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REVIEW ARTICLE

Pathogenesis, diagnosis, treatment, and herbal interventions for rheumatoid arthritis: A review

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder primarily targeting synovial joints, resulting in pain, stiffness, swelling, and progressive joint destruction. The disease is driven by proinflammatory cytokines such as interleukin (IL)-1β and IL-6, which promote synovial inflammation and cartilage degradation. RA affects not only the joints but also other organs, contributing to systemic complications such as cardiovascular disease, anemia, and osteoporosis. Despite the availability of disease-modifying antirheumatic drugs and biologics, their efficacy is often incomplete and frequently accompanied by adverse effects and high costs. This study presents a detailed overview of the etiology, pathogenesis, clinical manifestations, diagnostic strategies, and current treatment modalities of RA, emphasizing herbal medicine as a complementary approach. Botanicals with immunomodulatory and anti-inflammatory properties offer promising adjunctive benefits in RA management. Natural products such as *Curcuma longa*, *Aloe barbadensis*, and *Zingiber officinale* exhibit significant potential to reduce inflammation, modulate cytokine production, and improve patient outcomes. This review highlights the therapeutic promise of integrating herbal remedies with conventional pharmacological therapies, promoting a more holistic, effective, and safer management of RA.

Keywords: Rheumatoid arthritis; Autoimmune disease; Cytokines; Disease-modifying antirheumatic drug; Herbal medicine; Synovial inflammation

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1. Introduction

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune inflammatory disorder that primarily targets synovial joints. It also manifests systemically, affecting organs such as the lungs, heart, and eyes, leading to debilitating outcomes, including chronic pain, stiffness, joint deformities, reduced mobility, and a substantial decline in quality of life. Pathologically, RA involves persistent synovial inflammation driven by autoantibodies, T cell and B cell activation, and proinflammatory cytokines, notably interleukin (IL) 6 and tumor necrosis factor-alpha (TNF-α), resulting in cartilage and bone erosion.[1]

RA affects women 2–3 times more than men, with peak onset between the third and fifth decades of life.[2] Globally, RA is ranked among the leading causes of disability-adjusted life years due to musculoskeletal conditions. According to the Global Burden of Disease Study 2021, approximately 17.6 million people worldwide were living with

RA in 2020, and this number is projected to exceed 31 million by 2050 if current trends persist.[3] In India, recent systematic analyses estimate RA prevalence at 0.5–0.75%, with some urban and northern populations showing rates as high as 1%.[4,5]

Despite advances in therapeutics, including conventional disease-modifying antirheumatic drugs (DMARDs) and biologics, a significant proportion of RA patients continue to experience suboptimal disease control, adverse effects, or economic barriers to sustained treatment access.[6,7] These limitations underscore the growing interest in integrating complementary and alternative therapies, including herbal medicines, which offer immunomodulatory, anti-inflammatory, and antioxidant benefits with comparatively fewer side effects.[8]

Importantly, early diagnosis remains vital, as delayed intervention is associated with irreversible joint damage and systemic complications such as anemia, osteoporosis, cardiovascular disease, and increased mortality. The emergence of biomarkers such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) has enhanced diagnostic accuracy, though challenges persist in early-stage and seronegative cases.[9]

A recent review by Kaur *et al.* also discloses the pathophysiology, diagnosis, and herbal medicine-based therapeutic implications of RA, emphasizing the role of phytoconstituents.[10] In contrast, this manuscript discusses major medicinal plants, rather than only their isolated phytoconstituents, and integrates detailed discussions on RA pathogenesis, diagnostic approaches, conventional pharmacological treatments, and herbal interventions. This broader scope aims to provide a comprehensive, clinically oriented perspective, particularly relevant for settings where whole-plant preparations are more accessible than purified compounds.

The present review not only provides a comprehensive examination of the pathogenesis, clinical features, and current treatment landscape of RA but also critically evaluates the therapeutic potential of herbal interventions as adjunctive or alternative strategies. In doing so, it aims to foster a more holistic and personalized approach to RA management.

2. Risk factors for RA

RA is a multifactorial autoimmune condition with a complex etiology involving genetic predisposition, epigenetic regulation, environmental exposures, socioeconomic and occupational influences, lifestyle behaviors, and nutritional status (Figure 1). Understanding these risk factors is critical for early diagnosis and for developing preventive strategies.

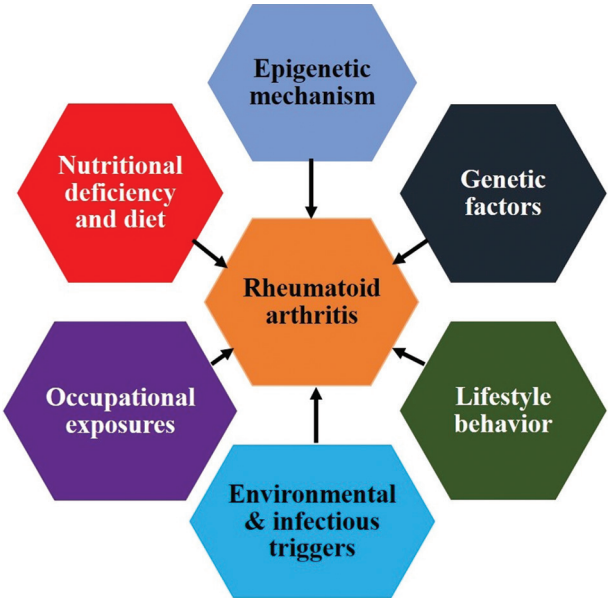

Figure 1. Various risk factors for rheumatoid arthritis

2.1. Genetic factors

Genetics plays a pivotal role in RA susceptibility. Monozygotic twins exhibit concordance rates between 9% and 15%, significantly higher than the 2–4% observed in dizygotic twins, confirming heritability. The *HLA-DRB1* gene within the major histocompatibility complex remains the most influential genetic locus, accounting for up to one-third of the genetic risk. Recent genome-wide association studies have identified over 100 RA-associated loci, with new candidate genes, such as *PTPN22*, *STAT4*, *IRF5*, and *CCR6*, linked to immune dysregulation and disease severity.[11]

