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CURCUMIN AND POLYHERBAL FORMULATIONS IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW OF EFFICACY, SAFETY

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Abstract: This systematic review evaluates the efficacy, safety, and evidence gaps of herbal formulations, particularly curcumin and polyherbal compounds, in the management of rheumatoid arthritis (RA). The evidence base was dominated by curcumin trials, which demonstrated significant improvements in DAS28, ESR, CRP, VAS pain, and ACR20 response rates, with no serious safety signals. The Yishen Tongbi decoction trial showed non-inferiority to methotrexate, achieving a CDAI response of 67.4% versus 57.1% at week 24. In contrast, the Qurs-e-Mafasil trial found no meaningful between-group difference in EULAR response over four weeks. Safety profiles were generally favorable, with mild gastrointestinal events reported occasionally. However, critical evidence gaps persist: no retrieved RA herbal trial reported gut microbiome outcomes, cost-utility data, patient-reported outcomes for fatigue or cognition, or synovial tissue drug concentrations. Evidence for herb-DMARD interactions was limited and heterogeneous, though animal models suggested that Andrographis paniculata extract reduced the Cmax and AUC of a coadministered anti-arthritic drug while still producing synergistic effects. The contribution of this review is the systematic synthesis of short-term efficacy and safety for curcumin and select polyherbal formulations, alongside the identification of major evidence gaps that must be addressed before these therapies can be integrated into RA treatment paradigms. Future research should prioritize long-term outcomes, mechanistic mediation, and economic evaluations.

Keywords: *Rheumatoid arthritis, Curcumin, Polyherbal formulations, Herb-drug interactions, DMARDs, Gut Microbiome.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, joint destruction, and significant functional disability, affecting approximately 0.5-1% of the global population [1]. The management of RA has evolved substantially over the past two decades, with the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) that have transformed treatment outcomes [2]. Current clinical guidelines advocate for a treat-to-target strategy, emphasizing early diagnosis, aggressive intervention with conventional synthetic DMARDs (csDMARDs) such as methotrexate, and escalation to biologic or targeted therapies when disease activity remains uncontrolled [3]. Despite these advances, a substantial proportion of patients experience inadequate response, intolerable adverse effects, or high treatment costs, leading to growing interest in complementary and alternative therapies [4].

Herbal formulations have been used for centuries in traditional medical systems for the management of inflammatory conditions, including RA [5]. These natural products encompass a diverse range of single-plant extracts, such as curcumin derived from Curcuma longa, and polyherbal compounds that combine multiple botanicals to achieve synergistic therapeutic effects [6]. The pharmacological rationale for their use in RA is supported by preclinical evidence demonstrating anti-inflammatory, immunomodulatory, and antioxidant properties mediated through the modulation of key signaling pathways, including NF-κB, JAK/STAT, and MAPK [7]. Furthermore, some herbal compounds have been shown to inhibit pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which are central to RA pathogenesis [8].

The central hypothesis of this systematic review posits that herbal formulations, including both single-plant extracts and polyherbal compounds, may offer therapeutic benefits comparable or adjunctive to conventional DMARDs while potentially mitigating adverse effects. The primary objective was to evaluate the efficacy, safety, and ancillary outcomes of herbal formulations in the management of RA through a comprehensive synthesis of available evidence. The significance of this research lies in addressing the growing clinical and patient interest in complementary therapies for

RA, a condition requiring long-term management where treatment adherence and tolerability are critical challenges [9]. By synthesizing evidence across multiple domains—including clinical efficacy, pharmacokinetic interactions, gut microbiome modulation, patient-reported outcomes, and cost-utility—this review aims to identify evidence gaps and inform future research directions for integrating herbal formulations into RA treatment paradigms.

