intricate interplay between innate and adaptive immune responses, chronic inflammation, oxidative stress, and dysregulated intracellular signaling pathways. Although the pathogenic mechanisms vary among rheumatoid arthritis (RA), osteoarthritis (OA), psoriatic arthritis (PsA), gout, and ankylosing spondylitis (AS), these diseases converge on common molecular cascades that promote synovial inflammation, cartilage degradation, osteoclast activation, and progressive joint destruction. Activation of resident macrophages, fibroblast-like synoviocytes (FLS), dendritic cells, neutrophils, T lymphocytes, B lymphocytes, and chondrocytes results in excessive secretion of pro-inflammatory cytokines, chemokines, prostaglandins, leukotrienes, and reactive oxygen species (ROS). These mediators activate several intracellular signaling pathways, including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphoinositide-3 kinase/protein kinase B (PI3K/Akt), Toll-like receptor (TLR), and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome pathways. Persistent activation of these signaling networks establishes a self-perpetuating inflammatory microenvironment that accelerates tissue injury and disease progression. Understanding these molecular mechanisms provides the scientific rationale for developing phytotherapeutic agents capable of simultaneously targeting multiple inflammatory pathways.

Role of Pro-inflammatory Cytokines in Arthritis

Cytokines are low-molecular-weight signaling proteins that regulate communication among

immune cells and coordinate inflammatory responses. In arthritic disorders, excessive production of pro-inflammatory cytokines disrupts tissue homeostasis by promoting leukocyte recruitment, angiogenesis, synovial hyperplasia, osteoclastogenesis, extracellular matrix degradation, and oxidative stress. These cytokines act synergistically rather than independently, amplifying inflammatory signaling through multiple positive feedback loops. Consequently, cytokines represent major therapeutic targets for both conventional biologics and emerging phytopharmaceutical interventions.

Tumor Necrosis Factor-Alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) is considered the principal inflammatory cytokine responsible for initiating and sustaining chronic joint inflammation. It is predominantly produced by activated macrophages, monocytes, dendritic cells, T lymphocytes, fibroblast-like synoviocytes, and chondrocytes following immune activation. Binding of TNF-α to its receptors (TNFR1 and TNFR2) initiates several intracellular signaling cascades, particularly NF-κB, MAPK, and PI3K/Akt pathways, resulting in transcription of numerous inflammatory genes. Elevated TNF-α concentrations stimulate expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), matrix metalloproteinases (MMP-1, MMP-3, MMP-9, and MMP-13), receptor activator of nuclear factor-kappa B ligand (RANKL), vascular endothelial growth factor (VEGF), and additional cytokines including IL-1β and IL-6. These mediators collectively promote synovial inflammation, angiogenesis, cartilage degradation, and osteoclast-mediated bone erosion. Continuous TNF-α signaling also inhibits extracellular matrix synthesis and accelerates chondrocyte apoptosis, thereby contributing to irreversible joint destruction.

Interleukin-1 Beta (IL-1β)

Interleukin-1β is another pivotal cytokine involved in arthritis pathogenesis and functions synergistically with TNF-α to amplify inflammatory responses. IL-1β is synthesized primarily by activated macrophages following inflammasome-mediated cleavage of its inactive precursor by caspase-1. Activation of IL-1 receptors stimulates NF-κB and MAPK signaling pathways, leading to increased transcription of inflammatory mediators.

IL-1β markedly enhances production of matrix metalloproteinases and aggrecanases, resulting in degradation of collagen type II and aggrecan within articular cartilage. Simultaneously, IL-1β suppresses synthesis of extracellular matrix proteins by chondrocytes, inhibits cartilage repair, promotes nitric oxide production, and induces oxidative stress. In gout, monosodium urate crystals activate the NLRP3 inflammasome, making IL-1β the dominant mediator responsible for acute inflammatory attacks.

Interleukin-6 (IL-6)

Interleukin-6 is a pleiotropic cytokine that bridges innate and adaptive immune responses. It is secreted by macrophages, fibroblast-like synoviocytes, endothelial cells, adipocytes, and activated T cells during inflammatory conditions. IL-6 exerts its biological effects through membrane-bound and soluble IL-6 receptors, activating predominantly the JAK/STAT signaling pathway.

Interleukin-17 (IL-17)

Interleukin-17, primarily produced by T-helper 17 (Th17) lymphocytes, plays a crucial role in chronic inflammatory arthritis. IL-17 stimulates synovial fibroblasts, macrophages, endothelial cells, and chondrocytes to produce TNF-α, IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), prostaglandin E2, nitric oxide, and matrix metalloproteinases.

Interferon-Gamma (IFN-γ)

Interferon-gamma is predominantly produced by activated T-helper 1 lymphocytes and natural killer (NK) cells. Although IFN-γ exhibits both pro-inflammatory and immunoregulatory properties, excessive production contributes to macrophage activation, enhanced antigen presentation, increased expression of major histocompatibility complex (MHC) molecules, and sustained cytokine production.

Table 4. Major Pro-inflammatory Cytokines Involved in Arthritis

Cytokine	Major Cellular Source	Principal Biological Functions	Pathological Consequences
TNF-α	Macrophages, FLS, T cells	NF-κB activation, cytokine induction	Synovitis, cartilage degradation, bone erosion
IL-1β	Macrophages	MMP induction, cartilage degradation	Chondrocyte apoptosis, inflammation
IL-6	Macrophages, FLS	JAK/STAT activation, B-cell	Chronic inflammation, osteoclastogenesis

		maturation	
IL-17	Th17 lymphocytes	RANKL induction, neutrophil recruitment	Bone destruction, chronic inflammation
IFN-γ	Th1 cells, NK cells	Macrophage activation, antigen presentation	Persistent immune activation

MAJOR INTRACELLULAR SIGNALING PATHWAYS[39-60]

Persistent inflammatory stimulation activates numerous intracellular signaling cascades responsible for regulating gene transcription, cytokine synthesis, apoptosis, oxidative stress, and extracellular matrix remodeling. Crosstalk among these pathways creates an interconnected molecular network that perpetuates disease progression.

NF-κB Signaling Pathway

The nuclear factor-kappa B (NF-κB) pathway is regarded as the master regulator of inflammatory gene expression in arthritis. Activation occurs following stimulation by TNF-α, IL-1β, Toll-like receptors, reactive oxygen species, bacterial lipopolysaccharides, and mechanical stress.