2.2. Epigenetic mechanisms

Epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNAs can influence RA development without altering DNA sequences. Environmental exposures such as smoking or poor diet can induce these epigenetic changes, thereby modulating gene expression relevant to RA onset.[12]

2.3. Environmental and infectious triggers

Pathogens, including *Porphyromonas gingivalis*, *Proteus mirabilis*, and *Mycoplasma*, have been linked to autoimmune activation in RA, potentially through mechanisms such as molecular mimicry and bystander activation. Chronic exposure to air pollutants, notably particulate matter (PM2.5), ozone, and nitrogen dioxide, is associated with heightened RA risk, especially in urban environments.[13]

2.4. Socioeconomic status

Lower socioeconomic status correlates with delayed RA diagnosis and poorer disease outcomes. Factors include limited health-care access, higher smoking rates, and poor nutritional habits. High socioeconomic status, conversely, is associated with early disease recognition and better management.[14]

2.5. Occupational exposures

Individuals working in industries with silica dust, organic solvents, or mineral oil exposure show significantly higher RA incidence. The chronic inhalation of silica particles stimulates immune responses via IL and TNF-α pathways, thereby triggering systemic inflammation.[15]

2.6. Lifestyle behaviors

Cigarette smoking remains the strongest modifiable risk factor. It promotes oxidative stress, citrullination, and *HLA-DRB1* shared epitope gene interactions, increasing susceptibility, especially to seropositive RA. Alcohol consumption presents conflicting findings; while excessive intake may exacerbate inflammation, moderate intake has been inversely associated with RA development in some populations.[16]

2.7. Nutritional deficiencies and diet

Vitamin D deficiency is implicated in RA pathogenesis due to its role in immune regulation. Recent trials suggest that long-term Vitamin D supplementation may reduce RA incidence by up to 40%. In addition, adherence to the Mediterranean diet—rich in olive oil, fish, and omega-3 fatty acids—has shown anti-inflammatory effects and protective potential against RA.[17] Conversely, Western diets high in sodium, saturated fats, and red meat are positively associated with systemic inflammation and RA risk.[18]

3. Pathophysiology of RA

RA is characterized by a cascade of aberrant immune events targeting synovial joints and progressing to systemic manifestations. The condition initiates with immune dysregulation involving antigen-presenting cells and T lymphocytes, leading to chronic synovitis and eventual destruction of cartilage and bone.[19]

3.1. Initiation and synovial inflammation

The disease begins when antigen-presenting dendritic cells capture autoantigens in genetically susceptible individuals. These dendritic cells mature and present peptides via major histocompatibility complex class II molecules to naïve $CD4^+$ T cells in lymphoid tissue, driving differentiation into T helper (Th) 1 and Th17 subsets, which secrete proinflammatory cytokines such as interferon-γ, IL-17, and TNF-α. These cytokines recruit additional immune cells, amplify inflammation, and mediate endothelial activation.[20,21]

3.2. Synovial hyperplasia and pannus formation

Activated T cells, along with B cells and macrophages, infiltrate the synovial membrane, triggering fibroblast-like synoviocytes to proliferate and form the pannus, a granulation tissue that invades cartilage and bone. Fibroblast-like synoviocytes secrete matrix metalloproteinases (MMPs) and inflammatory cytokines (IL-6, IL-15, and IL-18), further accelerating cartilage degradation.[22]

3.3. Role of cytokines

Cytokines are pivotal in sustaining chronic inflammation (Table 1). TNF-α and IL-1β drive leukocyte recruitment, osteoclast activation, and systemic effects such as fever and cachexia. IL-6 amplifies B cell differentiation and acute-phase responses, whereas IL-17, secreted by Th17 cells, enhances neutrophil recruitment and angiogenesis within the synovium. These cytokines act synergistically, promoting joint destruction.[23]

3.4. Contributions of immune cells

B cells produce RF and ACPA, initiating immune complex formation and complement activation. They also act as antigen-presenting cells and release pro-osteoclastogenic cytokines like receptor activator of nuclear factor-κB ligand, facilitating bone erosion.[24] Macrophages in the synovium are major producers of TNF-α, IL-1, and IL-6; their density correlates with disease activity.[25] Osteoclasts differentiate under the influence of receptor activator of nuclear factor-κB and TNF-α and are responsible for bone resorption at the cartilage-bone interface.[26]

3.5. Systemic effects and extra-articular manifestations

The systemic release of cytokines contributes to the development of anemia of chronic disease, fatigue,

Table 1. Various cytokines in the pathophysiology of rheumatoid arthritis

Key cytokines	Roles in rheumatoid arthritis
TNF-α	Synovial inflammation, joint destruction
IL-1	Enhances osteoclastogenesis, cartilage damage
IL-6	Acute-phase response, B-cell maturation
IL-17	Neutrophil recruitment, angiogenesis
IL-12/IL-23	Promotes Th1 and Th17 responses

Abbreviations: IL: Interleukin; Th: T helper; TNF: Tumor necrosis factor

osteoporosis, atherosclerosis, and depression. Common extra-articular features include rheumatoid nodules, interstitial lung disease, vasculitis, and pericarditis.[27]

4. Diagnosis of RA

Early and accurate diagnosis of RA is critical to reducing irreversible joint damage, preserving function, and improving long-term outcomes. Diagnostic protocols rely on a multifaceted clinical-laboratory-imaging approach and internationally accepted classification criteria.

