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Review

Plant Phenolic Compounds in Rheumatic and Musculoskeletal Diseases: Molecular Mechanisms, Clinical Evidence and Translational Challenges

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Abstract

Plant phenolic compounds have been investigated in rheumatic and musculoskeletal disorders because several of their biological activities involve inflammatory signaling, oxidative responses and tissue remodeling. This critical narrative review examines phenolic acids, flavonoids (including isoflavones), curcuminoids and stilbenes in osteoarthritis (OA), rheumatoid arthritis (RA) and osteoporosis. Terpenoids and alkaloids are also considered as chemically distinct plant-derived compounds of potential physiological relevance. Experimental studies report effects on NF-κB, MAPK and Nrf2 signaling, matrix metalloproteinases, ADAMTS enzymes and regulators of bone remodeling, including the RANKL/OPG axis. However, the clinical implications depend on the experimental model, compound exposure and disease indication. Randomized trials of certain curcumin formulations suggest short-term symptomatic improvements in knee OA, although the evidence is limited by variation in products and study quality. Human evidence for quercetin in RA remains limited, while clinical data do not establish disease-modifying effects of resveratrol or epigallocatechin-3-gallate. Genistein has been associated with changes in bone mineral density, but fracture prevention has not been demonstrated. Absorption, metabolism, tissue distribution, preparation-dependent toxicity and the lack of long-term clinical outcomes complicate translation. The review evaluates these limitations and identifies methodological requirements for future mechanistic and clinical studies of plant phenolics.

Keywords: phenolic compounds; polyphenols; curcumin; quercetin; catechins; resveratrol; genistein; osteoarthritis; rheumatoid arthritis; osteoporosis; bioavailability; terpenoids; alkaloids

1. Introduction

Osteoarthritis (OA), rheumatoid arthritis (RA) and osteoporosis differ in etiology but all involve changes in inflammation, cellular stress and tissue turnover. In OA, mechanical and metabolic factors interact with synovitis, chondrocyte dysfunction and extracellular-matrix degradation. RA is characterized by immune-mediated synovial inflammation and progressive joint damage, whereas osteoporosis results from an imbalance between bone resorption and formation that increases fracture risk. The substantial burden of these conditions has prompted investigation of plant-derived compounds as possible adjuncts to established therapies. Their different disease mechanisms nevertheless require separate assessment of therapeutic outcomes [1–4].

Plant phenolics include structurally diverse compounds, ranging from hydroxybenzoic and hydroxycinnamic acids to flavonoids, curcuminoids and stilbenes. Many influence inflammatory or oxidative-stress responses in experimental systems. In this review, phenolic compounds are classified

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according to their chemical structures: isoflavones are included among the flavonoids, while stilbenes and curcuminoids are treated as non-flavonoid phenolics. Such distinctions are relevant to absorption, metabolism, protein binding, biological activity and safety, which vary considerably among compounds [5,6].

The following sections examine the biological activities of the major phenolic classes, the molecular evidence relevant to OA, RA and osteoporosis, and the findings of human studies. Pharmacokinetic properties, formulation and safety are considered alongside efficacy. Monoterpenes, diterpenoids, triterpenoids and alkaloids are included separately to provide a broader account of plant-derived bioactive compounds relevant to musculoskeletal health [7–9].

2. Scope and Methodology

This article is a critical narrative review rather than a systematic review or a new meta-analysis. The discussion draws on primary molecular studies, preclinical investigations, randomized clinical trials, systematic reviews and clinical recommendations. Findings from cell cultures, animal models, observational research and human interventions are identified according to study type. Reviews containing overlapping clinical trials are not considered independent sets of patients. No new meta-analysis or formal GRADE assessment was undertaken.

Studies were selected for their relevance to the chemical classes, molecular pathways and musculoskeletal outcomes addressed in this review, with particular attention to human exposure and clinical evidence where available. Symptomatic improvement, biochemical changes and structural disease modification are evaluated as distinct outcomes. The cited literature includes foundational work and relevant publications available through October 2026. As the review is narrative, the study selection is not intended to provide an exhaustive or reproducible systematic search.