MAPK Signaling Pathway

Mitogen-activated protein kinase (MAPK) signaling regulates cellular proliferation, apoptosis, cytokine synthesis, stress responses, and inflammatory gene expression. Inflammatory cytokines activate MAPK cascades, leading to phosphorylation of transcription factors such as AP-1, CREB, and Elk-1. These transcription factors stimulate expression of MMPs, cytokines, COX-2, and inflammatory enzymes responsible for cartilage destruction and synovial proliferation.

JAK/STAT Signaling Pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway mediates intracellular signaling initiated by numerous cytokines including IL-6, IL-2, IL-12, IL-23, interferons, and granulocyte colony-stimulating factor. Binding of cytokines to their receptors activates JAK kinases, which phosphorylate STAT proteins. Activated STAT dimers subsequently migrate into the nucleus and regulate genes involved in inflammation, cell proliferation, apoptosis, immune differentiation, and autoantibody production.

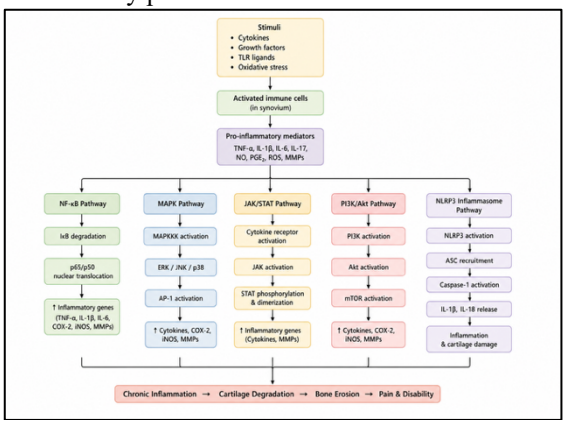

Figure 2. Molecular signaling pathways in arthritis

PI3K/Akt Signaling Pathway

The phosphoinositide-3 kinase/protein kinase B (PI3K/Akt) pathway regulates cell survival, metabolism, proliferation, autophagy, angiogenesis, and inflammatory responses. Activation occurs following stimulation by cytokines, growth factors, and oxidative stress.

Cyclooxygenase (COX) Pathway

Cyclooxygenase enzymes catalyze conversion of arachidonic acid into prostaglandins and thromboxanes.

- COX-1 is constitutively expressed and maintains physiological homeostasis.
- COX-2 is inducible and markedly upregulated during inflammation.

Overexpression of COX-2 increases prostaglandin E_2 synthesis, leading to pain, vasodilation, edema, fever, and inflammatory sensitization. Most NSAIDs exert their therapeutic effect through inhibition of COX enzymes, although prolonged use is associated with gastrointestinal, renal, and cardiovascular adverse effects.

Lipoxygenase (LOX) Pathway

Lipoxygenase enzymes convert arachidonic acid into leukotrienes and hydroxyeicosatetraenoic acids (HETEs), which contribute to leukocyte recruitment, vascular permeability, oxidative stress, and chronic inflammation. Among the LOX isoforms, 5-LOX plays the most important role in arthritis by promoting synthesis of leukotriene B_4, a potent neutrophil chemoattractant. Simultaneous inhibition of both COX and LOX pathways has gained considerable attention because dual inhibition may provide superior anti-inflammatory efficacy with fewer adverse effects.

OXIDATIVE STRESS IN ARTHRITIS[61-67]

Oxidative stress is recognized as one of the principal molecular mechanisms driving the initiation and progression of both inflammatory and degenerative arthritic disorders. It results from an imbalance between the excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the diminished capacity

of endogenous antioxidant defense systems to neutralize these reactive molecules. Under physiological conditions, low concentrations of ROS participate in normal cellular signaling, regulation of gene expression, immune defense, and maintenance of tissue homeostasis. However, persistent inflammatory stimulation within arthritic joints leads to uncontrolled ROS generation by activated macrophages, neutrophils, synovial fibroblasts, and chondrocytes, causing oxidative damage to proteins, lipids, nucleic acids, and extracellular matrix components. This oxidative microenvironment amplifies inflammatory signaling, accelerates cartilage degeneration, promotes osteoclast differentiation, and ultimately contributes to irreversible joint destruction.

Table 5. Oxidative Stress Biomarkers Commonly Evaluated in Experimental Arthritis

Biomarker	Biological Significance	Interpretation
ROS	Overall oxidative burden	Increased in arthritis
Malondialdehyde (MDA)	Lipid peroxidation marker	Elevated during disease progression
Nitric Oxide (NO)	Reactive nitrogen species	Increased due to iNOS activation
Superoxide Dismutase (SOD)	Antioxidant enzyme	Decreased in arthritic tissues
Catalase (CAT)	Hydrogen peroxide detoxification	Reduced activity
Glutathione Peroxidase (GPx)	Lipid peroxide detoxification	Reduced activity
Reduced Glutathione (GSH)	Intracellular antioxidant reserve	Depleted in chronic inflammation
8-Hydroxy-2′-deoxyguanosine (8-OHdG)	Oxidative DNA damage	Elevated in severe oxidative stress

CURRENT PHARMACOLOGICAL TREATMENT OF ARTHRITIS[68-72]

Arthritis is a chronic and progressive musculoskeletal disorder that requires long-term pharmacological intervention to alleviate pain, suppress inflammation, prevent structural joint damage, and preserve physical function. The selection of therapeutic agents depends on the type of arthritis, disease severity, clinical manifestations, and the presence of comorbid conditions. Current pharmacological management includes nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs), biological DMARDs (biologics), and targeted synthetic DMARDs such as Janus kinase (JAK) inhibitors. Although these medications have significantly improved disease outcomes over the past three decades, none provide a definitive cure for arthritis. Most currently available drugs primarily control inflammation and disease symptoms but do not completely restore damaged cartilage or reverse bone erosion. Furthermore, prolonged administration is frequently associated with adverse drug reactions, immunosuppression, treatment resistance, and substantial economic burden.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications for the symptomatic management of arthritis owing to their potent analgesic, antipyretic, and anti-inflammatory properties. These agents exert their therapeutic activity primarily through inhibition of cyclooxygenase (COX) enzymes responsible for converting arachidonic acid into prostaglandins, which mediate pain, inflammation, vasodilation, and fever. Two major cyclooxygenase isoforms have been identified: constitutively expressed COX-1, which maintains gastric mucosal integrity, renal blood flow, and platelet function, and inducible COX-2, which is markedly upregulated during inflammatory conditions.