4.1. Clinical assessment

Patients often present with symmetrical joint pain, morning stiffness lasting over 30 min, fatigue, fever, and generalized malaise. A high index of suspicion is essential, particularly when patients show polyarticular involvement of small joints like those of the hands and feet. Studies report that early diagnosis and intervention can prevent long-term disability in over 90% of RA patients.[28]

4.2. Laboratory tests

RF and ACPA are critical serological markers. While RF lacks specificity, ACPA has over 95% specificity, making it a key diagnostic biomarker.[29] C-reactive protein (CRP) and erythrocyte sedimentation rate are used to assess systemic inflammation. Elevated levels correlate with disease activity and prognosis.[30]

Recent advances have included novel autoantibodies such as anti-carbamylated protein antibodies, which may offer added sensitivity in seronegative RA cases.[31]

4.3. Imaging techniques

Ultrasound is widely used for both diagnosis and disease monitoring. Power Doppler ultrasound detects active synovitis and neovascularization; grayscale imaging identifies joint effusion and bone erosions. It is cost-effective and non-invasive but operator-dependent.[32]

Magnetic resonance imaging is highly sensitive in early RA and can detect synovial hypertrophy, bone marrow edema, and early erosions before they appear on X-ray. However, limitations include high cost and limited availability.[33] X-rays remain a standard tool for documenting joint space narrowing, periarticular osteopenia, and bony erosions, but lack sensitivity in early disease.[34]

4.4. The 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria

The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria[35] provide a scoring system out of 10 based on joint involvement (up to five points), serology (RF and ACPA; up to three points), acute-phase reactants (CRP and erythrocyte sedimentation rate; one point), and symptom duration ≥6 weeks (1 point).

A score of more than six is required for RA classification, provided other differential diagnoses such as lupus, psoriatic arthritis, and infection are ruled out.

4.5. Recent diagnostic enhancements

Artificial intelligence-driven algorithms are emerging to automate joint scoring in radiographic and ultrasound imaging.[36] Biomarker panels using multiplex platforms now aim to improve sensitivity in early or seronegative RA cases.[37]

5. Treatment of RA

The therapeutic goal in RA is to induce remission or, at a minimum, achieve low disease activity within the first 6 months of diagnosis to prevent irreversible joint deformity, disability, and systemic complications. Studies have shown that 80% of inadequately treated patients develop joint deformities, and 40% become disabled within 10 years.

Historically, RA management followed a step-wise approach: Starting with non-steroidal anti-inflammatory drugs (NSAIDs) and escalating to DMARDs as the disease progressed. This delayed strategy resulted in poor long-term outcomes.[38] The current Treat-to-Target paradigm, endorsed by the American College of Rheumatology and the European League Against Rheumatism, emphasizes early initiation of DMARDs and regular monitoring to adjust therapy promptly.[39]

5.1. Pharmacological treatments

5.1.1. NSAIDs

NSAIDs provide symptomatic relief from pain and stiffness but do not prevent joint damage. Common agents include ibuprofen, naproxen, diclofenac, and celecoxib. Cyclooxygenase (COX)-2 inhibitors (e.g., celecoxib) offer reduced gastrointestinal toxicity. NSAIDs are best used for initial symptom control while awaiting the effect of slower-acting DMARDs.[40]

5.1.2. Glucocorticoids

Glucocorticoids such as prednisone are effective for short-term symptom control and bridging therapy. However, long-term use is associated with osteoporosis, diabetes, and hypertension. Tapering is recommended as DMARDs take effect.[41]

5.1.3. Conventional synthetic DMARDs

Methotrexate is the first-line anchor drug. It inhibits dihydrofolate reductase, limiting lymphocyte proliferation. Folic acid coadministration reduces adverse effects. Methotrexate monotherapy is effective for most early RA cases.[42] Hydroxychloroquine, an antimalarial agent, modulates antigen presentation and inhibits monocyte cytokine secretion, reducing Th17-related cytokines.[43] In addition, sulfasalazine interferes with cytokine production (IL-8, monocyte chemoattractant protein), though mechanisms remain unclear. They are often combined with methotrexate in dual or triple therapy.[44] Leflunomide inhibits pyrimidine synthesis, suppressing T cell proliferation. However, it can be hepatotoxic and teratogenic.[45] Combination conventional synthetic DMARD therapy is more effective than monotherapy for moderate-to-severe RA.

5.1.4. Biological DMARDs

Biologics target specific immune pathways and are reserved for moderate-to-severe RA unresponsive to conventional synthetic DMARDs. TNF-α inhibitors (e.g., infliximab, adalimumab, and etanercept) block inflammation mediators and slow radiographic progression.[46] IL-6 inhibitors (e.g., tocilizumab) inhibit IL-6 signaling, reducing joint damage and systemic symptoms.[47] B cell depletion agents (e.g., rituximab) target $CD20^+$ B cells to reduce autoantibody production,[48] whereas T cell co-stimulation blockers (e.g., abatacept) inhibit CD28-CD80/86 signaling to prevent T cell activation.[49]

Recent biologics, although effective, are expensive and associated with immunosuppression risks, including tuberculosis and reactivation of latent infections.

5.1.5. Targeted synthetic DMARDs

Targeted synthetic DMARDs include Janus kinase inhibitors, such as tofacitinib and baricitinib, which block intracellular cytokine signaling. They offer oral convenience but may increase the risk of herpes zoster and thromboembolic events.[50]

5.2. Non-pharmacological approaches

A comprehensive RA management plan includes physical therapy to maintain joint mobility, occupational therapy for assistive device training, patient education to promote adherence, and dietary interventions, such as omega-3 fatty acids, for anti-inflammatory benefits.[51] Exercise and lifestyle modification significantly reduce fatigue and improve physical function.

6. Role of herbal and plant-based therapies in the management of RA

The limitations of conventional therapies such as NSAIDs and DMARDs—including partial symptom relief, long-term toxicity, and economic burden—have catalyzed global interest in complementary and alternative medicine. Among these, herbal plants (Table 2) offer anti-inflammatory, antioxidant, and immunomodulatory effects, making them promising candidates for adjunctive RA management.