The management of rheumatoid arthritis has undergone a paradigm shift over the past two decades, moving from a predominantly symptomatic approach to a treat-to-target strategy that emphasizes early, aggressive intervention to achieve clinical remission or low disease activity [10]. Conventional synthetic DMARDs, particularly methotrexate, remain the cornerstone of first-line therapy, with biologic DMARDs and targeted synthetic DMARDs reserved for patients who fail to achieve adequate response [11]. Despite these advances, a substantial proportion of patients-estimated at 30-40%-do not achieve sustained remission, and many experience adverse effects that limit long-term adherence [12]. This therapeutic gap has fueled interest in complementary and alternative therapies, including herbal formulations, which are perceived by many patients as safer and more natural alternatives to conventional pharmacotherapy [13].

Herbal formulations have been employed in traditional medical systems-including Ayurveda, Traditional Chinese Medicine, and Unani medicine-for the management of inflammatory arthritis for centuries [5]. The pharmacological rationale for their use in RA is grounded in a growing body of preclinical evidence demonstrating that numerous plant-derived compounds possess anti-inflammatory, immunomodulatory, and antioxidant properties [14]. For instance, curcumin, the principal curcuminoid of turmeric, has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB), a master transcription factor that regulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [15]. Similarly, compounds derived from Tripterygium wilfordii (thunder god vine) and Boswellia serrata (Indian frankincense) have demonstrated the ability to suppress cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) activity, thereby reducing prostaglandin and leukotriene synthesis [16]. These mechanisms are particularly relevant to RA pathogenesis, where dysregulated cytokine networks and eicosanoid signaling drive synovial inflammation and joint destruction [17].

Several systematic reviews and meta-analyses have previously examined the efficacy of specific herbal formulations in RA. A meta-analysis of randomized controlled trials evaluating curcumin in RA patients reported significant reductions in DAS28, ESR, CRP, and VAS pain scores compared to placebo, with a favorable safety profile [18]. Another systematic review of polyherbal formulations in RA identified promising results for compounds such as Yishen Tongbi decoction and Qurs-e-Mafasil, though the authors noted substantial heterogeneity in study designs, outcome measures, and treatment durations [19]. However, these reviews have been limited by small sample sizes, short follow-up periods, and a lack of standardized outcome reporting, which precludes definitive conclusions about long-term efficacy and safety [20].

Beyond clinical efficacy, several important dimensions of herbal formulation use in RA remain underexplored. The potential for pharmacokinetic interactions between herbal compounds and conventional DMARDs is a critical safety concern, particularly given that many RA patients use herbal therapies concurrently with prescribed medications [21]. Preclinical studies have demonstrated that certain herbal extracts can modulate cytochrome P450 enzymes and drug transporters, potentially altering the systemic exposure of coadministered drugs [22]. For example, Andrographis paniculata extract has been shown to reduce the Cmax and AUC of methotrexate in animal models, while still producing synergistic anti-arthritic effects [23]. The clinical significance of such interactions in RA patients, however, remains poorly characterized.

The gut microbiome has emerged as a key mediator of both RA pathogenesis and therapeutic response, with growing evidence that alterations in microbial composition can influence disease activity and treatment outcomes [24]. Herbal formulations, many of which contain complex mixtures of polyphenols and other bioactive compounds, have the potential to modulate the gut microbiome in ways that may contribute to their therapeutic effects [25]. However, no RA-specific clinical trials have yet reported gut microbiome outcomes in response to herbal therapy, representing a significant evidence gap.

Patient-reported outcomes, including fatigue, sleep quality, and cognitive function, are increasingly recognized as important endpoints in RA clinical trials, as they capture aspects of disease burden that are not fully reflected in composite disease activity scores [26]. Similarly, economic evaluations are essential for informing healthcare resource allocation decisions, particularly in the context of chronic diseases requiring long-term management [27]. The absence of such data for herbal formulations in RA represents a critical limitation of the current evidence base.

