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A REVIEW OF HERBAL TREATMENT: EFFICACY IN RHEUMATOID ARTHRITIS

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Abstract

Synovial inflammation, joint degeneration, and systemic consequences are the hallmarks of rheumatoid arthritis (RA), a chronic inflammatory disease. NSAIDs, DMARDs, and biologics are examples of conventional therapy that lower disease activity but frequently result in side effects and partial remission. With medicinal plants and polyherbal formulations exhibiting anti-inflammatory, immunomodulatory, antioxidant, and cartilage-protective qualities, herbal medicine provides a complimentary strategy. Herbs including Tinospora cordifolia, Withania somnifera, Boswellia serrata, and Curcuma longa are effective at reducing pain and enhancing joint function, according to preclinical and clinical research. Standardization, safety assessment, and clinical validation continue to present difficulties despite encouraging results. Opportunities for the evidence-based integration of herbal medicines into conventional RA management are presented by developments in systems pharmacology and phytopharmaceutical development.

Keywords:

Rheumatoid arthritis; herbal medicine; anti-inflammatory; immunomodulation; polyherbal formulations; phytopharmaceuticals; complementary therapy

1. Introduction

Persistent synovial inflammation, joint degeneration, and increasing disability are the hallmarks of rheumatoid arthritis (RA), a chronic, systemic inflammatory disease. About 0.5–1% of people worldwide suffer from RA, which not only decreases physical function but also dramatically lowers quality of life and raises morbidity because of related metabolic and cardiovascular problems (Smolen, Aletaha, & McInnes, 2018). The main goals of conventional management techniques, such as biologic agents, disease-modifying antirheumatic medications (DMARDs), and non-steroidal anti-inflammatory drugs (NSAIDs), are to avoid structural damage, control disease activity, and reduce inflammation. However, side effects, high prices, and incomplete illness remission in certain patients sometimes restrict the long-term use of these treatments.

With a centuries-long history in traditional systems like Ayurveda, Traditional Chinese Medicine (TCM), and Unani medicine, herbal treatment has evolved as a complementary and integrative strategy for RA care. Due to their anti-inflammatory, immunomodulatory, antioxidant, and cartilage-protective qualities, medicinal plants and polyherbal preparations can be used to address many pathogenic pathways associated with RA (Williamson, 2001; Li et al., 2011). A growing body of preclinical and clinical research demonstrates the effectiveness of a number of herbs, including Tinospora cordifolia, Withania somnifera, Boswellia serrata, and Curcuma longa, in decreasing inflammatory indicators, reducing pain, and enhancing functional outcomes.

Standardization, quality control, regulatory supervision, and systematic clinical evaluation continue to be obstacles despite the therapeutic potential. With regard to etiology, mechanisms of action, preclinical and clinical evidence, polyherbal formulations, safety issues, and future prospects, this review attempts to give a thorough overview of the function of herbal treatment in RA. This study emphasizes the possibility of evidence-based herbal remedies as supplements to traditional RA management by fusing traditional knowledge with contemporary scientific discoveries.

2. Pathophysiology of Rheumatoid Arthritis

The autoimmune, chronic inflammatory disease known as rheumatoid arthritis (RA) is characterized by progressive joint damage and ongoing synovial inflammation. Genetic

vulnerability and environmental stimuli interact intricately to cause immunological dysregulation and chronic inflammation, which in turn cause damage to cartilage and bone as well as systemic problems (Smolen et al., 2018).

2.1 Immunological Basis of RA

Both innate and adaptive immunity are involved in the dysregulated immune response that causes RA. People are predisposed to autoimmunity by genetic factors such certain HLA-DR alleles. Autoantibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), which cause joint inflammation and tissue damage, are produced in response to modified self-proteins such citrullinated peptides. Pannus development and prolonged synovial inflammation are caused by $CD4^+$ T helper cells, particularly Th1 and Th17 subsets, which stimulate B cells, macrophages, and fibroblast-like synoviocytes (Rezaei et al., 2021).