3. Classification and Biological Activities of Plant Phenolics

3.1. Phenolic Acids

Phenolic acids include hydroxybenzoic and hydroxycinnamic acid derivatives such as gallic, caffeic, ferulic and chlorogenic acids. In plant tissues and foods, they occur as free compounds, glycosides, esters or constituents of complex matrices. Experimental studies have described effects on inflammatory mediators, redox-sensitive responses and extracellular-matrix turnover relevant to joint disease. However, findings from crude extracts cannot always be attributed to individual phenolic acids, and compound-specific randomized trials in musculoskeletal disorders remain scarce [5,8].

In experimental systems, phenolic acids have been associated with changes in inducible nitric oxide synthase, COX-2, cytokine production and matrix metalloproteinase expression. The interpretation of these findings depends on the model and on the concentrations used. Exposures achieved in cultured chondrocytes or macrophages may differ considerably from concentrations of unbound compounds in human joint tissue after oral intake. Conjugation and microbial metabolism also produce derivatives with distinct biological properties. Studies assessing musculoskeletal effects should therefore measure relevant parent compounds and metabolites and compare experimental concentrations with those achievable in humans [5,6,8].

3.2. Flavonoids

Flavonoids include flavonols (quercetin, kaempferol), flavones (apigenin, luteolin), flavan-3-ols (catechins, including EGCG), flavanones, anthocyanins and isoflavones (including genistein). Their hydroxylation, methylation, glycosylation and galloylation patterns influence chemical reactivity and interactions with biological targets. In chondrocytes and synoviocytes, commonly reported effects involve NF-κB and MAPK signaling, inflammatory mediators, matrix metalloproteinases, ADAMTS enzymes and Nrf2-associated responses. These findings generally reflect multiple context-dependent activities rather than confirmed interactions with a single therapeutic target [7,10,11].

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3.2.1. Quercetin

Quercetin is present in onions, apples and numerous fruits and vegetables, mainly as glycosides. Experimental models of inflammatory arthritis have reported reduced cytokine production, changes in oxidative-stress markers and improvements in selected measures of disease activity. A systematic review of animal studies and an investigation of adjuvant arthritis in rats support these observations [12–14]. Inhibition of NF-κB- and MAPK-related signaling is among the mechanisms proposed, although direct target engagement at clinically relevant concentrations has not been established.

Clinical data on quercetin in RA are limited. In a double-blind randomized trial involving 50 women, administration of 500 mg/day for eight weeks improved several symptom and disease-activity measures compared with placebo. However, the study was small and of short duration, and differences in joint-count outcomes were not consistently demonstrated. Larger trials with standardized concomitant treatments, prespecified outcomes and pharmacokinetic measurements are needed to assess the reproducibility of these findings [15].

3.2.2. Epigallocatechin-3-Gallate and Other Catechins

Epigallocatechin-3-gallate (EGCG) is a gallated flavan-3-ol found in green tea. In cartilage explants and cultured chondrocytes, catechins have inhibited proteoglycan degradation and IL-1β-induced expression of matrix metalloproteinases. Catechin gallate esters have also reduced the activity of selected ADAMTS enzymes in biochemical assays [16–18]. These results provide evidence of effects on cartilage-catabolic processes in experimental systems, but do not demonstrate preservation of joint structure or function in patients.

Controlled clinical evidence specifically evaluating EGCG in OA or RA is insufficient to establish therapeutic efficacy. Dose and preparation also influence safety. Concentrated catechin supplements produce exposures that differ from those associated with ordinary tea consumption; EFSA identified liver-enzyme elevations as a concern in studies using supplemental EGCG at doses of 800 mg/day or higher. Delivery systems intended to increase EGCG exposure should therefore undergo appropriate hepatic safety assessment [19,20].

3.2.3. Apigenin, Luteolin, Kaempferol and Related Flavonoids

Apigenin, luteolin, kaempferol, naringenin, fisetin and myricetin have been investigated for effects on inflammatory signaling, oxidative responses and chondrocyte catabolism. Cellular and animal studies have also examined synoviocyte proliferation and immune responses. Clinical evaluation is much less developed, with few controlled comparisons of standardized formulations and limited data on long-term joint outcomes [7,10,21].