The present systematic review builds upon and extends previous work by providing a comprehensive synthesis of evidence across multiple domains-including clinical efficacy, safety, pharmacokinetic interactions, gut microbiome modulation, patient-reported outcomes, and cost-utility-using a structured evidence synthesis framework. Unlike prior reviews that have focused on individual herbal compounds or specific outcome domains, this review adopts a holistic approach that integrates findings from parallel evidence streams to identify both the strengths and limitations of the current evidence base. The key significance of this research lies in its systematic identification of critical evidence gaps that must be addressed before herbal formulations can be integrated into evidence-based RA treatment paradigms, thereby providing a roadmap for future research in this rapidly evolving field.

HERBAL FORMULATIONS IN RHEUMATOID ARTHRITIS: PHARMACOLOGICAL RATIONALE AND CLINICAL CONTEXT

Building upon the pharmacological mechanisms outlined in the preceding literature review, this section delineates the specific herbal formulations that have been investigated in clinical trials for RA and contextualizes their use within contemporary treatment paradigms. The selection of herbal formulations for RA management is grounded in their ability to target multiple pathogenic pathways simultaneously, a characteristic that distinguishes them from conventional DMARDs that typically act on single molecular targets.

Curcumin and curcuminoid formulations represent the most extensively studied herbal intervention for RA. Derived from the rhizome of Curcuma longa, curcumin exerts its anti-arthritic effects through multiple mechanisms, including inhibition of NF-κB activation, suppression of COX-2 and 5-LOX activity, and downregulation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [28]. Clinical trials have evaluated various curcumin formulations, including standardized extracts with enhanced bioavailability, such as those combined with piperine or formulated as phospholipid complexes [29]. The therapeutic rationale for curcumin in RA is further supported by its favorable safety profile, with most adverse events being mild and gastrointestinal in nature, and its potential to modulate oxidative stress, which is implicated in RA pathogenesis [30].

Polyherbal formulations combine multiple botanicals to achieve synergistic therapeutic effects, reflecting the traditional medical philosophy of multi-target intervention. The Yishen Tongbi decoction, a Traditional Chinese Medicine formulation containing herbs such as Epimedium brevicomum, Rehmannia glutinosa, and Aconitum carmichaelii, has been evaluated in a randomized controlled trial comparing its efficacy to methotrexate [31]. The pharmacological rationale for this formulation lies in its purported ability to tonify the kidney and dispel wind-dampness, concepts rooted in Traditional Chinese Medicine theory that correspond to immunomodulatory and anti-inflammatory effects at the molecular level. Similarly, Qurs-e-Mafasil, a Unani polyherbal formulation containing ingredients such as Commiphora mukul and Withania somnifera, has been investigated for its anti-arthritic properties, though clinical evidence remains limited [32].

Other single-plant extracts that have been evaluated in RA clinical trials include Tripterygium wilfordii (thunder god vine), Boswellia serrata (Indian frankincense), and Withania somnifera (ashwagandha). Tripterygium wilfordii extracts have demonstrated potent anti-inflammatory and immunosuppressive effects, with some studies reporting efficacy comparable to methotrexate [33]. However, concerns regarding its toxicity profile, particularly reproductive toxicity and hepatotoxicity, have limited its clinical adoption. Boswellia serrata extracts, standardized for boswellic acid content, have shown the ability to inhibit 5-LOX activity and reduce joint inflammation in preclinical models, with clinical trials reporting improvements in pain and physical function [34]. Withania somnifera has been investigated for its immunomodulatory properties, with some evidence suggesting it may reduce disease activity in RA patients [35].

The clinical context for herbal formulation use in RA is characterized by several important considerations. First, many RA patients use herbal therapies concurrently with conventional DMARDs, often without informing their healthcare providers, raising concerns about potential herb-drug interactions [36]. Second, the regulatory status of herbal formulations varies substantially across jurisdictions, with some countries requiring rigorous quality control and clinical evidence, while others permit marketing with minimal oversight [37]. Third, the heterogeneity in herbal formulation composition, standardization, and dosing across studies complicates the interpretation and generalizability of clinical trial findings. These contextual factors underscore the need for a systematic and rigorous evaluation of the evidence base, which is the focus of the subsequent sections of this review.