2.2 Role of Pro-Inflammatory Cytokines (TNF-α, IL-1β, IL-6)

The pathophysiology of RA is largely mediated by pro-inflammatory cytokines. Tumor necrosis factor-α (TNF-α) attracts leukocytes, promotes angiogenesis, increases the production of other cytokines and chemokines, and amplifies inflammatory cascades (Nakae et al., 2013). While interleukin-6 (IL-6) causes both local inflammation and systemic consequences such anemia and fatigue, interleukin-1β (IL-1β) contributes to cartilage matrix breakdown by activating matrix metalloproteinases and reducing collagen production (Naser et al., 2024; Smolen et al., 2018). Patients with RA have consistently shown elevated levels of TNF-α and IL-6, which are correlated with disease activity (Naser et al., 2024; Smolen et al., 2018).

2.3 Oxidative Stress and Synovial Inflammation

The pathophysiology of RA is significantly influenced by oxidative stress. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced by activated immune cells in the inflamed synovium, overpowering antioxidant defenses and causing oxidative damage to cellular proteins, lipids, and DNA. Nuclear factor-κB (NF-κB) and other redox-sensitive transcription factors are further activated by this oxidative environment, which increases pro-inflammatory mediators and prolongs inflammation (Mateen et al., 2016; Tiwari & Agarwal, 2013). In RA patients, higher disease activity ratings are correlated with elevated oxidative stress.

2.4 Joint Destruction and Systemic Complications

Pannus, an aggressive granulation tissue that invades bone and cartilage, is the result of chronic synovitis. Cartilage is broken down by proteolytic enzymes like matrix metalloproteinases produced by invading immune cells and fibroblast-like synoviocytes. Receptor activator of nuclear factor-κB ligand (RANKL), which promotes osteoclast development and activation and causes focal bone degradation, is the mediator of bone erosion (Gravallese et al., 2007; Smolen et al., 2018). Cardiovascular disease, osteoporosis, and interstitial lung disease are among the systemic consequences of RA, which are mostly brought on by ongoing inflammation and immunological dysregulation.

2.5 Molecular Targets Relevant to Herbal Interventions

Important molecular pathways linked to the pathogenesis of RA are appealing targets for treatment. Inflammatory amplification is primarily caused by pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, as well as transcription factors like NF-κB and signaling pathways like MAPK and JAK/STAT. Bioactive phytochemicals regulate enzymes that cause tissue damage, including matrix metalloproteinases, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). Furthermore, osteoclastogenesis and bone erosion can be decreased by targeting receptor activator of nuclear factor-κB ligand (RANKL), which offers a mechanistic explanation for herbal substances with anti-inflammatory and anti-osteoclastogenic qualities (Smolen et al., 2018; Gravallese et al., 2007).

3. Conventional Management of Rheumatoid Arthritis

Controlling disease activity, preventing joint destruction, maintaining function, and lowering systemic consequences are the goals of RA care. Although long-term use can have negative effects, pharmacological therapy continue to be the mainstay, which encourages research into complementary methods.

NSAIDs are frequently used to treat symptoms by inhibiting cyclooxygenase (COX), which lowers pain, stiffness, and inflammation. Although they are helpful in the short term, their usage as monotherapy is limited since they carry gastrointestinal, cardiovascular, and renal hazards and do not stop the disease from progressing (Smolen et al., 2018).

DMARDs have a key role in RA treatment by reducing immunological response and delaying joint deterioration. The first-line treatment is methotrexate; other options include hydroxychloroquine, leflunomide, and sulfasalazine. These drugs improve long-term results by inhibiting lymphocyte proliferation and cytokine production, but they need to be well watched because of the risk of infection, myelosuppression, and hepatotoxicity (McInnes & Schett, 2011).

Certain inflammatory mediators, including TNF-α, IL-6, and JAK pathways, are targeted by biologics and JAK inhibitors. Although they raise the risk of major infections, cancers, and thromboembolic events, they are helpful in situations of moderate-to-severe RA or DMARD resistance (Burmester & Pope, 2017).

Long-term safety and adverse consequences continue to be major obstacles. Adherence and quality of life may be negatively impacted by gastrointestinal, hepatic, hematologic, and metabolic problems brought on by long-term treatment. Accessibility is further restricted by high costs, especially for biologics (Smolen et al., 2018).