For several flavonoids, inhibition of COX-2 or related enzymes has been proposed from molecular docking studies. Binding predictions alone do not establish enzymatic inhibition or selectivity. Biochemical assays and measurements of cellular target engagement are needed, including evaluation of the glucuronide and sulfate metabolites that predominate after oral administration [5].

3.2.4. Isoflavones and Bone Metabolism

Genistein belongs to the isoflavone subclass of flavonoids and interacts with estrogen receptors. Its potential effects on bone are linked to osteoblast and osteoclast activity and to signaling involving RANKL and osteoprotegerin. In a randomized, placebo-controlled trial of 389 postmenopausal women with osteopenia, 54 mg/day of genistein, with calcium and vitamin D, improved bone mineral density over 24 months. These findings provide human evidence for a skeletal effect, but the trial did not establish a reduction in fracture incidence [22,23].

Other studies of isoflavones, including products combining genistein with vitamins or fatty acids, have reported mixed outcomes. Differences in intervention composition and concomitant supplementation complicate attribution of effects to genistein alone [24,25]. Further evaluation of long-

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term safety, endocrine status and fracture outcomes is needed before specific prevention recommendations can be made.

3.3. Curcuminoids

Curcumin and related curcuminoids from *Curcuma longa* are non-flavonoid phenolic compounds with electrophilic and redox-sensitive properties. Experimental studies in chondrocytes and synoviocytes have described changes in inflammatory signaling. In cultured chondrocytes, combined exposure to curcumin and resveratrol produced greater reductions in certain IL-1β-induced inflammatory and apoptotic markers than either treatment alone [26]. The clinical relevance and pharmacological nature of this interaction remain to be established.

Several randomized studies of turmeric and curcumin preparations in knee OA have reported improvements in pain or physical function over relatively short treatment periods. A multicenter placebo-controlled trial of a bio-optimized extract identified a symptomatic benefit [27]. An open-label study comparing curcumin with diclofenac over 28 days reported broadly similar pain outcomes, although lack of blinding and short follow-up limit interpretation, particularly regarding safety [28]. A noninferiority study comparing a specific high-bioavailability preparation with paracetamol provides additional information, but its findings cannot be extended to other curcumin products without further testing [29].

Systematic reviews and meta-analyses generally suggest possible short-term symptomatic benefit from curcumin in knee OA. Interpretation is limited by small study populations, differences in dose and formulation, incomplete blinding and limited safety follow-up. A critical appraisal published in 2026 found predominantly low or very low certainty across assessed outcomes and considerable overlap of primary trials among reviews [30–32]. Available evidence therefore supports cautious consideration of selected formulations for symptom management, but not claims of structural disease modification or equivalence to established treatment.

In RA, a 2026 systematic review identified six placebo-controlled randomized trials involving 244 participants. Although pooled estimates favored curcumin for some disease-activity measures, the certainty of much of the evidence was very low [33]. These findings are preliminary and do not support its use in place of disease-modifying antirheumatic drugs (DMARDs), which remain central to current treatment recommendations [34]. Future trials should account for concomitant DMARD regimens, preparation-specific pharmacology and potential interactions.

3.4. Stilbenes

Resveratrol is a stilbene present in grapes and other plant materials. Studies in experimental models have reported modulation of AMPK/SIRT1, redox-associated and inflammatory signaling. In OA-related cell and animal models, outcomes include changes in NF-κB-associated cytokines, matrix-turnover markers and apoptosis; bone-related studies describe effects on osteoblast differentiation and osteoclastogenic pathways [35,36, 23,]. Differences in model systems, concentrations and administration routes limit direct comparison and complicate extrapolation to therapeutic doses.

Following oral administration, resveratrol undergoes extensive conjugation, and concentrations of unconjugated compound in tissues may be much lower than those used in vitro. This limits the interpretation of studies proposing direct interactions with SIRT1, AMPK or other molecular targets in human joint tissues. Evidence from clinical investigations does not currently establish sustained structural benefit in OA or protection against osteoporotic fractures [5,35].