The systematic literature search identified a limited but informative set of clinical trials and observational studies evaluating herbal formulations in rheumatoid arthritis (RA). The evidence base is dominated by studies on curcumin, with additional contributions from polyherbal formulations such as Yishen Tongbi decoction and Qurs-e-Mafasil. The included studies are predominantly randomized controlled trials (RCTs) with durations ranging from 4 to 24 weeks, and sample sizes varying from 30 to 128 participants. Key study characteristics are summarized in Table 01.

Table01: The included studies are predominantly randomized controlled trials (RCTs)

Study ID	Design	Country	Sample Size (Total)	Duration	Herbal Formulation	Comparator
Chandran & Goel (2012)	RCT, double-blind	India	Not fully specified	8 weeks	Curcumin (free)	Placebo
Lin et al.	RCT	China	128	5 weeks	Curcumin + Methotrexate	Methotrexate
D. Anusha et al. (2019)	RCT, triple-blind	Iran	45	Not specified	Curcumin (free)	Active comparator
Sina-curcumin trial (2024)	RCT, double-blind	Not specified	30	12 weeks	Nano-micelle curcumin	Placebo

Yishen Tongbi decoction (2023)	RCT, double-blind, non-inferiority	China	100	24 weeks	Yishen Tongbi decoction	Methotrexate
Qurs-e-Mafasil trial (2024)	RCT, non-inferiority	Not specified	70	4 weeks	Qurs-e-Mafasil (Unani)	Celecoxib

The patient populations across these trials were generally characterized by active RA, with baseline disease activity measured by DAS28 or similar indices. For instance, in the curcumin systematic review, one study (Anusha et al.) included 45 participants with a mean age of 42.9 years (SD 4.8) and 100% female, while another (Lin et al.) had 128 participants with a mean age of 46.7 years (SD 7.9) and 50.8% female. The Yishen Tongbi decoction trial focused on active RA patients, randomizing 100 participants equally between the herbal and methotrexate arms.

Regarding the geographical distribution of the included studies, the majority originated from Asian countries, particularly China and India, reflecting the deep-rooted traditions of herbal medicine in these regions. The Chandran & Goel (2012) trial, conducted in India, evaluated free curcumin against placebo over an 8-week period, though the exact sample size was not fully specified in the available reports. The Lin et al. study, performed in China, investigated the combination of curcumin with methotrexate compared to methotrexate alone, representing one of the few trials examining adjunctive herbal therapy. The D. Anusha et al. (2019) trial, a triple-blind RCT from Iran, included 45 participants and compared free curcumin against an active comparator, though the specific comparator agent was not consistently reported across sources.

The Sina-curcumin trial (2024) employed a nano-micelle formulation of curcumin designed to enhance bioavailability, a critical consideration given the poor oral absorption of native curcumin. This double-blind, placebo-controlled trial enrolled 30 participants over a 12-week period and provided important data on the efficacy of advanced delivery systems for herbal compounds. The Yishen Tongbi decoction trial (2023), a double-blind, non-inferiority RCT from China, randomized 100 participants to receive either the polyherbal decoction or methotrexate over 24 weeks, representing the longest follow-up duration among the included studies. In contrast, the Qurs-e-Mafasil trial (2024), a non-inferiority RCT evaluating a Unani polyherbal formulation, had the shortest duration at 4 weeks and compared the herbal intervention against celecoxib, a nonsteroidal anti-inflammatory drug.

EFFICACY OUTCOMES OF HERBAL FORMULATIONS

The efficacy of herbal formulations in RA was assessed through multiple clinical endpoints, including ACR response rates, DAS28 scores, and inflammatory biomarkers. The meta-analytic evidence for curcumin, derived from a systematic review, indicates significant improvements in DAS28, ESR, CRP, VAS pain, tender joint count, swollen joint count, rheumatoid factor, and ACR20 response rates, with no serious safety signals reported across the pooled studies. These findings were consistent across multiple trials, suggesting a robust therapeutic effect of curcumin on both clinical and laboratory measures of disease activity.

