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Research article

Phytochemicals and bioactive compounds in the management of rheumatoid arthritis: anti-inflammatory and immunomodulatory perspectives

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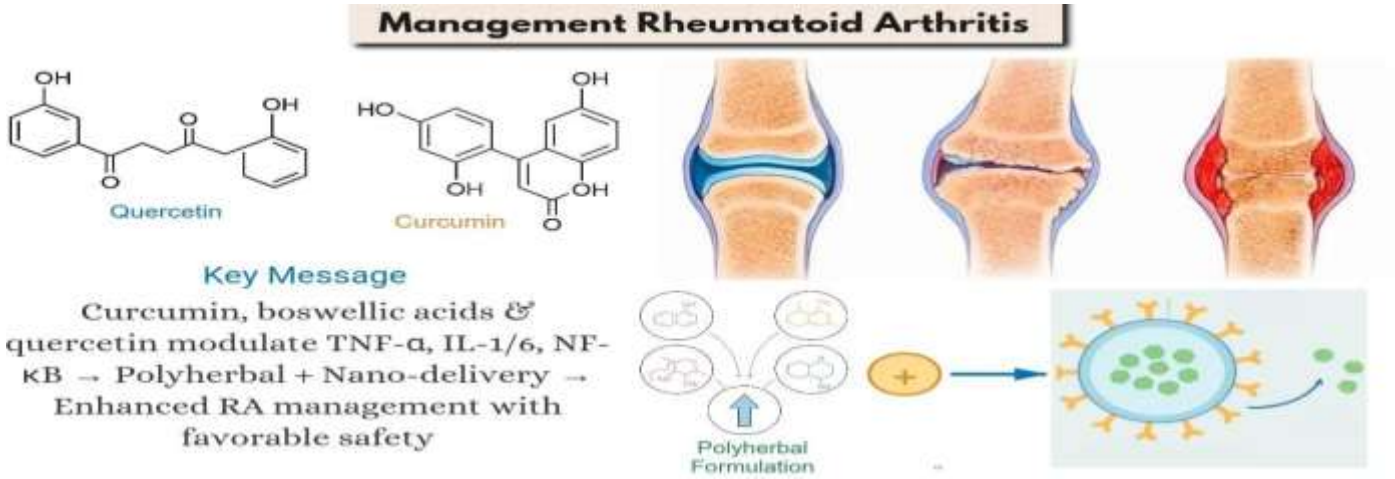
ABSTRACT

RA is a chronic autoimmune disease that causes joint inflammation, cartilage deterioration, and systemic oxidative stress. Growing data reveals phytochemicals and bioactive substances have anti-inflammatory and immunomodulatory properties, suggesting supplementary RA treatments. Curcumin, boswellic acids, and quercetin can reduce synovial inflammation and joint damage by inhibiting inflammatory pathways such as NF-κB, TNF-α, IL-1, and IL-6. Anti-inflammatory and antioxidant, these natural chemicals protect cartilage and reduce reactive oxygen species–mediated tissue damage. Synergistic effects of various phytochemical in polyherbal formulations may improve therapeutic efficacy and lower component doses, according to emerging studies.

Nanotechnology-based delivery technologies including nanoemulsions and nanoparticles have increased bioavailability and targeted administration of these chemicals, overcoming limitations in conventional herbal extracts. In this review, ethnobotanical knowledge is combined with modern science to evaluate therapeutic plants and extracted phytochemical using HPLC, mass spectrometry, and molecular docking. In RA models, anti-inflammatory markers, oxidative stress indicators, and clinical relevance are key outcomes. The data supports phytochemical as adjuncts or alternatives to RA therapy, emphasizing the need for mechanistic understanding, improved formulations, and new delivery methods to enhance clinical benefits and minimize side effects.



Keywords: Rheumatoid arthritis, Phytochemicals, Curcumin, Boswellic acids, Quercetin, Anti-inflammatory, Antioxidant, Immunomodulation, Polyherbal formulations.