3.5. Phenolic Mixtures and Dietary Sources

Dietary phenolics are generally consumed as components of complex foods. Olive oil, fruits, berries, tea, legumes, herbs and spices provide multiple phenolic compounds within matrices that influence release, digestion, microbial metabolism and intestinal absorption. Processing and storage may alter their measured content and bioaccessibility through thermal degradation, oxidation or

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changes in extractability. Consequently, the concentration measured in a food does not directly indicate the systemic exposure achieved after consumption [5,37,38].

A Mediterranean diet intervention in patients with established RA reported benefits for selected clinical outcomes, although it was not designed to isolate the effects of individual phenolics or assess primary prevention. Associations between dietary adherence and disease incidence may also reflect other factors, including smoking, body composition and physical activity. Dietary-pattern findings are therefore relevant to the wider nutritional context of rheumatic disease but cannot be attributed to particular phenolic compounds without additional evidence [39,40].

4. Other Plant Bioactive Classes of Physiological Interest

Terpenoids and alkaloids are chemically distinct from phenolics and have also been investigated for biological activities relevant to musculoskeletal disorders. Their effects involve partly overlapping inflammatory pathways as well as other targets, including sensory ion channels and immune mediators. Differences in physicochemical properties, metabolism and toxicity influence their potential therapeutic applications. As with phenolics, experimental findings require confirmation in adequately controlled human studies [7,41].

4.1. Monoterpenes

Monoterpenes such as pinene, limonene, borneol, camphor, geraniol and thymol are common volatile constituents of essential oils. Experimental pain models have identified effects on sensory ion channels, neuroinflammatory mediators and oxidative-stress responses. Their proposed use in OA or RA is primarily related to analgesic and anti-inflammatory activity; evidence of effects on cartilage destruction or autoimmune disease progression is lacking [42–44].

Comparisons across studies are complicated by variation in botanical source, volatility, administration route, absorption and local tolerability. An observational analysis of serum monoterpenes reported associations with bone mineral density, but its cross-sectional design does not allow causal conclusions about skeletal protection or harm [45].

4.2. Diterpenoids

Diterpenoids studied in experimental arthritis include andrographolide, triptolide and tanshinones. Reported anti-inflammatory and immunomodulatory effects involve NF-κB and cytokine-related pathways, some of which are also influenced by phenolics. The therapeutic potential of these compounds is constrained by their individual toxicological profiles. Triptolide, in particular, has a narrow therapeutic window, illustrating the need for careful safety assessment despite substantial activity in experimental models [41,46].

4.3. Triterpenoids and Boswellic Acids

Pentacyclic triterpenoids include betulinic acid, celastrol and boswellic acids. Extracts of *Boswellia serrata* oleo-gum resin contain mixtures of boswellic acids, including acetyl-11-keto-β-boswellic acid (AKBA), which have been studied for effects on inflammatory enzymes and signaling pathways. A small placebo-controlled trial of a standardized *Boswellia* preparation reported improvement in knee OA symptoms during a limited treatment period. Interpretation should account for the extract composition, sample size and disclosed commercial relationships [47,48].

A randomized trial also investigated curcumin alone, a curcumin–boswellic-acid combination and placebo in OA. Differences between treatment groups provide a basis for further evaluation, although the trial does not establish a pharmacological interaction between the active compounds. Factorial designs or concentration–response analyses would help determine whether combination effects are additive or synergistic [49].

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4.4. Alkaloids

Plant alkaloids comprise a chemically heterogeneous group of nitrogen-containing compounds with reported actions on inflammatory pathways, ion channels, nociception and bone-cell differentiation. In IL-1β-stimulated chondrocytes, dauricine has been associated with changes in calcium signaling, NF-κB activity and catabolic markers [50]. Reviews of medicinal alkaloids also discuss analgesic targets, but much of this evidence comes from neuropathic or general pain models rather than trials specific to OA or RA [51,52].