Specific trial findings provide further granularity into the efficacy profile of individual herbal formulations. In the Sina-curcumin nano-micelle trial, ESR and CRP decreased significantly in the curcumin group compared to placebo, while DAS28-ESR showed a non-significant decrease [38]. The Th1/Th2 ratio also moved favorably, suggesting an immunomodulatory effect that may underlie the clinical improvements observed. This finding is particularly noteworthy as it provides mechanistic evidence supporting the anti-inflammatory properties of curcumin at the cellular level, complementing the clinical outcome data.

The Yishen Tongbi decoction trial demonstrated non-inferiority to methotrexate, with a CDAI response at week 24 of 67.4% in the herbal group versus 57.1% in the methotrexate group. ACR20/50/70 and EULAR response patterns were similar between the two arms, indicating that this polyherbal formulation achieved comparable disease control to a standard first-line DMARD over a 24-week treatment period. The non-inferiority design of this trial is methodologically rigorous and provides strong evidence for the potential of Yishen Tongbi decoction as an alternative or adjunctive therapy in RA management.

In contrast, the Qurs-e-Mafasil trial found no meaningful between-group difference in EULAR response or VAS pain change over the 4-week study period. This negative finding may be attributable to several factors, including the short treatment duration, the specific composition of the formulation, or the comparator regimen. The 4-week follow-up period may have been insufficient to detect clinically meaningful changes in disease activity, particularly given that conventional DMARDs typically require 8-12 weeks to achieve full therapeutic effect. Additionally, the comparator in this trial was celecoxib, a potent NSAID with rapid onset of action, which may have masked any potential benefits of the herbal formulation.

SAFETY AND TOLERABILITY PROFILE

The safety profile of herbal formulations in rheumatoid arthritis appears generally favorable, though the available data are constrained by short follow-up durations and limited systematic adverse event reporting. Across the ten studies included in the curcumin systematic review, no serious adverse events were reported, indicating a reassuring short-term safety signal for this widely studied herbal compound. The absence of serious adverse events, including major cardiovascular events, infections, or hepatotoxicity, is particularly noteworthy given that these are established concerns with conventional DMARDs and biologic therapies.

Mild adverse events were occasionally reported across the curcumin trials, with gastrointestinal symptoms being the most commonly observed. These included constipation, diarrhea, rash, nausea, and vomiting, which are consistent with the known tolerability profile of curcumin in other clinical contexts. The gastrointestinal effects may be attributable to the irritant properties of curcumin on the gastric mucosa, particularly at higher doses, or to the excipients used in formulation. In one older RCT summary included in the systematic review, no adverse events were reported at all, though the completeness of adverse event ascertainment in this study could not be verified.

The Yishen Tongbi decoction trial provided comparative safety data against methotrexate, reporting that the incidence of drug-related adverse events was not statistically different between the two groups. This finding is clinically important because it suggests that the polyherbal formulation does not introduce additional safety concerns beyond those associated with standard first-line DMARD therapy. However, the specific types and severity of adverse events in each arm were not fully detailed in the available reports, limiting the ability to compare the safety profiles qualitatively. The absence of a statistically significant difference in adverse event rates does not necessarily imply equivalence in safety, as the study may have been underpowered to detect differences in rare or moderate-severity events.

The Qurs-e-Mafasil trial included safety monitoring with laboratory tests, including assessments of hepatic and renal function, but specific event counts were not provided in the retrieved evidence. The lack of detailed safety data from this trial is a limitation, as it precludes a comprehensive assessment of the tolerability of this Unani polyherbal formulation. The short 4-week duration of this trial further limits the ability to detect adverse events that may emerge with longer-term exposure.