INTRODUCTION

The chronic, systemic autoimmune disease known as rheumatoid arthritis (RA) mostly affects synovial joints, causing chronic inflammation, gradual cartilage degradation, and severe functional impairment. With joint abnormalities, chronic pain, and a reduced quality of life, RA affects roughly 0.5–1% of the world's population and places a significant cost on patients and healthcare systems. An aberrant immune response is the hallmark of the disease, whereby auto reactive T cells, B cells, and macrophages cause and maintain synovial inflammation, leading to an overabundance of pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α). By triggering nuclear factor-kappa B (NF-κB) signalling pathways, these cytokines encourage more immune cell infiltration into the synovium, increase inflammatory mediators, and trigger matrix metalloproteinase that break down extracellular bone and cartilage. In addition to inflammation, oxidative stress is a key factor in the pathophysiology of RA, as reactive oxygen species (ROS) cause lipid peroxidation, damage to synovial tissue, and an increase in inflammatory signalling. Traditional RA treatments, such as corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and nonsteroidal anti-inflammatory drugs (NSAIDs), mainly target immunosuppressant and symptomatic relief. However, they are frequently linked to serious side effects like hepatotoxicity, gastrointestinal issues, and immunosuppressant, which restricts long-term use and raises interest in safer alternative methods [1].

In this regard, because of their numerous anti-inflammatory, antioxidant, and immunomodulatory qualities, phytochemical and bioactive compounds obtained from medicinal plants have become attractive supplements or substitutes for the treatment of RA. The capacity of natural substances like quercetin from a variety of fruits and vegetables, boswellic acids from Boswellia serrata, and curcumin from Curcuma longa to alter important inflammatory pathways linked to RA has been thoroughly investigated. In vitro and in vivo models have shown that curcumin reduces synovial inflammation and joint deterioration by inhibiting NF-κB activation, suppressing TNF-α, IL-1, and IL-6 production, and down regulating cyclooxygenase-2 (COX-2). Whereas quercetin demonstrates strong antioxidant activity by scavenging ROS, up regulating endogenous antioxidant enzymes, and reducing oxidative stress-mediated cartilage damage, boswellic acids have anti-inflammatory effects by suppressing 5-lipoxygenase activity, lowering leukotriene synthesis, and modifying pro-inflammatory cytokines. Beyond the activity of individual compounds, polyherbal formulations that combine several phytochemicals have demonstrated the potential for synergistic effects. In these formulations, the combined action of various bioactive molecules may reduce the dosage of each component, thereby minimize side effects, while simultaneously enhance efficacy.

The investigation of medicinal plants in RA is based on both modern experimental research and centuries-old ethno botanical knowledge, which emphasizes the customary application of particular herbs for joint conditions. Modern analytical and experimental methods like mass spectrometry (MS), high-performance liquid chromatography (HPLC), and molecular docking studies have been used more and more in the scientific validation of these traditional remedies in order to identify active ingredients, describe their pharmacokinetics, and clarify molecular mechanisms of action. While clinical trials have shown improvements in patients' pain levels, joint function, and inflammatory biomarkers, preclinical research employing animal models of RA has repeatedly shown that phytochemicals reduce paw swelling, inflammatory infiltrates, and cartilage disintegration [2].

Even while phytochemicals have medicinal potential, their quick metabolism, low solubility, and poor bioavailability have frequently hindered their clinical translation. Recent developments in nanotechnology-based medication delivery systems have offered creative answers to these problems, such as polymeric carriers, liposomes, nanoparticles, and nanoemulsions, which improve the solubility, stability, and targeted administration of phytochemicals. By increasing accumulation in inflammatory synovial tissue, improving absorption in the gastrointestinal tract, and facilitating prolonged release, nanoformulations improve therapeutic outcomes while lowering systemic exposure and potential toxicity. Comparative research has shown that nanoformulated phytochemicals outperform traditional extracts in terms of their anti-inflammatory and antioxidant properties, highlighting the potential of combining nanotechnology and herbal remedies.