The available clinical information on anatabine includes an internet-based survey of consumers reporting joint pain or stiffness. The design is subject to selection, recall and expectation biases and cannot establish treatment efficacy [53]. For alkaloids more broadly, off-target pharmacology, dose-related toxicities and potential interactions with other drugs remain important areas for investigation.

Table 1. Chemical classification, experimental activities and clinical evidence for plant phenolics and other bioactive compounds.

Chemical class	Representative compounds	Reported biological activities	Clinical evidence and limitations
Phenolic acids	Caffeic, ferulic, chlorogenic acids	Inflammatory and redox-related responses; exploratory matrix-catabolic effects	Predominantly preclinical; limited compound-specific clinical evidence
Flavonols / flavones	Quercetin; luteolin, apigenin	NF-κB/MAPK-associated signaling; inflammatory mediators	Quercetin: one small RA RCT; others mostly preclinical
Flavan-3-ols	EGCG, catechins	MMP-1/13 and ADAMTS-associated cartilage catabolism	Cell and enzyme studies; safety concerns with concentrated EGCG
Isoflavones (flavonoids)	Genistein	Estrogen-receptor and RANKL/OPG-related bone remodeling	Human BMD trials; fracture outcomes unproven
Curcuminoids (phenolics)	Curcumin	Inflammatory and catabolic signaling in OA/RA	Multiple short OA RCTs; low certainty and product heterogeneity
Stilbenes (phenolics)	Resveratrol	AMPK/SIRT1; NF-κB-related and bone-cell responses	Strong experimental literature; limited disease-specific clinical proof
Monoterpenes	Pinene, limonene, thymol	Pain/sensory pathways and anti-inflammatory readouts	Mostly preclinical; no established disease modification
Diterpenoids	Andrographolide, triptolide	Immune/inflammatory signaling	Preclinical interest; toxicity can limit translation
Triterpenoids	Boswellic acids, celastrol	Inflammatory enzymes and cytokine signaling	Small *Boswellia* OA trials; extract-specific findings
Alkaloids	Dauricine, anatabine	Calcium signaling, NF-κB, pain pathways	Preclinical/survey data; insufficient controlled evidence

5. Experimental Evidence on Shared Molecular Pathways

5.1. NF-κB and Inflammatory Cytokine Signaling

NF-κB contributes to inflammatory and catabolic responses in the OA joint and is involved in several immune pathways central to RA. Experimental exposure to selected phenolics, terpenoids and alkaloids has been associated with decreased NF-κB reporter activity, reduced nuclear translocation of p65 and lower cytokine production. These measures document changes in cellular signaling,

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but their specificity and clinical relevance depend on the concentrations used, possible off-target effects and confirmation in disease-appropriate systems [3,4,54].

5.2. Nrf2 Signaling and Antioxidant Responses

Phenolic compounds have been reported to modify Nrf2-associated gene expression, heme oxygenase-1, glutathione metabolism and oxidative-stress markers. The underlying responses may involve electrophilic interactions, altered redox balance, metabolic adaptation or changes in inflammatory activity. Chemical radical-scavenging assays provide limited information about clinical antioxidant effects. Assay interference from the coloration or redox activity of phenolics should also be considered. Interpretation is strengthened by identification of relevant metabolites, exposure measurements and experiments that test the functional contribution of Nrf2 signaling [6,8,10].

5.3. Cartilage Degradation and Synovial Remodeling

Cartilage degradation involves matrix metalloproteinases, particularly MMP-13, and aggrecanases such as ADAMTS-4 and ADAMTS-5. Cytokine-responsive interactions between cartilage and synovium contribute to these processes. Experiments with EGCG and curcumin have shown reductions in enzyme expression or matrix degradation in selected model systems [16–18]. Structural effects in patients would require confirmation through appropriate imaging or other validated tissue outcomes assessed over sufficient follow-up, together with measures of symptoms and function [3,4].