6.1. *Curcuma longa* (Turmeric)

Curcumin, the active polyphenol in turmeric, has demonstrated potent inhibition of nuclear factor kappa B (NF-Kb) activation, suppression of COX-2 expression, and decreased production of prostaglandin E2 and IL-6, all key mediators in RA pathogenesis. In a collagen-induced arthritis (CIA) rat model, curcumin reduced arthritic scores in a dose-dependent manner, with the 110 mg/kg group showing the greatest anti-inflammatory benefit.[52]

6.2. *Aloe barbadensis* (Aloe vera)

Aloe demonstrates immunosuppressive, anti-inflammatory, and regenerative properties. It modulates mast cell activity, reduces TNF-α, and enhances fibroblast-mediated tissue repair. In animal studies, aloe extract led to a 50% reduction in synovial pouch vascularity, suggesting its potential in mitigating synovial inflammation.[53]

6.3. *Zingiber officinale* (Ginger)

Ginger contains gingerols and shogaols, which inhibit both prostaglandin and leukotriene biosynthesis. Diarylheptanoids in ginger have been shown to suppress 5-lipoxygenase, reducing inflammatory mediator production. Clinical trials have demonstrated its capacity to relieve joint pain and decrease markers of systemic inflammation.[54]

6.4. *Ginkgo biloba*

Ginkgo exerts its anti-RA effects through inhibition of mitogen-activated protein kinase/c-Jun N-terminal kinase and Wnt5a pathways, promoting apoptosis of synovial fibroblasts and reducing levels of MMP-3, IL-1β, IL-6, and TNF-α. This confirmed its efficacy in CIA mouse models by demonstrating reduced joint swelling and improved cartilage integrity.[55]

6.5. *Camellia sinensis* (Green tea)

Epigallocatechin-3-gallate, the active flavonoid in green tea, blocks NF-κB and TNF-α signaling pathways. It

Table 2. Herbal and plant-based therapies for rheumatoid arthritis

Plant name	Active components	Mechanism of action	Observed effects	References
Curcuma longa (Turmeric)	Curcumin	Inhibits NF-κB, COX-2, IL-6, and prostaglandin 2	Reduced arthritis score and inflammation in the CIA model	51
Aloe barbadensis (Aloe vera)	Polysaccharides, glycoproteins	Decreases TNF-α, modulates mast cells, and enhances repair	A 50% reduction in synovial vascularity in animal models	52
Zingiber officinale (Ginger)	Gingerols, shogaols	Inhibits prostaglandin and leukotriene biosynthesis	Reduced joint pain and inflammatory markers	53
Ginkgo biloba	Ginkgolides, flavonoids	Inhibits mitogen-activated protein kinase/c-Jun N-terminal kinase, Wnt5a; reduces IL-6, MMP-3	Decreased synovitis and improved cartilage	54
Camellia sinensis (Green tea)	Epigallocatechin-3-gallate	Inhibits NF-κB, TNF-α; antioxidant	Reduced leukocyte infiltration in joints	55
Crocus sativus (Saffron)	Crocin	Suppresses TNF-α, IL-1β	Decreased joint swelling and hyperplasia	56
Cannabis sativa	Cannabidiol, tetrahydrocannabinol	Cannabinoid receptor 2 agonist; reduces immune activation	Anti-inflammatory and analgesic effects	57
Arnica montana	Helenalin	Inhibits nitric oxide, TNF-α, and IL-6	Reduced oxidative stress and inflammation	58
Jatropha gossypifolia	Flavonoids	Inhibits lipid peroxidation and reactive oxygen species	Reduced paw edema in animal models	59
Nigella sativa (Black seed)	Thymoquinone	Inhibits IL-6 and TNF-α	A 45% reduction in arthritic score	60
Withania somnifera (Ashwagandha)	Withanolides	Modulates TNF-α, IL-1β; boosts regulatory T cells	A 36% reduction in paw swelling	61
Boswellia serrata	Boswellic acids	Inhibits 5-lipoxygenase, Th17 activity	A>30% reduction in joint stiffness	62
Perilla frutescens (Shiso)	Rosmarinic acid	Inhibits NF-κB, reduces IL-6, IL-1β	Improved cartilage, reduced inflammation	63
Tribulus terrestris	Saponins, Protodioscin	Inhibits COX and lipoxygenase enzymes	Reduced edema and histopathology score	64
Tinospora cordifolia (Guduchi)	Tinosporide, berberine-like alkaloids	Modulates Th1/Th2, reduces TNF-α	Lower arthritis score and oxidative stress	65
Sigesbeckia orientalis	Darutoside	Reduces MMP-9, angiogenesis, and immune infiltration	Reduced joint damage and stiffness	66
Uncaria tomentosa (Cat's Claw)	Oxindole alkaloids	Inhibits TNF-α, MMP-9; antioxidant	Reduced fatigue, improved pain scores	67

Abbreviations: COX: Cyclooxygenase; IL: Interleukin; MMP: Matrix metalloproteinase; NF-κB: Nuclear factor kappa B; Th: T helper cells; TNF: Tumor necrosis factor.

reduces leukocyte recruitment to inflamed joints and has shown positive outcomes in both *in vivo* and *in vitro* arthritic models.[56]

6.6. *Crocus sativus* (Saffron)

Crocin, a carotenoid in saffron, significantly reduces serum TNF-α and IL-1 levels. Recent pre-clinical evidence indicates its efficacy in reducing ankle joint swelling and synovial hyperplasia, particularly in combination with methotrexate.[57]

6.7. *Cannabis sativa*

Phytocannabinoids such as cannabidiol and tetrahydrocannabinol exhibit anti-inflammatory and analgesic activity through CB2 receptor agonism, reducing immune cell activation and pain perception. A recent scoping review emphasized its potential for symptom control, though regulatory and psychotropic concerns remain.[58]