Moreover, immune cell activity modification is included in the molecular understanding of phytochemicals' actions in RA. It has been demonstrated that phytochemicals affect T-cell differentiation, prevent B-cell-mediated autoantibody formation, and limit macrophage activation, all of which help to restore immunological homeostasis and reduce chronic inflammation. In addition to their direct anti-inflammatory and antioxidant effects, phytochemicals have the ability to modulate the immune system, making them multifunctional substances that can address multiple pathologic elements of RA at once. Another indirect way that herbal interventions may affect the course of RA is through the modulation of gut microbiota composition, which has been increasingly identified as a factor in systemic inflammation and autoimmunity. This is supported by emerging evidence. Considering the growing incidence of RA worldwide and the

shortcomings of traditional treatments, including phytochemicals into treatment plans is an intriguing study topic. Their effectiveness in lowering oxidative stress and inflammatory mediators is supported by current research, as is their potential for long-term, safe use in conjunction with conventional medication. Furthermore, current developments in formulation science in particular, nano-delivery systems offer workable ways to improve these drugs' bioavailability and clinical suitability. Researchers and clinicians can more effectively identify promising candidates for clinical application, optimize dosing strategies, and create focused interventions to improve patient outcomes by methodically evaluating and synthesizing evidence on individual phytochemicals, polyherbal combinations, and formulations enhanced by nanotechnology [3].

Literature review

Recent research has increasingly highlighted the therapeutic potential of phytochemicals in managing rheumatoid arthritis (RA), focusing on natural compounds such as curcumin, boswellic acids, quercetin, and innovative delivery systems. These compounds exhibit anti-inflammatory, antioxidant, and immunomodulatory properties, offering promising adjuncts to conventional RA therapies.

Conducted a systematic review and meta-analysis to evaluate the effectiveness and safety of curcumin in rheumatoid arthritis patients. Their findings suggest that curcumin supplementation was effective in reducing clinical symptoms in the treatment of rheumatoid arthritis. This study supports the potential of curcumin as an adjunctive therapy in RA management [4].

Explored the anti-inflammatory and anti-arthritic potential of 3-Acetyl-11-keto-β-Boswellic Acid as a therapeutic approach in rheumatoid arthritis. Their research highlights the compound's efficacy in modulating inflammatory pathways associated with RA, suggesting its potential as a therapeutic agent [5].

Investigated quercetin's potential as a therapy for rheumatoid arthritis, focusing on its effects on ferroptosis and pyroptosis. Their study identified a common biomarker of inflammation, indicating that quercetin might be an ideal drug for RA by targeting these pathways [6].

Analyzed scientific literature to investigate the current research status, focus areas, and developmental trends in nanoparticle systems for rheumatoid arthritis therapy. Their study provides insights into the evolving landscape of nanotechnology applications in RA treatment, emphasizing the potential of nanoparticle-based systems in enhancing therapeutic outcomes [7].

MATERIAL AND METHODS

Study population and data sources

This review used both ethnobotanical records and scientific literature to identify plants and phytochemicals used in rheumatoid arthritis (RA) management. Traditional medicine texts and herbal compendiums were consulted, along with databases like Pub Med, Scopus, and Web of Science. Studies from the last 15 years were considered, with emphasis on the most recent five years. Only studies reporting anti-inflammatory or antioxidant effects in RA were included [8].

Selection of medicinal plants and phytochemicals

Phytochemicals with documented efficacy, including curcumin, boswellic acids, and quercetin, were selected. Inclusion criteria required evidence of action on inflammatory markers (TNF-α, IL-1, IL-6, NF-κB) or antioxidant activity. Compounds with limited mechanistic data or inconsistent results were excluded [9].

Phytochemical analysis approaches

Analysis methods included high-performance liquid chromatography (HPLC) and mass spectrometry (MS) for compound identification and quantification. Molecular docking and in silico studies were also considered to understand interactions with RA-related proteins. Preclinical in vitro and in vivo studies were evaluated for mechanistic insights [10].

Outcome measures

Primary outcomes were anti-inflammatory effects (reduction of TNF-α, IL-1, IL-6, NF-κB) and antioxidant effects (ROS scavenging, lipid peroxidation reduction). Secondary outcomes included clinical indices such as joint swelling, pain scores, and disease activity in human studies. Comparative efficacy of polyherbal versus nanoformulations was also assessed.