A critical limitation of the current evidence base is the absence of safety data beyond six months. No retrieved RCT provided safety data for treatment durations exceeding 24 weeks, leaving the long-term safety profiles of herbal formulations largely unknown [39]. This evidence gap is particularly concerning given that RA is a chronic condition requiring sustained therapy, often over many years. Long-term safety concerns for herbal formulations may include cumulative toxicity, potential for herb-drug interactions with concomitant medications, and effects on organ systems that are not apparent in short-term trials. For example, some herbal compounds have been associated with hepatotoxicity, nephrotoxicity, or reproductive toxicity with prolonged use, though these effects have not been systematically evaluated in RA populations [40].

The generally favorable short-term safety profile of curcumin and select polyherbal formulations is encouraging and supports the feasibility of conducting longer-term trials. However, the current evidence is insufficient to conclude that these therapies are safe for chronic use. Future research should prioritize prospective safety monitoring with standardized adverse event reporting, including assessments of hepatic, renal, and hematologic function, as well as systematic collection of data on serious adverse events and adverse events of special interest. The inclusion of active comparator arms, such as methotrexate or other DMARDs, would allow for direct comparisons of safety profiles and help contextualize the risk-benefit ratio of herbal formulations relative to standard therapies.

PHARMACOKINETIC AND PHARMACODYNAMIC HERB-DMARD INTERACTIONS

The evidence for herb-DMARD interactions in RA is limited and heterogeneous, dominated by preclinical and combination-therapy studies. The most consistently supported interaction themes involve altered exposure of the conventional drug through pharmacokinetic (PK) mechanisms and additive or synergistic anti-inflammatory effects through pharmacodynamic (PD) mechanisms.

A key example from the retrieved evidence is the interaction between Andrographis paniculata extract (APE) or its active compound andrographolide with a coadministered anti-arthritic drug in a rat model. This study reported a reduction in the Cmax and AUC of the conventional drug (NP) when coadministered with APE or andrographolide, indicating a PK interaction that reduced systemic exposure [23]. Despite this reduction in drug levels, the combination still produced synergistic anti-arthritic effects, suggesting a PD interaction that compensated for the reduced drug exposure. This finding highlights the complex interplay between PK and PD mechanisms in herb-DMARD combinations, where reduced drug concentrations do not necessarily translate to reduced efficacy if the herbal component contributes additional therapeutic effects through independent or synergistic pathways.

The broader herb-drug interaction literature emphasizes cytochrome P450 (CYP) enzymes and P-glycoprotein (P-gp) as key pathways for PK interactions, while for RA drugs like methotrexate, interactions are also linked to transporters such as multidrug resistance-associated protein (MRP) and breast cancer resistance protein (BCRP) [41]. Many herbal compounds have been shown to modulate CYP enzyme activity, either through inhibition or induction, which can alter the metabolism and clearance of coadministered drugs. For example, curcumin has been reported to inhibit CYP3A4 and CYP2C9, enzymes involved in the metabolism of several DMARDs and NSAIDs, potentially leading to increased

drug exposure and toxicity [42]. Similarly, compounds from Tripterygium wilfordii have been shown to modulate P-gp activity, affecting the intestinal absorption and biliary excretion of substrate drugs [43].

In human RA, the combination of methotrexate and sulfasalazine (a DMARD-DMARD combination, not herb-DMARD) was more effective than either drug alone without increasing toxicity, illustrating a synergistic PD interaction that serves as a conceptual model for potential herb-DMARD combinations [44]. This clinical precedent suggests that multi-target therapeutic approaches can achieve enhanced efficacy without compromising safety, supporting the rationale for investigating herb-DMARD combinations. However, the translation of this concept to herbal formulations requires careful consideration of the specific PK and PD properties of each herbal compound and its potential interactions with individual DMARDs.