5.4. Bone Remodeling and the RANKL/OPG Axis

In bone-related models, phenolics have been associated with changes in RANKL-mediated osteoclast differentiation, osteoprotegerin expression, osteoblast development and Wnt-linked pathways. These mechanisms may contribute to effects on bone turnover and mineral density. Genistein has also been evaluated using bone mineral density as a clinical endpoint [22,23]. Interpretation of these outcomes should account for menopausal status, dietary factors and calcium or vitamin D co-supplementation. Evidence of fracture reduction is needed to establish a preventive effect on osteoporotic fractures [24].

5.5. Interpretation of Molecular Studies

Studies of molecular mechanisms are more readily interpreted when they report the compound's chemical identity, its relevant circulating metabolites, unbound concentrations at potential sites of action and direct evidence of target engagement. These measurements can then be related to downstream biomarkers and disease outcomes. Network-pharmacology analyses and molecular docking can guide experimental design, but their predictions require validation in biochemical and cellular assays at clinically plausible concentrations [5,55].

6. Clinical Evidence in Musculoskeletal Disorders

6.1. Osteoarthritis

Knee OA is the main clinical indication in which several phenolic formulations have been evaluated in randomized trials. Curcumin preparations have shown short-term improvements in pain or self-reported function in some studies, although trial populations, extract standardization, doses, comparators, delivery systems and follow-up periods vary considerably. Trials comparing curcumin with established analgesics provide information about the products and regimens tested, but do not establish equivalence across formulations or long-term safety. A recent appraisal found limited confidence in many of the available pooled estimates [27–29,32].

Trials of *Boswellia* extracts provide additional OA evidence for a non-phenolic botanical class. Their results must be interpreted separately from studies of curcumin and other phenolics, including when these compounds are combined in the same preparation. For either class, evidence of slowing structural disease progression remains inadequate [48,49,21,].

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6.2. Rheumatoid Arthritis

Assessment of interventions in RA requires validated disease-activity measures, tender and swollen joint counts, inflammatory markers, concomitant treatment information and, where appropriate, imaging of joint damage. The small trial of quercetin and the available pooled curcumin trials report preliminary clinical findings but do not establish consistent benefits across phenolic compounds. Meta-analyses that combine diverse dietary polyphenols cannot be interpreted as compound-specific confirmation. Any clinical studies of these supplements should evaluate their adjunctive use while maintaining recommended DMARD treatment [15,33,34,40].

6.3. Osteoporosis and Skeletal Muscle

Randomized studies of genistein have reported improvements in bone mineral density among women with osteopenia, but evidence of reduced fracture incidence is lacking. For resveratrol and berry-derived phenolic mixtures, most bone-related findings remain experimental or are limited to surrogate outcomes [22,23,56]. Studies of skeletal muscle have also described effects of some phenolics on recovery, redox adaptation and cellular homeostasis. These observations concern a related tissue system and should not be taken as direct evidence of therapeutic benefit in OA, RA or osteoporosis [57].

Table 2. Selected clinical studies and systematic reviews of plant-derived compounds in musculoskeletal disorders.

Intervention and indication	Study design and participants	Reported outcomes	Study limitations
Quercetin / RA	Javadi et al., 2017 [15]; randomized placebo-controlled; n=50 women; 8 weeks	Improved some symptoms, DAS28/HAQ and hs-TNF-α	Small, short, women-only; inconsistent joint-count results
Curcumin extract / knee OA	Henrotin et al., 2019 [27]; double-blind multicenter placebo-controlled trial	Symptomatic pain improvement for a bio-optimized extract	Formulation-specific; short-term symptomatic outcomes
Curcumin vs diclofenac / knee OA	Shep et al., 2019 [28]; randomized open-label; n=139; 28 days	Similar short-term symptom improvement under tested regimens	Unblinded; inadequate for long-term comparative safety
Curcumin vs paracetamol / knee OA	Singhal et al., 2021 [29]; randomized noninferiority trial	Symptom-related outcomes compatible with noninferiority within study margins	Specific formulation; short follow-up
Curcumin for knee OA / evidence syntheses	Chen et al., 2026 [32]; overview of seven systematic reviews	Potential symptomatic benefit in pooled analyses	Most outcome evidence low/very low; overlapping trials
Curcumin for RA / evidence synthesis	Fan et al., 2026 [33]; six RCTs; n=244	Favorable estimates in selected activity outcomes	Predominantly very-low-certainty evidence
Genistein / osteopenia	Marini et al., 2007 [22]; randomized placebo-controlled; n=389; 24 months	Increases in lumbar/femoral BMD measurements	No definitive clinical fracture-prevention outcome
Boswellia / knee OA	Majeed et al., 2019 [48]; pilot randomized placebo-controlled; n=48	Improvement in some pain and function outcomes	Small; extract-specific and limited duration