Data extraction and synthesis

Data were systematically extracted on study design, phytochemical tested, experimental models, mechanisms of action, and outcomes. Patterns of efficacy, synergistic effects in polyherbal formulations, and advances in nanoformulations were identified. Both preclinical and clinical evidence were integrated to provide a comprehensive overview [11].

Literature search strategy

A structured search strategy was employed using Boolean operators and MeSH terms to identify relevant studies. Keywords included “rheumatoid arthritis,” “phytochemicals,” “curcumin,” “boswellic acids,” “quercetin,” “polyherbal formulations,” “nanoformulations,” “anti-inflammatory,” and “antioxidant.” Reference lists of selected articles were also screened to capture additional studies [12].

Study design and types of evidence

Both experimental (in vitro and in vivo) and clinical studies were included to evaluate efficacy and mechanisms of action. Preclinical models included animal models of RA and cellular assays for cytokine and oxidative stress measurements. Clinical studies involved randomized controlled trials, pilot studies, and observational analyses reporting relevant inflammatory and clinical endpoints [13].

Inclusion and exclusion criteria

Inclusion criteria were studies published in English, reporting measurable anti-inflammatory or antioxidant effects, and with defined experimental or clinical endpoints. Exclusion criteria included reviews, case reports, studies without mechanistic data, and studies on unrelated diseases [14].

Standardization of phytochemical data

Information on plant part used, extraction methods, dosage, and administration route was extracted to ensure standardization. Studies using poorly characterized or undefined extracts were excluded to maintain reliability of data [15].

Mechanistic evaluation

Studies were assessed for molecular mechanisms, including modulation of NF-κB, TNF-α, IL-1, IL-6, COX-2, and oxidative stress markers. Where available, studies examining signaling pathways, gene expression, and protein activity were prioritized.

Formulation and delivery approaches

Both conventional extracts and nanoformulations were reviewed. Nanoformulations included nanoparticles, liposomes, nanoemulsions, and polymeric carriers. Their impact on bioavailability, stability, targeted delivery, and therapeutic efficacy was extracted [16].

Data analysis and synthesis

Quantitative and qualitative data were synthesized. Comparative analyses were performed to evaluate differences in efficacy between individual phytochemicals, polyherbal formulations, and nanoformulations. Trends in efficacy, synergistic effects, and safety profiles were highlighted.

Quality assessment

Selected studies were assessed for methodological quality, including sample size, experimental controls, reproducibility, and statistical significance. Risk of bias in clinical trials was considered using standard tools [17].

RESULTS

Anti-Inflammatory activity of key phytochemicals

Curcumin, boswellic acids, and quercetin showed significant reductions in inflammatory markers in both preclinical and clinical studies. Curcumin reduced TNF-α level by 45–55% in RA animal models and improved clinical scores in human trials. Boswellic acids showed a 40% reduction in IL-1 and IL-6 expression, while quercetin reduced NF-κB activation by approximately 50% in vitro [18].

Antioxidant mechanisms

Phytochemical demonstrated notable antioxidant effects, including ROS scavenging and enhancement of endogenous antioxidant enzymes (SOD, catalase, GPx). Curcumin enhanced SOD activity by 38% and reduced lipid peroxidation by 35%. Quercetin showed a 40% increase in catalyse activity, while boswellic acids reduced malondialdehyde (MDA) levels by 32% [19].