6.8. *Arnica montana*

Arnica's helenalin component exhibits anti-inflammatory activity by inhibiting nitric oxide synthesis, TNF-α, and IL-6. It has shown efficacy in CIA models by reducing oxidative stress and joint inflammation.[59]

6.9. *Jatropha gossypifolia*

The latex of this plant, rich in flavonoids, has been found to reduce paw edema and joint inflammation in carrageenan

and Freund's adjuvant-induced arthritis models, possibly via modulation of lipid peroxidation and reactive oxygen species.[60]

6.10. *Nigella sativa* (Black seed)

A review highlighted *N. sativa* as a potent herb due to its thymoquinone content, which reduces synovial inflammation by inhibiting IL-6 and TNF-α pathways. Its immunoregulatory effects were evident in pre-clinical models of RA, where black seed oil decreased arthritic score and joint stiffness by 45%.[61]

6.11. *Withania somnifera* (Ashwagandha)

Recent findings affirm ashwagandha's role as a TNF-α and IL-1β modulator, with adaptogenic effects that reduce systemic inflammation. A 2024 study reported a 36% reduction in paw swelling in CIA rats, with enhanced T-regulatory cell activity.[62]

6.12. *Boswellia serrata* (Indian frankincense)

Boswellic acids inhibit 5-lipoxygenase and modulate Th17 cell proliferation. A 2024 randomized controlled trial showed that *Boswellia* supplementation reduced joint stiffness and morning pain in RA patients by over 30% within 6 weeks.[63]

6.13. *Perilla frutescens* (Shiso)

P. frutescens, commonly known as shiso, is a medicinal herb native to East Asia and widely used in Korean and Japanese traditional medicine. Its leaves are rich in rosmarinic acid, a phenolic compound with strong anti-inflammatory activity. Studies have shown that *Perilla* extract can downregulate TNF-α, IL-6, and IL-1β by inhibiting the NF-κB signaling pathway, leading to reduced synovial inflammation in collagen-induced arthritic animal models. Its dual antioxidant and immunomodulatory action supports cartilage preservation and alleviation of joint stiffness.[64]

6.14. *Tribulus terrestris*

T. terrestris, a traditional Ayurvedic herb, is rich in saponins and protodioscin, which have shown potent anti-arthritic effects in experimental models. It exerts its effects by downregulating COX and lipoxygenase enzymes, thereby reducing leukocyte infiltration and oxidative damage in joint tissues. Animal studies have documented improvements in joint swelling, paw edema, and histopathological scores following treatment, suggesting its potential as a cost-effective, adjunct therapy for RA.[65]

6.15. *Tinospora cordifolia* (Guduchi)

Guduchi, or *T. cordifolia*, is one of the most studied Ayurvedic immunomodulators. Its active constituents, such as tinosporide and berberine-like alkaloids, have been shown to modulate Th1/Th2 balance, reduce TNF-α and IL-6, and enhance macrophage phagocytic activity. In adjuvant-induced arthritis models, guduchi reduced paw thickness, arthritis scores, and oxidative stress markers. Its safety and adaptogenic properties make it a popular supplement in integrative RA care in India.[66]

6.16. *Sigesbeckia orientalis*

Used in traditional Chinese medicine to "dispel wind-dampness," *S. orientalis* has recently attracted scientific attention for its antirheumatic properties. Darutoside, its main active compound, reduces synovial inflammation, angiogenesis, and immune cell infiltration. Animal studies confirmed significant reductions in joint stiffness, MMP-9 activity, and bone erosion, positioning it as a botanical with both anti-inflammatory and chondroprotective benefits.[67]

6.17. *Uncaria tomentosa* (Cat's claw)

Native to South America, *U. tomentosa* has long been used for inflammatory conditions. It contains oxindole alkaloids, which inhibit TNF-α, MMP-9, and suppress leukocyte migration. Clinical studies in RA patients report improved pain scores and reduced fatigue. It also has antioxidant effects, aiding in the reduction of reactive oxygen species and nitric oxide levels in joint tissues.[68,69]

7. Conclusion

RA remains a complex autoimmune disorder requiring multifaceted therapeutic strategies encompassing early diagnosis, immunological understanding, and tailored interventions. While conventional treatments such as DMARDs, biologics, and Janus kinase inhibitors have significantly advanced disease control, they remain limited due to high costs, side effects, and incomplete remission in many patients. Recent integrative approaches, particularly the exploration of herbal and plant-based therapies, have revealed promising anti-inflammatory, immunomodulatory, and chondroprotective effects from compounds such as curcumin, gingerols, thymoquinone, Boswellic acids, epigallocatechin-3-gallate, and cannabidiol, among others. Emerging botanicals—such as *P. frutescens*, *T. cordifolia*, *S. orientalis*, and *Centella asiatica*—modulate novel molecular targets, including NF-κB, COX/lipoxygenase, mitogen-activated protein kinases, and cytokine signaling, suggesting a potential paradigm shift toward adjunctive phytomedicine. Future perspectives call for well-powered, randomized clinical trials, herbal formulation standardization, biomarker-guided therapy selection, and regulatory integration to ensure efficacy and safety. Combining evidence-based phytotherapy with conventional regimens may usher in

a more holistic, personalized, and sustainable model for RA management, especially in resource-limited settings and for patients with multidrug intolerance or incomplete response.

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Conflict of interest

The authors declare that they have no competing interests.