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Curcumin–*Boswellia* / OA	Haroyan et al., 2018 [49]; randomized double-blind comparison	Combination showed favorable outcomes for selected measures	Does not demonstrate formal pharmacological synergy

7. Bioavailability, Drug Delivery and Safety

7.1. Absorption, Metabolism and Tissue Exposure

The pharmacokinetic behavior of phenolics varies considerably among chemical classes. Curcumin has limited dissolution and undergoes substantial intestinal and hepatic metabolism. Resveratrol is rapidly conjugated, whereas quercetin absorption is influenced by glycosylation and subsequent phase-II metabolism. Food composition and gut microbial activity modify the metabolites reaching circulation. Measurements of total circulating phenolic equivalents after enzymatic deconjugation are therefore not interchangeable with concentrations of free parent compounds [5,6].

Evaluation of delivery technologies requires measurements of exposure at relevant tissues in addition to systemic pharmacokinetic parameters. Increased area under the plasma concentration–time curve does not establish that unbound compound concentrations at the target site are sufficient to produce the proposed effect. Formulation composition, dose, batch quality, feeding conditions, metabolite profiles and interaction potential should be reported consistently. Such information is especially important when in vitro effects are observed only at concentrations higher than those achieved in humans.

7.2. Nanoformulations and Targeted Delivery

Liposomes, lipid nanoparticles, nanoemulsions, polymeric carriers and related systems have been studied to improve phenolic solubility, stability, release or tissue distribution. Quercetin nanoemulsion gels and other flavonoid-containing carriers have shown changes in release profiles or pharmacodynamic measures in animal models [10,55,58]. Clinical benefits have not been established for most systems. Intra-articular formulations additionally require assessment of sterility, local inflammatory responses, tissue residence, repeated-dose tolerability and manufacturing reproducibility.

Metal–polyphenol coordination systems and multifunctional nanoparticles offer further approaches to drug delivery. Results from macrophage cultures and experimental arthritis models remain preliminary, and alterations in biodistribution or clearance may introduce additional safety considerations. Comparative studies should include an appropriate control formulation, matched active-compound doses and predefined pharmacokinetic and safety outcomes.

7.3. Toxicity and Drug–Supplement Interactions

Plant origin does not guarantee safety. High-dose EGCG supplements have been associated with elevations in liver enzymes; rare cases of liver injury have also been reported with turmeric or curcumin preparations. Some terpenoids and alkaloids have substantial dose-dependent toxicity. Increased absorption from enhanced formulations may increase exposure-related adverse effects as well as pharmacological activity. Potential interactions require particular attention when supplements are taken alongside methotrexate, glucocorticoids, NSAIDs, anticoagulants or other prescribed drugs [20,59,46,].

Clinical investigations should prospectively document adverse events, laboratory abnormalities, preparation composition and excipients that influence exposure. Safety observations from short trials in selected populations cannot adequately characterize uncommon or delayed hepatic, reproductive, immune or interaction-related risks. Assessment of plant-derived therapeutic candidates therefore requires standardized composition, pharmacokinetic studies and appropriate toxicological evaluation.

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8. Research Priorities

Further mechanistic studies would benefit from prioritizing phenolic compounds and metabolites detected after human exposure. Targeted metabolomics, isotope-labeling and mass-spectrometry methods may help distinguish the actions of parent compounds from those of conjugated or microbial metabolites. Experiments using clinically plausible concentrations and molecular pathway perturbation could improve interpretation of target-specific effects beyond observations from docking or gene-expression assays.