Incomplete remission and side effects necessitate supplementary therapies. With its anti-inflammatory, immunomodulatory, and antioxidant qualities, herbal remedies may provide additional advantages such as lowering the dosage of conventional medications, increasing tolerance, and improving quality of life. However, prior to clinical integration, strong scientific validation, standardization, and safety assessment are crucial.

4. Role of Herbal Medicine in Rheumatoid Arthritis

For generations, RA has been treated with herbal therapy, which offers multi-targeted, culturally acceptable treatments that may be safer over time.

4.1 Historical and Ethnomedical Perspectives

For a very long time, people have used medicinal plants to treat inflammation, swelling, and joint discomfort. Plant-based treatments for RA-like illnesses including pain, stiffness, and deformity are described in ancient manuscripts from Europe, the Middle East, China, and India. Plants with analgesic, immunomodulatory, or anti-inflammatory properties, either separately or in combination, were the subject of empirical use. Many of these ancient methods have been

verified by contemporary ethnopharmacology, offering a scientific justification for investigating herbal therapies in RA (Fabricant & Farnsworth, 2001; Yuan et al., 2016).

4.2 Traditional Systems of Medicine

According to Ayurveda, RA (Amavata) is caused by toxin buildup, poor digestion, and Vata imbalance. Herbs like Withania somnifera, Boswellia serrata, Tinospora cordifolia, and Curcuma longa are used to treat this condition. Herbs like Tripterygium wilfordii and Paeonia lactiflora are used to treat RA, which is classified as Bi syndrome in TCM, by eliminating pathogenic elements and reestablishing immunological balance. Unani medicine uses Nigella sativa and Zingiber officinale to link RA-like illnesses to humoral imbalances. Every system has a strong emphasis on holistic methods that incorporate diet, lifestyle, and herbal therapy (Yuan et al., 2016; Sharma et al., 2017).

4.3 Mechanistic Basis

Herbal remedies influence several RA pathways. Polyphenols, flavonoids, terpenoids, and alkaloids are examples of bioactive substances that reduce oxidative stress, suppress NF-κB and MAPK/JAK-STAT pathways, and inhibit pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). Additionally, some herbs prevent bone degradation and preserve cartilage by inhibiting RANKL and matrix metalloproteinases. The intricate pathophysiology of RA is consistent with this multi-targeted activity (Pan et al., 2011; Li et al., 2020).

4.4 Advantages and Limitations

Broad pharmacological effects, cultural acceptability, cost, and the possibility of long-term use are all benefits of herbal medications. Because of their multi-component structure, they can simultaneously modulate oxidative stress, immunity, and inflammation, enhancing traditional therapies and possibly lowering medication dependency. Variability in plant sources, irregular dose, lack of standardization, and possible herb-drug interactions are some of the limitations. Large-scale RCTs to verify the safety and effectiveness of several treatments are also lacking. Integration into mainstream RA management requires strict validation, quality control, and regulatory oversight.

5. Mechanisms of Action of Anti-Arthritic Herbal Agents

Through a variety of specific mechanisms, herbal medications treat the complicated immunoinflammatory characteristics of rheumatoid arthritis (RA). Bioactive phytochemicals produce anti-inflammatory, immunomodulatory, antioxidant, and tissue-protective actions by modulating several pathways, in contrast to conventional medicines that frequently act on specific targets.

5.1 Anti-Inflammatory Effects

Curcumin, boswellic acids, gingerols, and catechins are examples of phytochemicals that reduce prostaglandin and nitric oxide synthesis by inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and downregulating COX-2 and iNOS. These medications reduce synovial hyperplasia and joint swelling by restricting leukocyte infiltration and synovial angiogenesis, which lessens the symptoms of RA (Aggarwal & Harikumar, 2009; Ammon, 2016).

5.2 Immunomodulation

Herbal remedies control immunological reactions without causing widespread immunosuppression. They suppress the formation of B-cell autoantibodies, regulate macrophage polarization, balance Th1/Th17 and Treg cells, and lessen antigen presentation. These actions provide benefits over long-term conventional immunosuppressants by suppressing autoimmune activity while maintaining host defenses (Spelman et al., 2006; Pan et al., 2013).