Traditional NSAIDs, including diclofenac, ibuprofen, naproxen, indomethacin, ketoprofen, aceclofenac, piroxicam, and meloxicam, inhibit both COX-1 and COX-2, whereas selective COX-2 inhibitors such as celecoxib and etoricoxib preferentially suppress inflammatory prostaglandin synthesis while producing comparatively fewer gastrointestinal complications.

Disease-Modifying Antirheumatic Drugs (DMARDs)

Disease-modifying antirheumatic drugs (DMARDs) constitute the cornerstone of rheumatoid arthritis treatment because they suppress the underlying autoimmune response and slow disease progression rather than merely alleviating symptoms. Unlike NSAIDs, DMARDs

inhibit immune activation, reduce synovial inflammation, delay radiographic progression, and preserve joint integrity.

Conventional synthetic DMARDs (csDMARDs) include methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. Among these, methotrexate remains the first-line therapeutic agent due to its well-established efficacy, affordability, and ability to reduce inflammatory cytokine production through inhibition of folate-dependent metabolic pathways and increased extracellular adenosine concentrations.

Biological Disease-Modifying Antirheumatic Drugs (Biologics)

Biological DMARDs have revolutionized arthritis treatment by specifically targeting cytokines, immune receptors, and inflammatory cells involved in disease pathogenesis. These genetically engineered monoclonal antibodies and fusion proteins selectively inhibit key inflammatory mediators responsible for chronic synovial inflammation.

Tumor necrosis factor inhibitors, including infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol, represent the most widely prescribed biologics. Additional biological agents target interleukin-6 receptors (tocilizumab, sarilumab), CD20-positive B lymphocytes (rituximab), T-cell co-stimulation (abatacept), and interleukin-17 or interleukin-23 signaling pathways used particularly in psoriatic arthritis and ankylosing spondylitis.

Glucocorticoids

Glucocorticoids remain among the most potent anti-inflammatory agents available for rapid control of acute inflammatory exacerbations in arthritis. Commonly used corticosteroids include prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone.

Janus Kinase (JAK) Inhibitors

Janus kinase inhibitors represent a newer class of targeted synthetic DMARDs that inhibit intracellular cytokine signaling rather than extracellular cytokine activity. Currently approved JAK inhibitors include tofacitinib, baricitinib, upadacitinib, filgotinib, and deucravacitinib. These orally administered agents effectively reduce disease activity, improve physical function, inhibit structural joint damage, and demonstrate rapid clinical efficacy, particularly in patients exhibiting inadequate responses to conventional DMARDs or biologics.

Advantages of Current Pharmacological Therapies

Modern pharmacotherapy has transformed arthritis management by substantially reducing inflammation, preventing disability, and improving long-term patient outcomes. Conventional and targeted therapies effectively suppress inflammatory cytokines, reduce joint swelling, alleviate pain, improve mobility, and slow radiographic progression. Biologic agents have dramatically improved remission rates in rheumatoid arthritis and other inflammatory arthritides, while JAK inhibitors provide convenient oral alternatives to injectable biologics. Early initiation of DMARD therapy has significantly decreased the incidence of irreversible joint deformities and improved overall quality of life.

Limitations of Current Pharmacological Therapies

Despite remarkable therapeutic advances, current pharmacological interventions possess several important limitations. Most medications primarily suppress inflammatory symptoms without completely reversing cartilage degeneration or restoring damaged joint architecture. Therapeutic response varies considerably among individuals owing to genetic variability, disease heterogeneity, and development of drug resistance. Long-term treatment frequently requires combination therapy, continuous clinical monitoring, and dose adjustments.

NEED FOR HERBAL MEDICINES IN ARTHRITIS MANAGEMENT[73-78]

The limitations associated with conventional pharmacotherapy have stimulated increasing interest in plant-derived therapeutic agents as complementary or alternative approaches for arthritis management. Medicinal plants possess a remarkable diversity of bioactive phytoconstituents, including polyphenols, flavonoids, terpenoids, alkaloids, saponins, tannins, and glycosides, which collectively exhibit anti-inflammatory, antioxidant, immunomodulatory, analgesic, and chondroprotective activities. Unlike many synthetic drugs that primarily target a single molecular pathway, phytochemicals frequently modulate multiple signaling cascades simultaneously, including NF-κB, MAPK, JAK/STAT, PI3K/Akt, Nrf2/HO-1, COX-2, 5-LOX, TLR, and NLRP3 inflammasome pathways. This multitarget pharmacological profile enables simultaneous suppression of inflammatory cytokines, oxidative stress, matrix metalloproteinases, osteoclastogenesis, and apoptosis while enhancing endogenous antioxidant defenses.

Several medicinal plants, such as Curcuma longa, *Boswellia serrata, Withania somnifera, Zingiber officinale, Tinospora cordifolia, Nigella sativa, Camellia sinensis, Moringa oleifera*, and *Terminalia species*, have demonstrated promising anti-arthritic efficacy in preclinical studies and selected clinical trials. Their principal phytoconstituents—including curcumin, boswellic acids, withanolides, gingerols, thymoquinone, epigallocatechin gallate, quercetin, kaempferol, and resveratrol—exert synergistic effects by targeting

multiple inflammatory mediators with comparatively favorable safety profiles. Furthermore, phytotherapeutic agents may reduce dependence on corticosteroids and NSAIDs when used as adjunctive therapy, potentially minimizing drug-related toxicity.

IMPORTANCE OF PHYTOTHERAPY IN ARTHRITIS MANAGEMENT[74-78]

Phytotherapy, commonly defined as the prevention and treatment of diseases using medicinal plants and their bioactive constituents, has emerged as one of the most promising therapeutic approaches for the management of chronic inflammatory disorders, including arthritis. For centuries, medicinal plants have served as the foundation of healthcare systems across diverse civilizations, providing effective remedies for pain, inflammation, musculoskeletal disorders, and autoimmune diseases. In recent decades, scientific advances in phytochemistry, pharmacology, molecular biology, and biotechnology have provided substantial evidence supporting the anti-inflammatory, antioxidant, immunomodulatory, analgesic, and chondroprotective properties of numerous medicinal plants.