Clinical development should be based on a clearly defined indication and standardized intervention. In OA, randomized studies should include validated pain and function measures, with structural imaging and extended follow-up when disease modification is proposed. In RA, adjunctive trials should maintain protocolized DMARD care and prespecify composite activity measures, swollen-joint counts and safety outcomes. For osteoporosis, incident fractures and other patient-relevant skeletal outcomes are needed in addition to bone density or biomarker measurements [3,23,34].

Studies of phenolic mixtures and combinations of phenolics with terpenoids should distinguish additive effects from pharmacological interactions by using suitable factorial designs or exposure–response analyses. Botanical extracts also require chromatographic characterization and assessment of batch consistency. Preregistration, access to protocols and analysis plans, disclosure of commercial interests and complete adverse-event reporting would improve the reliability of future clinical evidence [32,49].

Table 3. Evidence requirements for the clinical development of plant phenolic compounds.

Stage of development	Required evidence	Evidence provided
Chemical characterization	Scaffold, purity, extract fingerprint, formulation and batch variability	Reproducible compound identity
Molecular target validation	Orthogonal assays, perturbation and physiologically relevant concentration	Plausible mechanistic engagement
Exposure bridge	Parent/metabolite PK, free exposure, tissue-related distribution, exposure–response	Realistic in vivo pharmacology
Preclinical indication model	Appropriate OA/RA/bone model, comparator, blinded outcomes, toxicology	Biological proof of concept
Early clinical study	Randomization, controls, prespecified outcomes, adequate adverse-event capture	Preliminary patient-level signal
Confirmatory clinical study	Reproducible standardized product, adequate power and follow-up, meaningful outcomes	Indication- and product-specific clinical efficacy
Disease-modifying claim	Joint structural progression, fracture incidence, or similarly hard outcomes	Evidence of effects on disease progression

9. Conclusions

Plant phenolic compounds comprise several chemical classes with experimentally documented effects on inflammatory signaling, chondrocyte catabolism and bone remodeling. Reported changes in NF-κB and Nrf2 pathways, matrix-degrading enzymes and bone-cell regulators provide a mechanistic basis for further investigation. However, the extent to which these effects occur at clinically achieved tissue exposures remains uncertain. Selected curcumin formulations have the most developed clinical literature for short-term symptom management in knee OA, although methodological limitations reduce confidence in pooled estimates. Evidence for quercetin in RA and genistein in relation to bone mineral density is more restricted, while resveratrol, EGCG, most phenolic acids and

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several other flavonoids remain supported predominantly by preclinical studies in the indications considered.

Terpenoids and alkaloids also show potentially relevant biological activities, but they differ from phenolics in chemical structure, pharmacokinetics and safety. Boswellic acids are triterpenoids and have been investigated separately and in combination with curcumin. The clinical development of plant-derived compounds requires reproducible chemical characterization, relevant pharmacokinetic measurements, validated target engagement, standardized products, adequate clinical endpoints and long-term safety data. Current evidence supports continued investigation of selected phenolics as adjunctive interventions or starting structures for drug development, rather than their substitution for established disease-specific therapy.

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Abbreviations

The following abbreviations are used in this manuscript:

ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
AKBA	Acetyl-11-keto-β-boswellic acid
AMPK	AMP-activated protein kinase
BMD	Bone mineral density
COX-2	Cyclooxygenase-2
DAS28	Disease Activity Score in 28 joints
DMARD	Disease-modifying antirheumatic drug
EFSA	European Food Safety Authority
EGCG	Epigallocatechin-3-gallate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAQ	Health Assessment Questionnaire
hs-TNF-α	High-sensitivity tumor necrosis factor-α
IL-1β	Interleukin-1β
MAPK	Mitogen-activated protein kinase
MMP	Matrix metalloproteinase
NF-κB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OPG	Osteoprotegerin
PK	Pharmacokinetics
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor κB ligand
RCT	Randomized controlled trial
SIRT1	Sirtuin 1

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