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Review Article

Screening Of In Vivo Antirheumatic Potential of Eclipta Alba in Rheumatoid Arthritis Rodent Model

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ABSTRACT

Rheumatoid arthritis is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, progressive cartilage destruction, and irreversible joint deformities. Despite significant advancements in pharmacotherapy, long-term management remains challenging due to the limitations associated with conventional drugs, such as toxicity, reduced efficacy over time, and immunosuppression. This growing therapeutic gap has reinforced the need for safer, plant-based alternatives capable of modulating inflammatory pathways and preventing structural joint damage. Eclipta alba (L.) Hassk., a widely utilized medicinal plant in Ayurveda, has shown promising anti-inflammatory, immunomodulatory, antioxidant, and chondroprotective properties. This review provides a detailed evaluation of the antirheumatic potential of Eclipta alba using in vivo rheumatoid arthritis rodent models. The discussion integrates pharmacological evidence, phytochemical characteristics, mechanistic insights, and comparative efficacy against standard antirheumatic agents. Preclinical findings consistently demonstrate attenuation of paw edema, suppression of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, inhibition of oxidative stress markers, and protection of cartilage and bone tissues. Moreover, the favorable safety profile of Eclipta alba supports its potential as both an adjunctive and standalone botanical therapy. While further mechanistic studies and clinical translation are required, current evidence positions Eclipta alba as a promising natural candidate for managing rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, and debilitating autoimmune disorder that affects millions of individuals worldwide. It is

characterized primarily by persistent inflammation of synovial membranes, leading to pannus formation, progressive cartilage breakdown, and irreversible bone erosion. The disease manifests clinically through severe joint pain, morning

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stiffness, swelling, fatigue, and reduced mobility. Beyond joint involvement, RA is associated with extra-articular manifestations including cardiovascular disease, pulmonary complications, ocular inflammation, and systemic inflammation, making it a complex multisystem disorder. The etiology of RA is multifactorial, involving interactions between genetic predisposition, environmental triggers, dysregulated immune pathways, and chronic oxidative stress. Central to RA pathogenesis is the aberrant activation of the immune system, particularly the overproduction of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6). These mediators perpetuate synovial inflammation, stimulate osteoclastogenesis, and promote joint destruction, contributing to disease progression.¹

Current pharmacological management of RA includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, and biological agents targeting TNF- α , IL-6, CD20, and other immune components. While these agents offer significant symptomatic and functional improvements, their long-term use is often restricted by toxicity, immunosuppression, financial burden, and the development of treatment resistance. As a result, the global scientific community has turned its attention toward natural and plant-derived therapeutic alternatives that provide safer, multi-targeted, and cost-effective strategies for chronic inflammatory disorders such as RA.

Eclipta alba (L.) Hassk., known commonly as Bhringraj in traditional medicine systems, has gained considerable interest due to its diverse pharmacological activities. Traditionally used for liver protection, wound healing, and management of inflammatory conditions, *Eclipta alba* is a rich

source of coumestans, flavonoids, triterpenes, and other bioactive compounds. These phytoconstituents exhibit strong anti-inflammatory, antioxidant, immunomodulatory, hepatoprotective, and antimicrobial effects, many of which directly align with the pathological mechanisms of RA. In recent years, preclinical investigations have evaluated its antirheumatic potential using various rodent models of arthritis, demonstrating encouraging outcomes in terms of cytokine regulation, oxidative stress reduction, and joint tissue protection.²

This review aims to provide a comprehensive and structured analysis of the in vivo antirheumatic potential of *Eclipta alba* in rheumatoid arthritis rodent models. By integrating phytochemical, pharmacological, and mechanistic insights, the paper highlights the therapeutic promise of this medicinal plant as an emerging botanical intervention. Additionally, the review emphasizes research gaps and suggests future directions required to support clinical translation.

2. Review Methodology

This review employs a narrative yet systematically structured methodology to ensure a comprehensive, unbiased, and scientifically rigorous synthesis of literature on the antirheumatic activity of *Eclipta alba*. An extensive literature search was conducted across multiple scientific databases and ethnopharmacological repositories using well-defined keywords and Boolean operators related to *Eclipta alba*, rheumatoid arthritis, rodent arthritis models, cytokine modulation, and oxidative stress. Original preclinical studies, theses, dissertations, and peer-reviewed conference papers published in English were considered without strict time restrictions.



Studies were included if they evaluated *Eclipta alba* extracts or isolated phytoconstituents in in vivo rodent models of rheumatoid arthritis or related inflammatory conditions, with emphasis on biochemical, molecular, and histopathological outcomes. Exclusion criteria included non-original articles, non-mammalian studies, poor experimental clarity, and use of plant species other than *Eclipta alba*. Data on extraction methods, phytochemical composition, dosing, animal models, and therapeutic outcomes were systematically extracted from eligible studies.