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References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023-2038.

   doi: 10.1016/S0140-6736(16)30173-8

2. Tanaka, Y. A review of upadacitinib in rheumatoid arthritis. *Mod Rheumatol*. 2020;30(5):779-787.

   doi: 10.1080/14397595.2020.1782049

3. Black RJ, Cross M, Haile LM, *et al*. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: A systematic analysis of the global burden of disease study 2021. *Lancet Rheumatol*. 2023;5(10):e594-e610.

   doi: 10.1016/S2665-9913(23)00211-4

4. Radu AF, Bungau SG. Management of rheumatoid arthritis: An overview. *Cells*. 2021;10(11):2857.

   doi: 10.3390/cells10112857

5. Garg R, Garg A. The research trends and scientometric assessment of rheumatoid arthritis in India during 2016-2021. *Curr Rheumatol Rev*. 2023;19(1):26-35.

   doi: 10.2174/1573397118666220804162313

6. Putrik P, Ramiro S, Kvien TK, *et al*. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis*. 2014;73(1):198-206.

   doi: 10.1136/annrheumdis-2012-202603

7. Smolen JS, Landewé RBM, Bergstra SA, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis*. 2023;82(1):3-18.

   doi: 10.1136/ard-2022-223356corr1

8. Ashiq K, Ashiq S, Mobashar A, *et al*. An updated review on rheumatoid arthritis (RA): Epidemiology, pathophysiology, diagnosis, and the current approaches for its treatment. *Sudan J Med Sci*. 2023;18:539-551.

   doi: 10.18502/sjms.v18i4.14742

9. Singh JA, Saag KG, Bridges SL, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.

   doi: 10.1002/art.39480

10. Kaur C, Mishra Y, Kumar R, *et al*. Pathophysiology, diagnosis, and herbal medicine-based therapeutic implication of rheumatoid arthritis: An overview. *Inflammopharmacology*. 2024;32(3):1705-1720.

    doi: 10.1007/s10787-024-01445-8

11. Kurkó J, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis - a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45:170-179.

    doi: 10.1007/s12016-012-8346-7

12. Danieli MG, Casciaro M, Paladini A, *et al*. Exposome: Epigenetics and autoimmune diseases. *Autoimmun Rev*. 2024;23:103584.

    doi: 10.1016/j.autrev.2024.103584

13. Venetsanopoulou AI, Alamanos Y, Voulgari PV, Drosos AA. Epidemiology and risk factors for rheumatoid arthritis development. *Mediterr J Rheumato*l. 2023;34(4):404-413.

    doi: 10.31138/mjr.301223.eaf

14. Molina E, Del Rincon I, Restrepo JF, Battafarano DF, Escalante A. Association of socioeconomic status with treatment delays, disease activity, joint damage, and disability in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2015;67(7):940-946.

    doi: 10.1002/acr.22542

15. Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. *Int Immunopharmacol*. 2002;2(2-3):303-313.

doi: 10.1016/s1567-5769(01)00181-3

16. Novella-Navarro M, Plasencia-Rodríguez C, Nuño L, Balsa A. Risk factors for developing rheumatoid arthritis in patients with undifferentiated arthritis and inflammatory arthralgia. *Front Med (Lausanne)*. 2021;8:668898.

doi: 10.3389/fmed.2021.668898

17. Heidari B, Hajian-Tilaki K, Babaei M. Vitamin D deficiency and rheumatoid arthritis: Epidemiological, immunological, clinical and therapeutic aspects. *Mediterr J Rheumatol*. 2019;30(2):94-102.

doi: 10.31138/mjr.30.2.94

18. Philippou E, Nikiphorou E. Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. *Autoimmun Rev*. 2018;17(11):1074-1077.

doi: 10.1016/j.autrev.2018.05.009

19. Khan S, Mohan K, Muzammil S, Alam MA, Khayyam KU. Current prospects in rheumatoid arthritis: Pathophysiology, genetics, and treatments. *Recent Adv Antiinfect Drug Discov*. 2024;19(1):36-55.

doi: 10.2174/2772434418666230406083149

20. Sweeney SE, Firestein GS. Rheumatoid arthritis: Regulation of synovial inflammation. *Int J Biochem Cell Biol*. 2004;36(3):372-378.

doi: 10.1016/s1357-2725(03)00259-0

21. Wehr P, Purvis H, Law SC, Thomas R. Dendritic cells, T cells and their interaction in rheumatoid arthritis. *Clin Exp Immunol*. 2019;196(1):12-27.

doi: 10.1111/cei.13256

22. Makkar R, Sehgal A, Singh S, *et al*. Current trends in epigenetic, cellular and molecular pathways in management of rheumatoid arthritis. *Inflammopharmacology*. 2023;31(4):1577-1588.

doi: 10.1007/s10787-023-01262-5

23. Koper-Lenkiewicz OM, Sutkowska K, Wawrusiewicz-Kurylonek N, Kowalewska E, Matowicka-Karna J. Proinflammatory cytokines (IL-1, -6, -8, -15, -17, -18, -23, TNF-α) single nucleotide polymorphisms in rheumatoid arthritis-a literature review. *Int J Mol Sci*. 2022;23(4):2106.

doi: 10.3390/ijms23042106

24. Mishra AP, Kumar R, Harilal S, Nigam M, Datta D, Singh S. Emerging landscape of *in vitro* models for assessing rheumatoid arthritis management. *ACS Pharmacol Transl Sci*. 2024;7(8):2280-2305.

doi: 10.1021/acsptsci.4c00260

25. Wu D, Huang Y, Zhao J, *et al*. Synovial macrophages drive severe joint destruction in established rheumatoid arthritis. *Sci Rep*. 2025;15(1):12111.

doi: 10.1038/s41598-025-93784-x

26. Takeshita A, Nishida K, Yoshida A, *et al*. RANKL expression in chondrocytes and its promotion by lymphotoxin-α in the course of cartilage destruction during rheumatoid arthritis. *PLoS One*. 2021;16(7):e0254268.

doi: 10.1371/journal.pone.0254268

27. Bonfiglioli KR, de Medeiros Ribeiro AC, Carnieletto AP, *et al*. Extra-articular manifestations of rheumatoid arthritis remain a major challenge: Data from a large, multi-centric cohort. *Adv Rheumatol*. 2023;63:34.