5.3 Antioxidant Activity

Joint injury and synovial inflammation are caused by oxidative stress. Herbs high in polyphenols, flavonoids, and tannins improve endogenous antioxidant enzymes (glutathione peroxidase, catalase, and superoxide dismutase) and scavenge reactive oxygen and nitrogen species. This slows the progression of the disease by reducing oxidative damage to cartilage and synovial cells (Mateen et al., 2016; Pan et al., 2011).

5.4 Protection of Cartilage and Bone

Herbal substances protect cartilage integrity and lessen bone resorption by inhibiting matrix metalloproteinases (MMPs) and RANKL-induced osteoclastogenesis. They protect structural

joints and may decrease radiographic progression by focusing on both osteoclast activity and cartilage breakdown (Goldring & Gravallese, 2000; Ammon, 2016).

5.5 Modulation of Signaling Pathways

Important intracellular pathways that are essential for cytokine generation and synovial proliferation, such as NF-κB, MAPK (ERK, JNK, p38), and JAK/STAT, are modulated by herbal phytochemicals. While MAPK and JAK/STAT regulation lowers cytokine signaling, NF-κB inhibition stops the production of inflammatory genes. The anti-arthritic effectiveness of herbal remedies has a solid molecular foundation thanks to their multi-pathway activities (Aggarwal et al., 2006; Li et al., 2020).

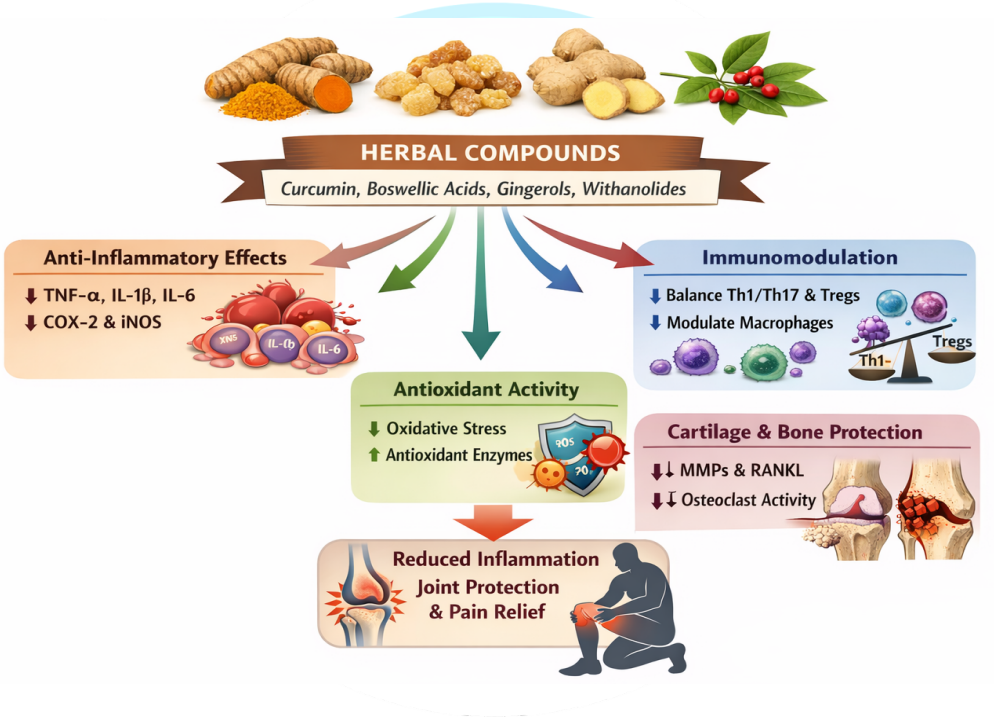

Fig 1: Mechanism of Herbal Agents in RA

6. Preclinical Evidence of Herbal Treatments

Important mechanistic and effectiveness information about herbal remedies for rheumatoid arthritis (RA) is provided by preclinical research. Anti-inflammatory, immunomodulatory, antioxidant, and joint-protective properties have been shown in both in vitro and in vivo models, bridging traditional use and clinical evaluation.