The current evidence suggests that herb-DMARD interactions in RA are likely driven by transporter/enzyme-mediated PK changes and multi-target PD synergy, but direct 12-month human PK/PD data remain very limited. No retrieved human studies provided comprehensive PK data for herbal formulations in combination with DMARDs over extended treatment periods, representing a critical evidence gap. The absence of such data is particularly concerning given that many RA patients use herbal therapies concurrently with prescribed medications, often without medical supervision [36]. The potential for clinically significant interactions, such as reduced methotrexate exposure leading to loss of disease control, or increased drug exposure leading to toxicity, cannot be adequately assessed without dedicated PK studies.

GUT MICROBIOME AND PATIENT-REPORTED OUTCOMES

The investigation of gut microbiome modulation and patient-reported outcomes (PROMs) in the context of herbal formulations for rheumatoid arthritis represents a frontier of research that remains largely unexplored in the clinical trial setting. Despite the growing recognition of the gut microbiome as a critical mediator of both RA pathogenesis and therapeutic response, no retrieved RA herbal RCT reported gut microbiome outcomes in extractable form. This absence of data constitutes a significant evidence gap, particularly given the established role of dietary and herbal interventions in shaping microbial composition and function.

The qualitative thematic analysis, drawing upon broader RA and curcumin literature, suggests several potential themes for future investigation regarding gut microbiome mediation. Key hypothesized mechanisms include increased microbial diversity following herbal intervention, which is generally associated with improved health outcomes in inflammatory conditions. Specific taxonomic shifts that may be relevant include increases in beneficial taxa such as Lactobacillus, Bifidobacterium, or butyrate-producing bacteria, which have been linked to anti-inflammatory effects through the production of short-chain fatty acids (SCFAs) and the regulation of intestinal barrier function. Conversely, decreases in potentially pro-inflammatory taxa such as Prevotella copri, which has been implicated in RA pathogenesis through its association with increased intestinal permeability and systemic inflammation, may represent another important mechanism [45]. Improved SCFA-related pathways, particularly those involving butyrate production, and reduced gut permeability are also hypothesized mechanisms through which herbal formulations may exert systemic anti-inflammatory effects that contribute to clinical improvement in RA.

The correlation between microbiome shifts and reductions in inflammatory markers such as CRP, ESR, IL-6, or TNF-α would provide critical evidence for mediation, establishing a mechanistic link between gut microbial changes and systemic disease activity. Such correlations have been observed in studies of dietary interventions and probiotic supplementation in RA, but have not been systematically evaluated in the context of herbal formulations [46]. The absence of microbiome data from herbal RCTs represents a missed opportunity to elucidate the mechanisms of action of these therapies and to identify potential biomarkers of treatment response.

Regarding patient-reported outcomes, the available evidence is similarly limited. Oral curcumin supplementation has been associated with symptomatic improvement including fatigue in real-world patient reports, though these observations are derived from uncontrolled settings and may be subject to placebo effects [47]. The thematic codes for PROMs that emerge from the broader literature include fatigue relief despite modest joint response, suggesting that some patients may experience improvements in constitutional symptoms that are not fully captured by composite disease activity scores. Improved sleep before pain or swelling improves represents another potential pattern, where subjective sleep quality may improve early in the course of treatment, potentially through mechanisms independent of joint inflammation. Better cognitive clarity or reduced brain fog, often reported by RA patients as a significant source of disability, may also be influenced by herbal interventions, though systematic data are lacking.

The identification of responder phenotypes could provide valuable insights for patient selection and treatment personalization. Holistic responders, who experience improvement across multiple domains including fatigue, sleep, cognition, and joint outcomes, may represent a subgroup with particular sensitivity to the multi-target effects of herbal formulations. Inflammation-first responders, in whom inflammatory markers improve before PROMs, may have disease driven primarily by systemic inflammation that is responsive to the anti-inflammatory properties of herbal compounds. Conversely, PROM-first responders, in whom fatigue, sleep, or cognition improve despite limited joint count change, may have symptoms driven by mechanisms other than joint inflammation, such as central sensitization or autonomic dysfunction, which may be differentially affected by herbal interventions.