doi: 10.1186/s42358-023-00318-y

28. Trivedi J. Clinical presentation and diagnosis of rheumatoid arthritis. *Ann Clin Med Case Rep*. 2024;13(18):1-7.

29. Iyengar KP, Vaish A, Nune A. Anti-cyclic citrullinated peptide antibody (ACPA) and rheumatoid arthritis: Clinical relevance. *J Clin Orthop Trauma*. 2022;24:101729.

doi: 10.1016/j.jcot.2021.101729

30. Alharthi AH, Al-Shehri SHA, Albarqi MAA, *et al*. Laboratory markers of inflammation: CRP and ESR in clinical practice. *J Int Crisis Risk Commun Res*. 2024;7(S8):2376.

doi: 10.63278/jicrcr.vi.1233

31. Van Delft MA, Verheul MK, Burgers LE, *et al*. The anti-CarP antibody response is of overall low avidity despite extensive isotype switching. *Ann Rheum Dis*. 2020;79(1):63.

32. Cho MJ, Chai JW, Kim DH, Kim HJ, Seo J. Ultrasonographic differential diagnosis of medial elbow pain. *Ultrasonography*. 2024;43(5):299-213.

doi: 10.14366/usg.24102

33. Weaver JS, Omar I, Mar W, Kauser AS, Mlady GW, Taljanovic M. Magnetic resonance imaging of rheumatological diseases. *Pol J Radiol*. 2022;87(1):93-112.

doi: 10.5114/pjr.2022.113390

34. Sambri A, Spinnato P, Tedeschi S, *et al*. Bone and joint infections: The role of imaging in tailoring diagnosis to improve patients' care. *J Pers Med*. 2021;11(12):1317.

doi: 10.3390/jpm11121317

35. De Stefano L, Cassione EB, Sakellariou G, *et al*. Tender joints in early autoantibody-negative rheumatoid arthritis: Should they be included in the scoring of joint involvement of the 2010 ACR/EULAR classification criteria? *Semin Arthritis Rheum*. 2025;55:152637.

doi: 10.1016/j.semarthrit.2025.152637

36. Bird A, Oakden-Rayner L, McMaster C, *et al*. Artificial intelligence and the future of radiographic scoring in rheumatoid arthritis: A viewpoint. *Arthritis Res Ther*. 2022;24(1):268.

doi: 10.1186/s13075-022-02972-x

37. Perera J, Delrosso CA, Nerviani A, Pitzalis C. Clinical phenotypes, serological biomarkers, and synovial features defining seropositive and seronegative rheumatoid arthritis: A literature review. *Cells*. 2024;13(9):743.

doi: 10.3390/cells13090743

38. Gupta R, Sharma R. Advancement in the management of rheumatoid arthritis. *RPS Pharmacol Rep.* 2023;2(1):rqad005.

doi: 10.1093/rpsppr/rqad005

39. Vlad AL, Popazu C, Lescai AM, Voinescu DC, Baltă AAȘ. Where do we stand in the management of rheumatoid arthritis ahead of EULAR/ACR 2025? *Clin Pract*. 2025;15(6):103.

doi: 10.3390/clinpract15060103

40. Lin Y, Chen Y, Deng R, *et al*. Delivery of neutrophil membrane encapsulated non-steroidal anti-inflammatory drugs by degradable biopolymer microneedle patch for rheumatoid arthritis therapy. *Nano Today*. 2023;49:101791.

doi: 10.1016/j.nantod.2023.101791

41. Krause D, Mai A, Klaassen-Mielke R, *et al*. The efficacy of short-term bridging strategies with high- and low-dose prednisolone on radiographic and clinical outcomes in active early rheumatoid arthritis: A double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol*. 2022;74(10):1628-1637.

doi: 10.1002/art.42245

42. Sherbini AA. *Investigating Methotrexate Associated Adverse Events in Patients with Rheumatoid Arthritis [dissertation]*. Manchester: Univ Manchester; 2023. Available from: https://www.proquest.com/openview/c9b2ccfabc0d5c80e9cb918769f5f359/1?pq-origsite=gscholar&cbl=2026366&diss=y [Last accessed on 2025 Sep 05].

43. Krueger J, Santinon F, Kazanova A, *et al*. Hydroxychloroquine (HCQ) decreases the benefit of anti-PD-1 immune checkpoint blockade in tumor immunotherapy. *PLoS One*. 2021;16(6):e0251731.

doi: 10.1371/journal.pone.0251731

44. Shams S, Martinez JM, Dawson JR, *et al*. The therapeutic landscape of rheumatoid arthritis: Current state and future directions. *Front Pharmacol*. 2021;12:680043.

doi: 10.3389/fphar.2021.680043

45. Pulungan Y, Saputra AK, Purnamasari D, Wijayanti N, Sari LR. Conventional synthetic disease-modifying antirheumatic drugs (csDMARD) in rheumatoid arthritis during pregnancy and lactation: A review. *Indones J Pharmacol Ther*. 2022;3(1):1-7.

doi: 10.22146/ijpther.3297

46. Dar E, Abbas M, Nazir S, Abbas M. Novel management, cure and complications-control of rheumatoid arthritis with traditional and modern remedies: A review. *Pharm Chem J*. 2024;58(1):1-9.

doi: 10.1007/s11094-024-03238-3

47. Taylor PC, Feist E, Pope JE, *et al*. What have we learnt from the inhibition of IL-6 in RA and what are the clinical opportunities for patient outcomes? *Ther Adv Musculoskelet Dis*. 2024;16:1-19.

doi: 10.1177/1759720X241283340

48. Alghazali T, Saleh RO, Uthirapathy S, *et al*. Rheumatoid arthritis unmasked: The power of B cell depletion therapy. *Mol Biol Rep.* 2025;52(1):254.

doi: 10.1007/s11033-025-10366-w

49. Meng Q, Liu H, Liu J, Pang Y, Liu Q. Advances in immunotherapy modalities for atherosclerosis. *Front Pharmacol*. 2023;13:1079185.