6.1 In Vitro Studies

Excessive proliferation, cytokine production, and resistance to apoptosis are characteristics of RA-derived fibroblast-like synoviocytes, macrophages, and T cells. Curcumin, boswellic acids, and withanolides are examples of herbal compounds that have direct anti-inflammatory and immunomodulatory effects. They also suppress pro-inflammatory cytokines (TNF α, IL 1β, and IL 6), downregulate NF κB, reduce nitric oxide, and inhibit COX-2 and iNOS (Aggarwal & Harikumar, 2009; Ammon, 2016).

6.2 Animal Models

Human RA is replicated in models of collagen-induced and adjuvant-induced arthritis. While maintaining cartilage and bone integrity, herbal extracts lessen paw edema, joint inflammation, cytokine levels, and osteoclast activation. Histopathology and arthritic severity scores are consistently improved by curcumin and boswellic acid (Goldring & Gravallese, 2000; Li et al., 2020).

6.3 Key Outcomes

By blocking matrix metalloproteinases and RANKL-mediated bone degradation, herbal remedies reduce inflammatory indicators, oxidative stress, and discomfort, enhance mobility, and preserve joint integrity (Mateen et al., 2016; Ammon, 2016).

6.4 Translational Relevance

Multi-targeted herbal treatments have favorable safety profiles and are supported by preclinical research as RA adjuncts or alternatives. However, standardized formulations and clinical trials are required to verify efficacy in humans due to heterogeneity in extracts, dosage, and species-specific responses (Li et al., 2020).

7. Clinically Evaluated Medicinal Plants in Rheumatoid Arthritis

Because of their anti-inflammatory, immunomodulatory, and antioxidant qualities, a number of medicinal plants have demonstrated clinical usefulness in treating rheumatoid arthritis. While Withania somnifera relieves pain, edema, and exhaustion (Choudhary et al., 2017), Curcuma longa decreases pain and inflammatory indicators with safety superior to NSAIDs (Chandran & Goel, 2012; Daily et al., 2016). Zingiber officinale reduces pain and inflammation by inhibiting prostaglandins and cytokines (Altman & Marcussen, 2001; Aryaeian et al., 2019),

whereas Boswellia serrata enhances joint function and preserves cartilage (Ammon, 2016; Sengupta et al., 2011). Camellia sinensis has antioxidant and cartilage-protective properties, while Tinospora cordifolia modifies immune cells (Sharma et al., 2012; Singh et al., 2012). Other herbs, such as Nigella sativa and Tripterygium wilfordii, have promise but need more clinical confirmation.

Table 1. Key Medicinal Plants Used in Rheumatoid Arthritis

Medicinal Plant	Active Constituents	Mechanism of Action	Preclinical Evidence	Clinical Evidence
Curcuma longa	Curcuminoids	Anti-inflammatory, antioxidant, NF-κB inhibition	Rodent models: reduced joint inflammation and oxidative stress	RCT: reduced DAS28, CRP, pain scores
Withania somnifera	Withanolides	Immunomodulatory, anti-inflammatory	In vitro: inhibited cytokine production; animal arthritis models	Clinical improvement in joint pain and function
Boswellia serrata	Boswellic acids	Anti-inflammatory via 5-LOX inhibition, cartilage protection	Rat arthritis models: reduced paw edema and bone erosion	Clinical trials: improved pain and physical function
Tinospora cordifolia	Alkaloids, glycosides	Immunomodulatory, antioxidant	Animal models: reduced TNF-α, IL-1β, oxidative stress	Adjunct therapy improved DAS28 and morning stiffness
Zingiber officinale	Gingerols, shogaols	Anti-inflammatory via COX/LOX inhibition	Rodent arthritis: decreased edema, TNF-α	Reduced pain scores in small clinical trials

8. Polyherbal Formulations and Herbal Combinations

A fundamental component of traditional medicine, polyherbal formulations combine several medicinal plants to produce greater therapeutic efficacy through multi-targeted and synergistic activities. This makes them especially effective for complex disorders like rheumatoid arthritis (RA).