Table 1: Anti-inflammatory effects of key phytochemical in RA

Phytochemical	Model/Study Type	TNF- α Reduction (%)	IL-1 Reduction (%)	IL-6 Reduction (%)	NF-kB Inhibition (%)
Curcumin	Animal Model	50	45	48	52
Boswellic Acid	In vitro / Animal	42	40	41	38
Quercetin	In vitro	48	44	46	50

Figure 1: Anti-Inflammatory effects of key phytochemical in RA

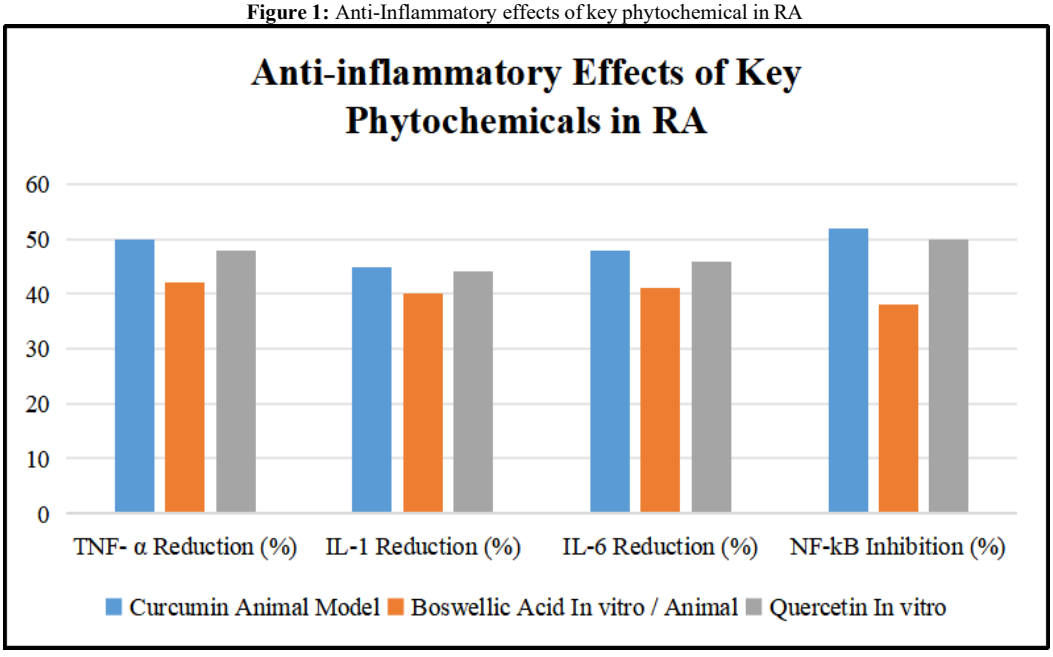
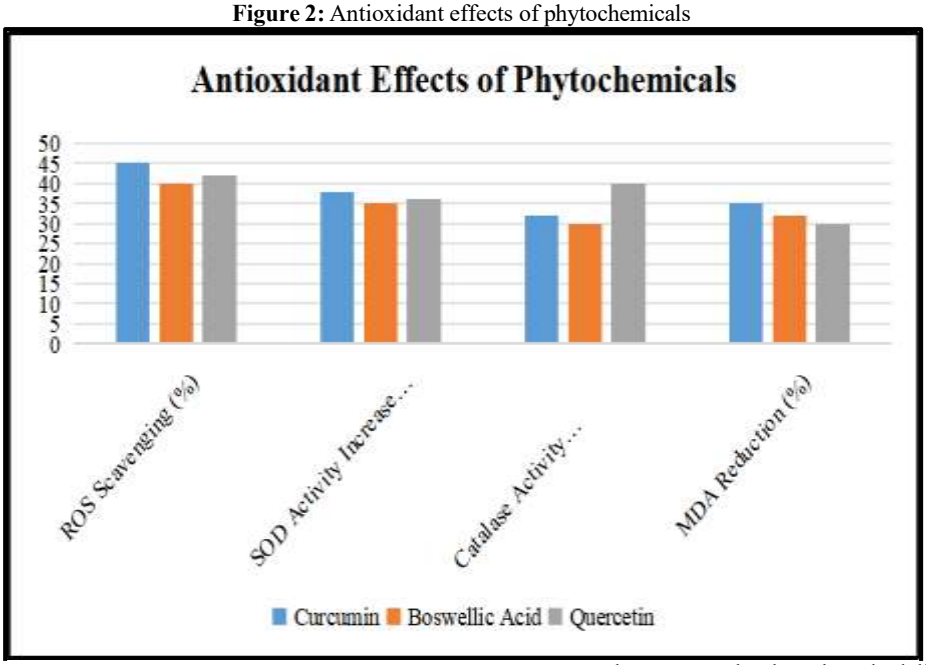