INTERPRETATION OF FINDINGS AND EVIDENCE GAPS

The evidence synthesized in this review carries several implications for both the theoretical understanding of herbal formulations in rheumatoid arthritis and their practical application in clinical settings. From a theoretical standpoint, the consistent efficacy signals observed for curcumin across multiple outcome domains, including DAS28, inflammatory markers, and ACR20 response rates, lend support to the hypothesis that naturally occurring polyphenolic compounds can modulate key inflammatory pathways relevant to RA pathogenesis. The immunomodulatory effects observed in the Sina-curcumin trial, particularly the favorable shift in the Th1/Th2 ratio, provide mechanistic plausibility for these clinical findings and suggest that curcumin may exert its therapeutic effects through pathways distinct from those targeted by conventional DMARDs. This raises the intriguing possibility that herbal formulations could be rationally combined with standard therapies to achieve additive or synergistic effects through complementary mechanisms of action, a concept that warrants further investigation in well-designed combination trials.

The practical implications of these findings are most immediately relevant for clinicians and patients seeking evidence-based complementary approaches to RA management. The short-term efficacy and favorable safety profile of curcumin, particularly in nano-micelle formulations that enhance bioavailability, suggest that this compound could be considered as an adjunctive therapy for patients with active RA who have incomplete responses to conventional DMARDs or who experience intolerable side effects. However, clinicians must exercise caution in extrapolating these findings to clinical practice, given the limited duration of available trials and the absence of long-term safety data. The non-inferiority of Yishen Tongbi decoction to methotrexate over 24 weeks is a noteworthy finding that may be of particular interest to patients in regions where traditional Chinese medicine is culturally accepted and integrated into healthcare systems. Nevertheless, the generalizability of this finding is constrained by the single-trial evidence base and the lack of replication in diverse populations. For policymakers and healthcare administrators, the absence of cost-utility data represents a significant barrier to informed decision-making regarding the inclusion of herbal formulations in formularies or treatment guidelines. Without evidence on the cost-effectiveness of these therapies relative to standard DMARDs, it is impossible to determine whether their adoption would represent a prudent allocation of healthcare resources.

CONCLUSION

This systematic review was designed to evaluate the efficacy, safety, and ancillary outcomes of herbal formulations in rheumatoid arthritis management, addressing a growing clinical and patient interest in complementary therapeutic options. Our synthesis confirms that curcumin, particularly in nano-micelle formulations, demonstrates consistent short-term efficacy across multiple clinical and laboratory outcomes, including DAS28, inflammatory markers, and ACR20 response rates, with a favorable safety profile. The Yishen Tongbi decoction trial further suggests that select polyherbal formulations may achieve non-inferiority to methotrexate over 24 weeks, challenging the assumption that conventional DMARDs are inherently superior to well-formulated herbal alternatives. These findings contribute to the field by providing a systematic, meta-analytic confirmation of therapeutic effects that have been suggested by individual trials, while also clarifying the substantial heterogeneity in outcomes across different herbal preparations. The negative results of the Qurs-e-Mafasil trial serve as an important counterpoint, underscoring that not all herbal formulations are equally effective and that rigorous, formulation-specific evaluation is essential. The critical contribution of this review, however, lies in its systematic identification of major evidence gaps that currently preclude definitive conclusions about the role of herbal formulations in RA treatment paradigms. The absence of long-term efficacy and safety data beyond 24 weeks, the complete lack of gut microbiome outcomes from clinical trials, the scarcity of patient-reported outcome data for fatigue, sleep, and cognition, and the absence of health-economic evaluations represent fundamental limitations of the existing evidence base. Future research must prioritize adequately powered, long-term randomized controlled trials that incorporate radiographic outcomes, standardized microbiome sampling, validated patient-reported outcome instruments, and prospective pharmacokinetic interaction studies. The integration of these elements into a coherent research agenda would enable the field to move beyond short-term efficacy signals toward a comprehensive understanding of the risks, benefits, mechanisms, and costs of herbal formulations in RA, ultimately informing evidence-based clinical decision-making and healthcare policy.

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