Traditional Medicine and the Historical Evolution of Phytotherapy

The use of medicinal plants for treating inflammatory and musculoskeletal disorders dates back several thousand years. Ancient civilizations in India, China, Egypt, Greece, Africa, and the Middle East extensively documented the therapeutic properties of herbs for relieving joint pain, swelling, stiffness, and mobility impairment. Traditional medicinal systems developed sophisticated approaches to disease diagnosis and herbal formulation based on empirical observations accumulated over generations.

Ayurveda and Arthritis Management

Ayurveda, one of the oldest holistic systems of medicine, originated in India more than 3,000 years ago and remains an integral component of healthcare throughout South Asia. According to Ayurvedic philosophy, arthritis is primarily classified under Sandhivata, Amavata, and Vatarakta, depending upon disease etiology and clinical manifestations. These disorders are believed to result from imbalance of the Vata dosha, accumulation of Ama (metabolic toxins), impaired digestive metabolism (Agni), and disturbed tissue homeostasis.

Important Ayurvedic medicinal plants employed in arthritis management include:

- *Curcuma longa (Turmeric)*
- *Boswellia serrata (Indian Frankincense)*
- *Withania somnifera (Ashwagandha)*
- *Tinospora cordifolia (Guduchi)*
- *Zingiber officinale (Ginger)*
- *Commiphora mukul (Guggul)*
- *Terminalia chebula*
- *Emblica officinalis*
- *Azadirachta indica*
- *Moringa oleifera*

These plants contain curcuminoids, boswellic acids, withanolides, gingerols, guggulsterones, flavonoids, tannins, and phenolic acids that suppress NF-κB activation, inhibit cyclooxygenase and lipoxygenase enzymes, reduce inflammatory cytokines, decrease oxidative stress, and protect cartilage from degradation.

Traditional Chinese Medicine (TCM)

Traditional Chinese Medicine (TCM) represents another highly developed medical system with a documented history extending over two millennia. In TCM philosophy, arthritic disorders are generally classified as Bi syndrome, which develops following obstruction of the body's energy pathways (meridians) by pathogenic factors including wind, cold, dampness, and heat. The therapeutic objective focuses on restoring the harmonious flow of Qi, improving blood circulation, strengthening vital organs, and eliminating pathogenic influences.

Common medicinal plants employed in TCM include:

- *Tripterygium wilfordii*
- *Angelica sinensis*
- *Paeonia lactiflora*
- *Astragalus membranaceus*
- *Glycyrrhiza uralensis*
- *Salvia miltiorrhiza*
- *Scutellaria baicalensis*
- *Panax ginseng*

African Traditional Medicine

African traditional medicine constitutes one of the oldest healthcare systems globally and remains the principal source of medical care for millions of people across the African continent. Indigenous African medicinal knowledge has been transmitted orally through generations and incorporates a wide diversity of medicinal plants possessing anti-inflammatory, analgesic, antimicrobial, and antioxidant activities. Arthritic disorders are traditionally managed using decoctions, infusions, poultices, powders, and topical herbal preparations prepared from roots, bark, leaves, seeds, and fruits.

Medicinal plants frequently employed in African ethnomedicine include:

- *Harpagophytum procumbens (Devil's Claw)*
- *Sutherlandia frutescens*
- *Warburgia salutaris*
- *Hypoxis hemerocallidea*
- *Zanthoxylum capense*
- *Aloe ferox*
- *Moringa oleifera*
- *Sclerocarya birrea*

Numerous phytochemicals isolated from African medicinal plants exhibit inhibition of prostaglandin synthesis, suppression of inflammatory cytokines,

reduction of oxidative stress, and attenuation of cartilage degeneration. Devil's Claw, in particular, has gained considerable international recognition because of its iridoid glycosides (harpagoside), which demonstrate clinically significant analgesic and anti-inflammatory activity in osteoarthritis and chronic musculoskeletal disorders.

Modern Phytotherapy

Modern phytotherapy integrates traditional medicinal knowledge with contemporary advances in phytochemistry, pharmacology, molecular biology, genomics, metabolomics, and evidence-based medicine. Unlike traditional empirical approaches, modern phytotherapy emphasizes scientific validation of medicinal plants through rigorous botanical authentication, phytochemical standardization, pharmacological evaluation, toxicological assessment, clinical trials, and quality control.

The discovery of sophisticated analytical techniques such as HPLC, LC-MS/MS, GC-MS, NMR spectroscopy, metabolomics, molecular docking, network pharmacology, transcriptomics, proteomics, and artificial intelligence has substantially improved understanding of plant-derived therapeutics. These technologies facilitate identification of active phytoconstituents, elucidation of molecular targets, prediction of herb-drug interactions, optimization of herbal formulations, and development of standardized phytopharmaceutical products.

Modern phytotherapy also incorporates advanced drug delivery systems including nanoparticles, phytosomes, nanoemulsions, liposomes, solid lipid nanoparticles, and polymeric nanocarriers to improve the solubility, bioavailability, stability, and tissue targeting of poorly water-soluble phytochemicals such as curcumin, resveratrol, quercetin, and boswellic acids.

Advantages of Phytotherapy over Synthetic Drugs

The increasing popularity of phytotherapy in arthritis management is primarily attributed to its multitarget pharmacological activity, favorable safety profile, and compatibility with long-term treatment. Medicinal plants contain structurally diverse phytochemicals that simultaneously regulate multiple inflammatory and oxidative signaling pathways, thereby providing broader therapeutic effects than many conventional single-target drugs.

Unlike synthetic anti-inflammatory agents that frequently produce gastrointestinal toxicity, cardiovascular complications, nephrotoxicity, hepatotoxicity, and immunosuppression during prolonged use, many medicinal plants exhibit comparatively lower toxicity while offering antioxidant, immunomodulatory, chondroprotective, and tissue-regenerative properties.

Furthermore, phytoconstituents frequently demonstrate synergistic interactions, whereby multiple compounds within the same plant enhance overall pharmacological efficacy through complementary mechanisms of action. Such synergism may reduce the required therapeutic dose and minimize adverse reactions.