8.1 Rationale

Single-target medications frequently fail to fully address the immunological dysregulation, oxidative stress, chronic inflammation, and joint degradation associated with RA. Polyherbal treatments target a variety of molecules, such as tissue-degrading enzymes, immune cells, oxidative processes, and cytokines. Samyoga, or combination therapy, is emphasized in traditional systems such as Ayurveda in order to improve bioavailability, decrease toxicity, and increase efficacy. These combinations have the potential to improve results at lower dosages through pharmacological additive or synergistic effects (Williamson, 2001; Parasuraman et al., 2014).

8.2 Traditional Formulations

For Amavata, Ayurveda uses preparations like Yograj Guggulu, Mahayograj Guggulu, Simhanada Guggulu, and Dashamula combinations that include Boswellia serrata, Commiphora mukul, Withania somnifera, Tinospora cordifolia, and Zingiber officinale. While Unani therapy uses anti-inflammatory herbs to restore humoral balance, TCM uses multi-herb prescriptions such as Du Huo Ji Sheng Tang and Gui Zhi Shao Yao Zhi Mu Tang for Bi syndrome. Systematic clinical validation is still scarce despite conventional use and preclinical evidence (Yuan et al., 2016).

8.3 Synergistic Effects

By boosting anti-inflammatory, immunomodulatory, antioxidant, and cartilage-protective properties, synergism enables polyherbal combinations to have more therapeutic effects than individual herbs. For instance, in experimental arthritis, curcumin combined with boswellic acids enhances joint protection and cytokine suppression. Clinically, polyherbal formulations improve function while reducing inflammatory indicators, discomfort, edema, and morning stiffness. In line with the comprehensive and disease-modifying objectives of RA care, synergistic dosage can help reduce adverse effects (Wagner & Ulrich-Merzenich, 2009).

8.4 Standardization Challenges

Standardization and quality control are major challenges for polyherbal treatments. Inconsistent phytochemical profiles result from differences in plant species, origin, harvesting, and processing. Potential herb-herb and herb-drug interactions—particularly with DMARDs—need to be carefully considered, and many active ingredients confound marker identification and dose optimization. Compared to synthetic medications, regulatory control is frequently laxer, leading to inconsistent quality and results. For safe and successful incorporation into RA therapy, these issues must be resolved through sophisticated analytical techniques, consistent production, and thorough clinical studies (Parasuraman et al., 2014; Ekor, 2014).

Table 2. Polyherbal Formulations in Rheumatoid Arthritis

Formulation Name	Component Herbs	Traditional System	Mechanism	Reported Clinical Outcome
Yograj Guggulu	*Boswellia serrata*, *Commiphora mukul*, *Withania somnifera*	Ayurveda	Anti-inflammatory, immunomodulatory, cartilage-protective	Reduced pain, morning stiffness, improved joint mobility
Mahayograj Guggulu	Multiple herbs including *Guggulu* and *Dashamoola*	Ayurveda	Anti-inflammatory, analgesic	Improved joint pain, physical function
Du Huo Ji Sheng Tang	*Angelica pubescens*, *Taxillus chinensis*, others	TCM	Analgesic, anti-inflammatory, joint-protective	Enhanced joint function and reduced stiffness
Gui Zhi Shao Yao Zhi Mu Tang	Cinnamon twig, peony root, and others	TCM	Anti-inflammatory, analgesic	Reduced pain and improved mobility in RA patients

9. Clinical Evidence and Human Studies

The supplementary use of herbal treatments for rheumatoid arthritis (RA) is supported by clinical trials. Curcumin, Boswellia serrata, ginger, and polyherbal formulations have been shown in RCTs to reduce pain, joint swelling, and inflammatory indicators, frequently with greater tolerance and efficacy equivalent to NSAIDs (Chandran & Goel, 2012; Ammon, 2016; Aryaeian et al., 2019). When paired with traditional DMARDs, observational and comparative studies show higher adherence, decreased analgesic use, and enhanced quality of life (Daily et al., 2016). DAS28, pain scores, and biochemical markers (CRP, ESR), which consistently show improvement, are commonly used to measure efficacy. Herbal therapies are useful supplemental treatments, especially in early-stage RA or for patients who are intolerant to long-term pharmacotherapy, because of their safety and multi-targeted effects, even though they are typically less effective than DMARDs or biologics for structural disease modification (Smolen et al., 2018).