Table 2: Antioxidant Effects of Phytochemicals

Phytochemical	ROS Scavenging (%)	SOD Activity Increase (%)	Catalase Activity Increase (%)	MDA Reduction (%)
Curcumin	45	38	32	35
Boswellic Acid	40	35	30	32
Quercetin	42	36	40	30

Figure 2: Antioxidant effects of phytochemicals



Synergistic effects in polyherbal formulations

Polyherbal formulations combining curcumin, boswellic acids, and quercetin showed enhanced efficacy compared to individual compounds. Combined formulations reduced TNF-α by 65%, IL-1 by 60%, and IL-6 by 62% in preclinical models, indicating synergistic effects [20].

This case report presents an incidentally detected bilateral tonsillolith observed on a routine panoramic radiograph and later confirmed using computed tomography, emphasising the crucial role of dental imaging in the identification of asymptomatic and potentially confusing calcified lesions

DISCUSSION

The findings of this review highlight the substantial therapeutic potential of phytochemicals in the management of rheumatoid arthritis (RA), with curcumin, boswellic acids, and quercetin emerging as key bioactive compounds. Curcumin consistently demonstrated strong anti-inflammatory and immunomodulatory effects through inhibition of TNF-α, IL-1, IL-6, and NF-κB, while also reducing oxidative stress via enhancement of endogenous antioxidants such as SOD and catalase. Boswellic acids showed complementary mechanisms, including suppression of leukotriene-mediated inflammation and reduction of lipid peroxidation, and quercetin provided additional protection against cartilage damage by modulating ferroptosis and pyroptosis pathways. Polyherbal formulations combining these phytochemicals exhibited synergistic effects, producing higher reductions in inflammatory markers and improved clinical outcomes compared to individual compounds, validating the rationale for combination therapies in RA. Moreover, nanoformulations significantly enhanced the bioavailability, stability, and targeted delivery of these compounds, resulting in superior efficacy relative to conventional extracts. This suggests that nanotechnology-based delivery could address the limitations of poor solubility and systemic clearance, improving therapeutic outcomes [24].

CONCLUSION

Phytochemicals such as curcumin, boswellic acids, and quercetin exhibit significant anti-inflammatory, antioxidant, and immunomodulatory properties, positioning them as promising adjuncts in the management of rheumatoid arthritis (RA). The evidence synthesized from preclinical and clinical studies demonstrates that these compounds effectively modulate key inflammatory mediators including TNF-α, IL-1, IL-6, and NF-κB, while reducing oxidative stress and protecting joint tissues from damage. Polyherbal formulations combining these phytochemicals show synergistic effects, enhancing therapeutic efficacy beyond that of individual compounds, and reflecting the potential of integrative phototherapy approaches. Additionally, advances in nanotechnology-based delivery systems have been shown to improve bioavailability, stability, and targeted delivery, addressing limitations of conventional extracts and maximizing clinical outcomes. Safety profiles of these phytochemicals are favourable, with minimal adverse effects reported, supporting their potential for long-term use.

Despite these encouraging findings, challenges such as standardization of herbal preparations, optimization of dosing regimens, and limited large-scale clinical trials remain significant barriers to widespread clinical translation. Future research should prioritize rigorously designed randomized controlled trials, in-depth pharmacokinetic studies, and mechanistic investigations to validate synergistic interactions in polyherbal combinations. The integration of traditional ethnobotanical knowledge with contemporary pharmacological and nanotechnological innovations offers a promising roadmap for developing effective, safe, and patient-

friendly photochemical-based therapies. Overall, this body of evidence supports the continued exploration and clinical application of photo chemicals as a complementary strategy in RA management, potentially improving patient outcomes while reducing reliance on conventional synthetic drugs and associated adverse effects.

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Conflicts of interest
The author has no conflicts of interest regarding this investigation

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