Table 6. Comparison of Traditional Medical Systems Used in Arthritis Management

Traditional System	Region of Origin	Fundamental Concept	Representative Anti-arthritic Medicinal Plants	Principal Therapeutic Actions
Ayurveda	India	Restoration of Dosha balance and elimination of Ama	Curcuma longa, Boswellia serrata, Withania somnifera, Tinospora cordifolia	Anti-inflammatory, antioxidant, immunomodulatory
Traditional Chinese Medicine	China	Restoration of Qi and meridian balance	Tripterygium wilfordii, Angelica sinensis, Paeonia lactiflora, Astragalus membranaceus	Cytokine suppression, immune regulation
African Traditional Medici	Africa	Indigenous ethnomedicine and	Harpagophytum procumbens, Hypoxis	Analgesic, anti-inflammatory, antioxidant

ne		holistic healing	hemerocallidea, Aloe ferox, Moringa oleifera	

BIOACTIVE PHYTOCONSTITUENTS IN ARTHRITIS MANAGEMENT[79-92]

Medicinal plants are rich sources of bioactive phytoconstituents that possess anti-inflammatory, antioxidant, immunomodulatory, analgesic, and chondroprotective properties. These compounds regulate multiple molecular targets implicated in arthritis, including pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-17), transcription factors (NF-κB and AP-1), signaling pathways (MAPK, JAK/STAT, and PI3K/Akt), inflammatory enzymes (COX-2, 5-LOX, and iNOS), and oxidative stress mediators. Owing to their multitarget mechanisms of action, phytochemicals have emerged as promising therapeutic agents for the prevention and management of rheumatoid arthritis and osteoarthritis.

Polyphenols

Polyphenols are among the most extensively investigated phytochemicals because of their potent antioxidant and anti-inflammatory activities. They suppress inflammatory cytokines, inhibit NF-κB activation, reduce oxidative stress, and protect cartilage from degradation. Major polyphenols, including curcumin, resveratrol, gallic acid, and ellagic acid, have demonstrated significant anti-arthritic activity by reducing synovial inflammation, cartilage destruction, and oxidative damage in experimental studies, with curcumin and resveratrol also showing encouraging clinical benefits.

Flavonoids

Flavonoids constitute a major class of polyphenolic compounds with remarkable antioxidant, anti-inflammatory, and immunomodulatory properties. Representative flavonoids such as quercetin, kaempferol, luteolin, apigenin, catechins (EGCG), and rutin inhibit NF-κB, MAPK, JAK/STAT, and NLRP3 signaling pathways, decrease inflammatory cytokine production, reduce oxidative stress, and protect cartilage from degeneration. These compounds have shown substantial efficacy in both in vitro and in vivo models of arthritis.

Alkaloids

Alkaloids are nitrogen-containing secondary metabolites with significant anti-inflammatory and immunomodulatory activities. Compounds such as berberine, colchicine, and tetrandrine suppress inflammatory cytokines, inhibit NF-κB and NLRP3 inflammasome activation, and reduce oxidative stress. Several alkaloids have demonstrated therapeutic potential in experimental models and clinical management of rheumatoid arthritis and gout.

Terpenoids

Terpenoids represent one of the largest classes of plant metabolites and include boswellic acids, andrographolide, ursolic acid, and oleanolic acid. These compounds inhibit COX-2, 5-LOX, NF-κB, and pro-inflammatory cytokines, thereby reducing joint inflammation, cartilage degeneration, and bone destruction.

Saponins

Saponins are glycosidic compounds that exhibit anti-inflammatory, antioxidant, and immunomodulatory effects. Ginsenosides from Panax ginseng are among the most extensively studied saponins and have demonstrated the ability to suppress TNF-α, IL-1β, oxidative stress, and immune cell activation, thereby improving joint health.

Glycosides

Plant glycosides, including salicin, aucubin, and iridoid glycosides, possess analgesic and anti-inflammatory activities. They reduce prostaglandin synthesis, inflammatory mediator release, and oxidative stress, leading to improved joint function and pain relief.

Tannins

Tannins are high-molecular-weight polyphenols with strong antioxidant properties. They inhibit lipid peroxidation, decrease inflammatory cytokine production, and protect cartilage by preserving extracellular matrix integrity and reducing oxidative damage.

Steroids

Plant-derived phytosterols such as β-sitosterol, stigmasterol, and campesterol exhibit immunomodulatory and anti-inflammatory activities by suppressing inflammatory cytokines, reducing oxidative stress, and regulating immune cell responses.

Coumarins

Coumarins, including esculetin, scopoletin, and umbelliferone, possess potent anti-inflammatory and antioxidant properties. They inhibit COX-2, LOX, NF-κB, and inflammatory cytokines while protecting cartilage from degradation and improving joint function.

Overall, the diverse classes of phytoconstituents exert complementary and multitarget pharmacological actions, making medicinal plants a promising source of safer and more effective therapeutic agents for the prevention and management of arthritis.

Table 7. Major Bioactive Phytoconstituents with Anti-Arthritic Potential

Phytochemica	Representative	Major Pla	Chemical	Principal Mol	Experimenta	Clinical

l Class	Compound	nt Source	Class/Structure	ecular Targets	l Evidence	Evidence
Polyphenols	Curcumin	*Curcuma longa*	Diarylheptanoid	NF-κB, MAPK, COX-2, TNF-α	Extensive	Strong
	Resveratrol	*Vitis vinifera*	Stilbene	SIRT1, NF-κB, PI3K/Akt	Extensive	Moderate
	Gallic acid	*Tea, grapes*	Phenolic acid	COX-2, iNOS, TNF-α	Extensive	Limited
	Ellagic acid	*Pomegranate*	Polyphenolic dilactone	NF-κB, Nrf2	Moderate	Limited
Flavonoids	Quercetin	*Onion, apple*	Flavonol	NF-κB, MAPK, NLRP3	Extensive	Moderate
	Kaempferol	*Broccoli, spinach*	Flavonol	MAPK, COX-2	Moderate	Limited
	Luteolin	*Celery, parsley*	Flavone	JAK/STAT, NF-κB	Moderate	Limited
	Apigenin	*Chamomile*	Flavone	COX-2, MMPs	Moderate	Limited
	Catechin (EGCG)	*Green tea*	Flavan-3-ol	NF-κB, ROS	Extensive	Moderate
	Rutin	*Buckwheat, citrus*	Flavonoid glycoside	TNF-α, IL-1β	Moderate	Limited
Alkaloids	Berberine	*Berberis spp.*	Isoquinoline alkaloid	AMPK, NF-κB	Extensive	Moderate
	Colchicine	*Colchicum autumnale*	Tropolone alkaloid	NLRP3 inflammasome	Extensive	Strong (Gout)
Terpenoids	Boswellic acids	*Boswellia serrata*	Pentacyclic triterpenoid	5-LOX, NF-κB	Extensive	Strong
	Andrographolide	*Andrographis*	Diterpenoid	NF-κB, STAT3	Moderate	Limited