10. Safety, Toxicity, and Herb–Drug Interactions

Due to their natural origin and long history of traditional use, herbal medicines are generally regarded as safe. However, systematic evaluation of their safety, toxicity, and potential interactions is crucial, especially in chronic conditions like rheumatoid arthritis (RA), where polypharmacy and long-term therapy are common.

10.1 Acute and Chronic Toxicity Studies

Many anti-arthritic medicinal plants, such as Curcuma longa, Withania somnifera, Boswellia serrata, and Tinospora cordifolia, appear to have a large margin of safety when used within therapeutic dose ranges, according to preclinical toxicity studies. Studies on acute poisoning in rodents typically show high LD_{00} values without any notable behavioral changes or mortality. Studies on sub-chronic and chronic toxicity have shown negligible effects on hematological, biochemical, and histopathological parameters, indicating their relative safety for extended usage.

However, the extraction techniques, dose, length of exposure, and plant part utilized all have a significant impact on the toxicity results. Compared to conventionally manufactured formulations, concentrated extracts and non-standardized preparations may be riskier.

Consequently, it is important to exercise caution when extrapolating safety data from traditional use to contemporary clinical practice (Teschke et al., 2015).

10.2 Adverse Effects and Contraindications

Herbal treatments are not without side effects, although being generally well accepted. The most commonly reported adverse effects, especially with curcumin and ginger intake, are gastrointestinal problems, such as nausea, diarrhea, and abdominal discomfort. Hepatotoxicity and moderate gastrointestinal problems have been linked to Boswellia serrata.

Certain populations may not be able to use certain herbs. For instance, if taken improperly, immunostimulatory herbs like Tinospora cordifolia may worsen autoimmune activity. Because of its possible thyroid-stimulating properties, Withania somnifera should be taken with caution in people with thyroid conditions. Furthermore, there is still insufficient research on the safety of several herbal remedies during pregnancy and lactation, which calls for cautious use (Ekor, 2014).

10.3 Herb–Drug Interactions with DMARDs and Biologics

Since patients with rheumatoid arthritis sometimes utilize herbal therapy in addition to DMARDs, corticosteroids, or biologics, herb-drug interactions are a crucial factor to take into account. Certain herbal components have the ability to modify drug transporters and cytochrome P450 enzymes, which may change the pharmacokinetics of prescription medications. For instance, curcumin may influence the metabolism of methotrexate by affecting CYP3A4 and P-glycoprotein activity, whereas ginger and green tea may intensify the anticoagulant effects of NSAIDs, raising the risk of bleeding. Although there is currently little clinical data, immunomodulatory herbs may theoretically interfere with biologics that target the TNF-α or IL-6 pathways. Combining herbal and conventional medicines requires close observation and honest communication between patients and medical professionals (Izzo & Ernst, 2009).

10.4 Regulatory Concerns and Quality Control

The clinical integration of herbal medications is still significantly hampered by inadequate regulatory oversight and quality control. Inconsistent phytochemical profiles and therapeutic results are caused by differences in plant identification, growing, harvesting, and production.

There have been reports of adulteration using synthetic medications, pesticides, microbial toxins, and heavy metal contamination, all of which pose serious safety issues. Numerous herbal items are sold as dietary supplements with little need for clinical efficacy or preclinical safety testing. To guarantee the safety, effectiveness, and repeatability of herbal treatments for rheumatoid arthritis, regulatory frameworks must be strengthened, good manufacturing standards (GMP) must be enforced, and modern analytical techniques must be used for standardization (WHO, 2013; Ekor, 2014).

Table 3. Safety, Toxicity, and Herb–Drug Interactions

Herb / Formulation	Reported Adverse Effects	Contraindications	Known Herb–Drug Interactions
Curcuma longa	Mild GI upset, nausea	Gallstones, high doses	May affect CYP3A4 metabolism of DMARDs
Boswellia serrata	Mild nausea	Pregnancy caution	Minimal known interactions with NSAIDs
Withania somnifera	GI discomfort, dizziness	Thyroid disorders	Potential additive effects with immunosuppressants
Tinospora cordifolia	Mild fever, GI upset	Autoimmune flare caution	May alter efficacy of biologics (theoretical)
Polyherbal formulations	Mild GI effects, allergic reactions	Pregnancy, chronic illness	Possible additive or antagonistic effects with DMARDs/NSAIDs