doi: 10.3389/fphar.2022.1079185

50. Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: A mechanisms-based approach. *Nat Rev Rheumatol*. 2022;18(3):133-145.

doi: 10.1038/s41584-021-00726-8

51. Franchinotti R, Moler M, Paulenas E, Saura JP, Andreu MF. Non-pharmacological interventions for feeding disorders in pediatrics: A scoping review. *Occup Ther Health Care*. 2024;38(1):1-35.

doi: 10.1080/07380577.2024.2401732

52. Makuch S, Więcek K, Woźniak M. The immunomodulatory and anti-inflammatory effect of curcumin on immune cell populations, cytokines, and *in vivo* models of rheumatoid arthritis. *Pharmaceuticals (Basel)*. 2021;14(4):309.

doi: 10.3390/ph14040309

53. Rahman T, Jahan R, Chowdhury AR, Rahmatullah M. Potential therapeutic benefits of *Aloe barbadensis* in treatment of rheumatoid arthritis. *J Autoimmune Dis Rheumatol*. 2014;2(1):35-44.

doi: 10.12970/2310-9874.2014.02.01.6

54. Maryam H, Azhar S, Akhtar MN, *et al*. Role of bioactive components of ginger in management of osteoarthritis: A review. *Int J Food Prop.* 2023;26(1):1903-1913.

doi: 10.1080/10942912.2023.2236811

55. Xie C, Jiang J, Liu J, Yuan G, Zhao Z. Ginkgolide B attenuates collagen-induced rheumatoid arthritis and regulates fibroblast-like synoviocytes-mediated apoptosis and inflammation. *Ann Transl Med*. 2020;8(22):1497.

doi: 10.21037/atm-20-6420

56. Mokra, D, Joskova, M, Mokry, J. Therapeutic effects of green tea polyphenol (−)-Epigallocatechin-3-gallate (EGCG) in

relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. *Int J Mol Sci*. 2022;24(1):340.

doi: 10.3390/ijms24010340

57. Chrastina, M, Dráfi, F, Pružinská, K, *et al*. *Crocus sativus* L. extract (saffron) effectively reduces arthritic and inflammatory parameters in monotherapy and in combination with methotrexate in adjuvant arthritis. *Nutrients*. 2023;15(19):4108.

doi: 10.3390/nu15194108

58. Da Nóbrega Marinho AM, da Silva Neto RWG. Anti-inflammatory effects of cannabinoids. *BrJP.* 2023;6:31-37.

doi: 10.5935/2595-0118.20230010-en

59. Sharma S, Arif M, Nirala RK, Gupta R, Thakur SC. Cumulative therapeutic effects of phytochemicals in *Arnica montana* flower extract alleviated collagen-induced arthritis: Inhibition of both pro-inflammatory mediators and oxidative stress. *J Sci Food Agric*. 2016;96(5):1500-1510.

doi: 10.1002/jsfa.7252

60. Ahmed AS, Chopde CT, Kashmiri ZN. Assessment of anti-inflammatory and anti-arthritis activity of *Jatropha gossypifolia* in rats. *Int J Pharm Pharm Sci.* 2015;7(1):258-260.

61. Wahab S, Alsayari A. Potential pharmacological applications of *Nigella* seeds with a focus on *Nigella sativa* and its constituents against chronic inflammatory diseases: Progress and future opportunities. *Plants (Basel)*. 2023;12(22):3829.

doi: 10.3390/plants12223829

62. Haque MT, Rahman, N, Faruk MO, *et al*. Potential of analgesic and anti-inflammatory activity of *Withania somnifera* Linn. leaves. *Asian J Res Med Pharm Sci*. 2025;14(3):117-125.

doi: 10.9734/ajrimps/2025/v14i3324

63. Ansari P, Reberio AD, Ansari NJ, *et al*. Therapeutic potential of medicinal plants and their phytoconstituents in diabetes, cancer, infections, cardiovascular diseases, inflammation and gastrointestinal disorders. *Biomedicines*. 2025;13(2):454.

doi: 10.3390/biomedicines13020454

64. Kim N, Kim SY, Kim SW, *et al*. Efficacy of *Perilla frutescens* (L.) Britton var. frutescens extract on mild knee joint pain: A randomized controlled trial. *Front Pharmacol.* 2023;14:1114410.

doi: 10.3389/fphar.2023.1114410

65. Park YJ, Cho YR, Oh JS, Ahn EK. Effects of *Tribulus terrestris* on monosodium iodoacetate-induced osteoarthritis pain in rats. *Mol Med Rep.* 2017;16(4):5303-5311.

doi: 10.3892/mmr.2017.7296

66. Prasad S, Kulshreshtha A, Lall R, Gupta SC. Inflammation and ROS in arthritis: Management by Ayurvedic medicinal plants. *Food Funct*. 2021;12(18):8227-8247.

doi: 10.1039/D1FO01078F

67. Linghu KG, Xiong SH, Zhao GD, *et al*. *Sigesbeckia orientalis* L. extract alleviated the collagen type II-induced arthritis through inhibiting multi-target-mediated synovial hyperplasia and inflammation. *Front Pharmacol*. 2020;11:547913.

doi: 10.3389/fphar.2020.547913

68. Arado GM, Amatto PPG, Marins, M, *et al*. Anti-inflammatory and/or immunomodulatory activities of *Uncaria tomentosa* (cat's claw) extracts: A systematic review and meta-analysis of *in vivo* studies. *Front Pharmacol*. 2024;15:1378408.

doi: 10.3389/fphar.2024.1378408

69. Coelho LJ, do Nascimento GNL. Anti-inflammatory and diuretic activity of *Uncaria tomentosa* (cat's claw): Systematic review. *Rev Cereus*. 2020;12(2):119-129.

doi: 10.18605/2175-7275/cereus.v12n2p119-129