		panicula ta				
Saponins	Ginsenosides	*Panax ginseng*	Triterpenoid saponin	TNF-α, IL-6	Moderate	Moderate
Glycosides	Salicin	*Salix alba*	Phenolic glycoside	COX pathway	Extensive	Moderate
Tannins	Tannic acid	*Terminalia spp.*	Hydrolysable tannin	ROS, MMPs	Moderate	Limited
Steroids	β-Sitosterol	*Various plants*	Phytosterol	NF-κB, TNF-α	Moderate	Limited
Coumarins	Esculetin	*Fraxinus spp.*	Coumarin	COX-2, LOX	Moderate	Limited

MEDICINAL PLANTS WITH ANTI-ARTHRITIC POTENTIAL[82-93]

Medicinal plants have gained considerable attention as potential therapeutic agents for arthritis due to their anti-inflammatory, antioxidant, immunomodulatory, analgesic, and chondroprotective activities. These plants contain diverse bioactive phytoconstituents such as polyphenols, flavonoids, terpenoids, alkaloids, saponins, tannins, glycosides, and steroids, which regulate multiple molecular targets including TNF-α, IL-1β, IL-6, NF-κB, MAPK, JAK/STAT, COX-2, LOX, NLRP3 inflammasome, and oxidative stress pathways. Numerous *in vitro, in vivo*, and clinical studies support their efficacy in reducing inflammation, preventing cartilage degradation, and improving joint function.

Table 8. Major Medicinal Plants with Reported Anti-Arthritic Activity

Plant	**Family**	**Part Used**	**Major Active Constituents**	**Experimental Model**	**Mechanism of Action**	**Representative Reference***
Curcuma longa	Zingiberaceae	Rhizome	Curcumin	CIA, CFA	NF-κB, COX-2, TNF-α inhibition	Daily et al., 2016
Boswellia serrata	Burseraceae	Resin	Boswellic acids	OA, RA	5-LOX inhibition	Sengupta et al., 2018
Withania somnifera	Solanaceae	Root	Withanolides	FCA	Antioxidant, immunomodulatory	Chandran et al., 2019
Tinospora cordifolia	Menispermaceae	Stem	Tinosporaside	CIA	Cytokine suppression	Sharma et al., 2018
Zingiber officinale	Zingiberaceae	Rhizome	Gingerols, Shogaols	CFA	COX/LOX inhibition	Bartels et al., 2015
Nigella sativa	Ranunculaceae	Seed	Thymoquinone	RA model	NF-κB inhibition	Hadi et al., 2016
Justi	Acan	Le	Flav	Trit	Antio	Expe

ciabetonica	thaceae	af	onoids, Phenolics	onmodel	xidant, antihyperlipidemic	rimentalstudy
Justiciagendarussa	Acanthaceae	Leaf	Flavonoids	CFA	Anti-inflammatory	Kim et al., 2017
Vigna trilobata	Fabaceae	Wholeplant	Polyphenols	Triton model	Antioxidant	Experimentalstudy
Vigna radiata	Fabaceae	Seed	Flavonoids	In vitro	ROS scavenging	Lee et al., 2018
Terminalia chebula	Combretaceae	Fruit	Gallic acid	CIA	Antioxidant	Saleem et al., 2019
Terminalia bellirica	Combretaceae	Fruit	Ellagic acid	RA	COX-2 inhibition	Kumar et al., 2020
Terminalia arjuna	Combretaceae	Bark	Triterpenoids	CFA	Anti-inflammatory	Dwivedi et al., 2017
Terminalia cata	Combretaceae	Leaf	Punicalagin	Experimental	Antioxidant	Experimentalstud
ppa				arthritis		y
Moringa oleifera	Moringaceae	Leaf	Quercetin, Kaempferol	CFA	Cytokine inhibition	Verga ra-Jimenez et al., 2017
Azadirachta indica	Meliaceae	Leaf	Nimbin	RA	Immunomodulatory	Biswas et al., 2018
Ocimum sanctum	Lamiaceae	Leaf	Eugenol	CFA	COX-2 inhibition	Mondal et al., 2016
Aloe vera	Asphodelaceae	Leafgel	Aloin	Experimental arthritis	Wound healing, anti-inflammatory	Surjushe et al., 2018
Camellia sinensis	Theaceae	Leaf	EGCG	OA	NF-κB inhibition	Ahmed et al., 2019
Phyllanthus emblica	Phyllanthaceae	Fruit	Ascorbic acid, Gallic acid	RA	Antioxidant	Scartezzini et al., 2020
Andrographis	Acanthaceae	Whole	Andrographoli	CIA	STAT3 inhibi	Burgos et al.,

paniculata		plant	de		tion	2017
Panax ginseng	Araliaceae	Root	Ginsenosides	RA	Immunomodulatory	Kim et al., 2018
Salix alba	Salicaceae	Bark	Salicin	OA	Prostaglandin inhibition	Vlachojannis et al., 2015
Tripterygium wilfordii	Celastraceae	Root	Triptolide	RA	TNF-α inhibition	Fan et al., 2016
Angelica sinensis	Apiaceae	Root	Ferulic acid	RA	Antioxidant	Wang et al., 2018
Paeonia lactiflora	Paeoniaceae	Root	Paeoniflorin	RA	Cytokine suppression	Zhang et al., 2019
Astragalus membranaceus	Fabaceae	Root	Astragalosides	RA	Immune regulation	Li et al., 2020
Scutellaria baicalensis	Lamiaceae	Root	Baicalin	OA	NF-κB inhibition	Chen et al., 2018
Berberis aristata	Berberidaceae	Root	Berberine		K activation	Shahidi et al., 2019
Glycyrrhiza glabra	Fabaceae	Root	Glycyrrhizin	RA	Anti-inflammatory	Asl & Hosseinzadeh, 2018
Centella asiatica	Apiaceae	Whole plant	Asiaticoside	OA	Collagen protection	Brinkhaus et al., 2017
Allium sativum	Amaryllidaceae	Bulb	Allicin	RA	Antioxidant	Bayan et al., 2016
Punica granatum	Lythraceae	Fruit	Punicalagin	OA	MMP inhibition	Shukla et al., 2019
Cinnamomum verum	Lauraceae	Bark	Cinnamaldehyde	RA	COX-2 inhibition	Ranasinghe et al., 2018
Aegle marmelos	Rutaceae	Leaf	Marmelosin	RA	Anti-inflammatory	Singh et al., 2017
Vitex negundo	Lamiaceae	Leaf	Flavonoids	CFA	Analgesic	Dharmasiri et al., 2018