11. Standardization, Quality Control, and Regulatory Aspects

Strong standardization and quality control are necessary to guarantee the safety, effectiveness, and repeatability of herbal treatments for rheumatoid arthritis (RA). Phytochemical composition and therapeutic results can be greatly impacted by variations in plant species, origin, culture, harvesting, and processing. Although frequently employed, marker-based standardization—such as measuring curcuminoids in Curcuma longa or boswellic acids in Boswellia serrata—may not accurately represent the multi-component character of herbal compositions. Botanical authenticity, phytochemical fingerprinting, and contamination testing with methods like HPLC and LC-MS are all part of strict quality control. Many herbal products

are categorized as dietary supplements or traditional medicines, and they frequently lack required clinical efficacy or long-term safety studies. Regulatory control varies throughout the world. To facilitate the evidence-based integration of herbal medicines into the management of RA, harmonized guidelines, enforcement of good manufacturing procedures, and post-marketing surveillance are essential.

12. Limitations and Research Gaps

Herbal treatments for rheumatoid arthritis (RA) are becoming more popular, although there are still a number of obstacles preventing their practical application. Preclinical and clinical research are less comparable due to study heterogeneity, which includes differences in formulations, dosage, and treatment length. The evidence for long-term efficacy and disease change is weakened by the fact that many trials are small, brief, and lack strict randomization or blinding. With the majority of research coming from in vitro or animal models, mechanistic understanding, pharmacokinetics, and bioavailability of herbal ingredients in humans are still poorly understood. Inadequate quality control and standardization also lead to uneven safety profiles and therapeutic results. Furthermore, incorporation into traditional RA care is hampered by a lack of long-term safety evidence, possible herb-drug interactions with DMARDs and biologics, and inconsistent regulations. To establish herbal medicines as evidence-based supplemental therapy for RA, these gaps must be filled by standardized formulations, large-scale trials, pharmacovigilance, and mechanistic research.

13. Future Perspectives

In individuals with rheumatoid arthritis who are refractory to long-term conventional medication, have mild to moderate inflammation, or have early-stage disease, herbal medicine shows potential as a supplemental treatment. Standardized formulations, evidence-based procedures, and cooperative clinical guidelines are necessary for integration into mainstream management in order to improve patient adherence, safety, and efficacy (Smolen et al., 2018; Williamson, 2001). The bioavailability, therapeutic results, and consistency of herbal products are enhanced by developments in phytopharmaceuticals, such as encapsulation, sustained-release formulations, and nanotechnology-based delivery methods (Li et al., 2020; Ichim & Booker, 2021). Multi-target modeling, herb-drug interaction prediction, and logical tailored therapy design are made possible by emerging technologies such omics technologies, systems

pharmacology, and artificial intelligence (Li et al., 2011; Yuan et al., 2016). Herbal treatments can be customized to each patient's unique genetic, immunological, and metabolic profile using biomarker-guided and precision medicine techniques, maximizing effectiveness while reducing side effects and enhancing traditional DMARDs and biologics.

14. Conclusion

Herbal treatments, which target several pathological pathways such as inflammation, oxidative stress, and immunological dysregulation, present a viable supplementary strategy for the treatment of rheumatoid arthritis. The effectiveness of important medicinal plants like Curcuma longa, Withania somnifera, Boswellia serrata, and polyherbal formulations in reducing pain, enhancing joint function, and modifying disease activity is supported by both preclinical and clinical research. Herbal composition diversity, the absence of standardized formulations, the scarcity of large-scale clinical trials, and the possibility of herb-drug interactions continue to be major obstacles. Developments in systems pharmacology, omics technology, artificial intelligence, and phytopharmaceutical research provide new ways to enhance safety, optimize multi-component herbal medicines, and enable customized treatment plans. As long as strict standardization, quality control, and clinical validation are maintained, incorporating evidence-based herbal medicine into mainstream RA management alongside conventional therapies has the potential to improve therapeutic outcomes, lessen side effects, and improve patient quality of life.

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16. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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