Boerhaavia diffusa	Nyctaginaceae	Root	Punarnavine	RA	Antioxidant	Chandan et al., 2017
Sida cordifolia	Malvaceae	Whole plant	Ephedrine alkaloids	RA	Anti-inflammatory	Sutradhar et al., 2019
Clematis gouriana	Ranunculaceae	Leaf	Flavonoids	Experimental arthritis	Antioxidant	Experimental study
Harpagophytum procumbens	Pedaliaceae	Root	Harpagoside	OA	COX-2 inhibition	Chrubasik et al., 2016

EXPERIMENTAL PHARMACOLOGY[94-105]

Experimental pharmacology is essential for validating the anti-arthritic efficacy of medicinal plants and their bioactive phytoconstituents. Both in vitro and in vivo studies are employed to evaluate anti-inflammatory, antioxidant, immunomodulatory, analgesic, and chondroprotective activities. These models provide mechanistic insights into disease modulation and generate preclinical evidence supporting the development of phytotherapeutic agents for arthritis.

In Vitro Studies

In vitro studies are widely used to investigate the molecular mechanisms of phytochemicals using inflammatory and joint-related cell lines. Commonly used models include RAW 264.7 murine macrophages, THP-1 human monocytes/macrophages, fibroblast-like synoviocytes (FLS), macrophages, and fibroblasts. These cell models mimic inflammatory responses associated with rheumatoid arthritis and osteoarthritis.

The anti-arthritic activity is assessed by measuring inflammatory cytokines, oxidative stress, cell viability, and expression of inflammatory proteins. Common assays include ELISA for cytokine estimation (TNF-α, IL-1β, IL-6), MTT assay for cell viability, Western blotting for protein expression (NF-κB, COX-2, iNOS, MAPKs), RT-PCR/qPCR for gene expression, ROS assays for intracellular oxidative stress, and the Griess assay for nitric oxide production. Most phytochemicals significantly suppress inflammatory mediators, reduce ROS and NO generation, inhibit NF-κB/MAPK signaling, and protect synoviocytes and chondrocytes from inflammatory injury.

In Vivo Studies

Animal models are indispensable for evaluating the therapeutic efficacy, safety, and disease-modifying effects of medicinal plants under physiological conditions. Frequently used models include collagen-induced arthritis (CIA), adjuvant-induced arthritis (AIA), Complete/Freund's Complete Adjuvant (CFA/FCA)-induced arthritis, carrageenan-induced paw edema, and the formalin-induced pain model. These models reproduce many pathological features of human arthritis, including synovial inflammation, cartilage destruction, bone erosion, and pain.

Plant extracts are generally administered orally at doses ranging from 50–500 mg/kg, while isolated phytoconstituents are evaluated at 5–100 mg/kg for 7–42 days, depending on the experimental protocol. Therapeutic efficacy is determined by measuring paw edema, arthritis score, joint diameter, body weight, pain response, and locomotor activity.

Histopathological Evaluation

Histopathological examination is performed to confirm tissue-level protection. Effective phytotherapeutic treatments reduce synovial hyperplasia, inflammatory cell infiltration, pannus formation, cartilage degradation, and bone erosion, while preserving normal joint architecture and reducing osteoclast-mediated bone destruction.

Biochemical Markers

Biochemical analysis is used to evaluate systemic inflammation and oxidative stress. Common inflammatory biomarkers include TNF-α, IL-1β, IL-6, IL-17, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), COX-2, iNOS, matrix metalloproteinases (MMPs), and RANKL. Oxidative stress is assessed using malondialdehyde (MDA), reactive oxygen species (ROS), nitric oxide (NO), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH). Successful treatment typically decreases inflammatory and oxidative biomarkers while restoring endogenous antioxidant enzyme activity.

Table 9. Experimental Pharmacology Used in Anti-Arthritic Research

Category	Model/Assay	Typical	Major

		Dose/Duration	Outcomes
***In Vitro* Models**	RAW 264.7 macrophages	1–100 μM	↓ TNF-α, IL-1β, IL-6, NO, ROS
	THP-1 monocytes	1–100 μM	↓ Cytokines, inflammasome activation
	Synoviocytes (FLS)	5–50 μM	↓ MMPs, COX-2, apoptosis
	Macrophages/ Fibroblasts	Variable	↓ Inflammation, ↑ Cell protection
Assays	ELISA, MTT, Western blot, RT-PCR, ROS, Griess assay	—	Cytokines, cell viability, gene/protein expression, oxidative stress
***In Vivo* Models**	CIA, AIA, CFA/FCA	50–500 mg/kg, 21–42 days	↓ Arthritis score, joint swelling, cartilage damage
	Carrageenan-induced edema	50–500 mg/kg, acute	↓ Paw edema, anti-inflammatory activity
	Formalin-induced model	50–300 mg/kg	↓ Pain and inflammation
Histopathology	Joint tissue analysis	End of study	↓ Synovitis, pannus, cartilage and bone erosion
Biochemical Markers	TNF-α, IL-1β, IL-6, MDA, ROS, NO, SOD, CAT, GPx, GSH, MMPs	Serum/Tissue	↓ Inflammation and oxidative stress; ↑ Antioxidant defense

MOLECULAR TARGETS OF PHYTOCHEMICALS IN ARTHRITIS[106-136]

The therapeutic efficacy of medicinal plants in arthritis is primarily attributed to their ability to regulate multiple molecular targets involved in inflammation, oxidative stress, immune dysfunction, cartilage degradation, and bone resorption. Unlike conventional drugs that often inhibit a single target, phytochemicals simultaneously modulate several intracellular signaling pathways, including NF-κB, MAPK, JAK/STAT, PI3K/Akt, Nrf2/HO-1, COX-2, 5-LOX, TLR4, and NLRP3 inflammasome. This multitarget mechanism contributes to reduced cytokine production, suppression of oxidative

stress, inhibition of matrix metalloproteinases (MMPs), and protection against cartilage and bone destruction.

Table 10. Molecular Targets and Signaling Pathways of Major Anti-Arthritic Phytochemicals

Phytochemical	Major Plant Source	Molecular Target	Signaling Pathway	Pharmacological Effect
Curcumin	*Curcuma longa*	NF-κB, COX-2, TNF-α, IL-1β	NF-κB, MAPK, Nrf2	↓ Inflammation, ↓ Cytokines, ↑ Antioxidant defense
Resveratrol	*Vitis vinifera*	SIRT1, NF-κB, TNF-α	PI3K/Akt, AMPK, Nrf2	↓ Oxidative stress, ↓ Chondrocyte apoptosis
Gallic Acid	*Tea, Terminalia spp.*	COX-2, iNOS, ROS	NF-κB, Nrf2	↓ Inflammation, ↓ Lipid peroxidation
Ellagic Acid	*Punica granatum*	NF-κB, IL-6, TNF-α	NF-κB, Nrf2	↓ Cytokines, ↑ Antioxidant enzymes
Quercetin	*Onion, Apple*	TNF-α, IL-1β, NLRP3	NF-κB, MAPK	↓ Inflammation, ↓ Cartilage degradation
Kaempferol	*Broccoli, Spinach*	COX-2, iNOS	MAPK, PI3K/Akt	↓ Oxidative stress, ↓ Cytokines
Luteolin	*Celery, Parsley*	IL-6, STAT3	JAK/STAT, NF-κB	↓ Inflammatory signaling
Apigenin	*Chamomile*	COX-2, MMPs	MAPK, NF-κB	↓ Cartilage destruction
Catechin (EGCG)	*Camellia sinensis*	MMP-13, NF-κB	MAPK, Nrf2	↓ ROS, ↑ Chondroprotection
Rutin	*Buckwheat, Citrus*	TNF-α, IL-1β	NF-κB	↓ Inflammation, ↑ Antioxidant activity
Berberine	*Berberis aristata*	AMPK, NF-κB	AMPK, PI3K/Akt	↓ Cytokines, ↓ Synovitis
Colchicine	*Colchicum autumnale*	NLRP3 Inflammasome	Inflammasome pathway	↓ IL-1β, ↓ Gout inflammation
Boswellic Acids	*Boswellia serrata*	5-LOX	Leukotriene pathway	↓ Leukotriene synthesis, ↓ Joint inflammation
Andrographolide	*Andrographis*	STAT3, NF-κB	JAK/STAT	↓ Immune activation

	panicu lata			
Ginseno sides	*Panax ginsen g*	TNF-α, IL-6	NF-κB, PI3K/ Akt	Immuno modulato ry activity
Thymoq uinone	*Nigell a sativa*	NF-κB, COX-2	Nrf2, NF-κB	↓ Oxidative stress, ↓ Cytokines
Withano lides	*Witha nia somnif era*	NF-κB, IL-6	MAPK , PI3K/ Akt	↓ Synovial inflamma tion
Gingero ls	*Zingib er officin ale*	COX-2, 5-LOX	Arachi donic acid pathwa y	↓ Pain and inflamma tion
Tannic Acid	*Termi nalia spp.*	ROS, MMPs	Nrf2	↓ Oxidative damage
β-Siteter ol	*Variou s plants*	TNF-α, IL-6	NF-κB	Immuno modulato ry effect
Esculeti n	*Fraxin us spp.*	COX-2, LOX	NF-κB	↓ Inflamma tion
Salicin	*Salix alba*	COX enzym es	Prostag landin pathwa y	Analgesic and anti-inflamma tory
Asiatico side	*Centel la asiatic a*	TGF-β, Collag en	PI3K/ Akt	Cartilage repair and wound healing
Glycyrr hizin	*Glycyr rhiza glabra*	HMGB 1, NF-κB	NF-κB	↓ Inflamma tory cytokines

CONCLUSION:

Arthritis remains a major global health challenge characterized by chronic inflammation, oxidative stress, immune dysregulation, cartilage degradation, and progressive joint destruction. Although current pharmacological therapies, including NSAIDs, DMARDs, biologics, glucocorticoids, and JAK inhibitors, have significantly improved disease management, their long-term use is often limited by adverse effects, high cost, and variable therapeutic response. These limitations have intensified interest in medicinal plants and bioactive phytoconstituents as safer and multitarget therapeutic alternatives.

The evidence reviewed demonstrates that phytochemicals such as curcumin, resveratrol, quercetin, kaempferol, luteolin, catechins, boswellic acids, thymoquinone, berberine, and numerous other natural compounds effectively modulate key molecular pathways involved in arthritis, including NF-κB, MAPK, JAK/STAT, PI3K/Akt, COX-2, 5-LOX, and the NLRP3 inflammasome. Through these mechanisms, they suppress inflammatory cytokines, reduce oxidative stress, preserve cartilage integrity, inhibit osteoclast-mediated bone resorption, and improve overall joint function. Extensive in vitro and in vivo investigations, together with growing clinical evidence, support the therapeutic potential of a wide range of medicinal plants, including *Curcuma longa, Boswellia serrata, Withania somnifera, Tinospora cordifolia, Nigella sativa, Zingiber officinale, Moringa oleifera, Terminalia species, Justicia species,* and *Vigna species.*

Future research should prioritize the standardization of herbal preparations, identification of bioactive markers, pharmacokinetic and toxicological evaluation, optimization of advanced drug delivery systems, and large-scale randomized clinical trials to establish efficacy and long-term safety. The integration of phytochemistry, molecular pharmacology, network pharmacology, artificial intelligence, nanotechnology, and precision medicine is expected to accelerate the development of scientifically validated phytopharmaceuticals. Overall, phytotherapy represents a promising complementary strategy for the prevention and management of arthritis and offers substantial opportunities for the development of novel disease-modifying therapies with improved efficacy, reduced toxicity, and enhanced patient outcomes.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interests.

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