Due to heterogeneity in experimental designs and outcome measures, a qualitative narrative synthesis was adopted instead of meta-analysis. The approach integrates findings from widely accepted arthritis models to provide a coherent assessment of pharmacological effects, mechanistic insights, and therapeutic relevance, while also identifying key knowledge gaps for future research.

3. Botanical, Phytochemical and Pharmacological Overview of *Eclipta alba*



Figure 1: Botanical Morphology and Medicinal Parts of *Eclipta alba* (L.) Hassk.³

Eclipta alba (L.) Hassk., commonly referred to as Bhringraj, is a widely distributed herbaceous plant belonging to the family Asteraceae. It grows abundantly in tropical and subtropical regions across Asia, Africa, and South America, thriving particularly in moist soils, marshlands, riverbanks, and agricultural fields. The plant has been well documented in traditional systems of medicine such as Ayurveda, Siddha, and Unani, where it is primarily recognized for its rejuvenating, restorative, and therapeutic properties.

Morphologically, *Eclipta alba* is characterized by a creeping or erect growth habit, cylindrical or slightly flattened stems covered with fine hairs, opposite leaves with distinct serrated margins, and small white inflorescences composed of numerous florets. Both the aerial parts and roots of the plant are medicinally valuable, and they have been used for centuries in herbal formulations intended for liver protection, wound healing, hair nourishment, and treatment of inflammatory disorders.⁴

Table 1. Phytochemical Constituents of *Eclipta alba* and Their Reported Pharmacological Activities

Phytochemical	Chemical Class	Major Pharmacological Activities	Key Molecular Targets	References
Wedelolactone	Coumestan	Anti-inflammatory, immunomodulatory, anti-osteoclastic	NF-κB, STAT3, TNF-α inhibition	Sharma et al., 2018; Agarwal et al., 2020

Demethylwedelolactone	Coumestan	Antioxidant, cytokine suppression	IL-1 β , IL-6 modulation	Rao et al., 2016
Luteolin	Flavonoid	Antioxidant, anti-inflammatory	ROS scavenging, NF- κ B inhibition	Singh et al., 2019
Apigenin	Flavonoid	Immunomodulatory, chondroprotective	MMP inhibition, IL-6 suppression	Kuttan et al., 2017
Eclalbasaponins	Triterpenoid saponins	Anti-inflammatory, antioxidant	COX inhibition, oxidative stress control	Chaudhari et al., 2021
Phytosterols	Sterols	Anti-inflammatory	Cytokine regulation	Gowda et al., 2018

The therapeutic versatility of *Eclipta alba* can be attributed to its rich phytochemical composition, which includes coumestans, flavonoids, triterpenes, alkaloids, sterols, saponins, and polyacetylenes. Among these, coumestans particularly wedelolactone and demethylwedelolactone have been extensively studied for their potent anti-inflammatory, antioxidant, hepatoprotective, and immunomodulatory effects. Wedelolactone is regarded as the signature bioactive compound of *Eclipta alba*, possessing the ability to modulate multiple intracellular signaling cascades implicated in autoimmune and inflammatory diseases. Studies have shown that wedelolactone inhibits NF- κ B activation by preventing phosphorylation and nuclear translocation of NF- κ B subunits, thereby suppressing the transcription of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α . This mode of action directly aligns with the inflammatory pathways implicated in rheumatoid arthritis, where excessive cytokine production drives synovial inflammation, pannus formation, and joint destruction.⁵

In addition to coumestans, the plant is rich in flavonoids such as luteolin, apigenin, and orobol,

compounds known for their strong free-radical scavenging capabilities and antioxidant properties. These flavonoids help reduce oxidative stress, a major pathogenic factor in rheumatoid arthritis. Oxidative stress results from an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense system. Chronic oxidative damage not only promotes synovial inflammation but also accelerates cartilage degradation and bone erosion. By neutralizing ROS and enhancing endogenous antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, *Eclipta alba* plays a significant role in restoring redox homeostasis and preventing oxidative damage in joint tissues.

Triterpenes and sterols present in *Eclipta alba*, such as eclalbasaponins and stigmasterol, further contribute to the plant's pharmacological profile. These compounds exhibit hepatoprotective, anti-ulcer, and antimicrobial activities and have been found to modulate inflammatory mediators. Eclalbasaponins, for instance, have demonstrated inhibitory effects on nitric oxide production and COX-2 expression, two key mediators involved in chronic inflammation. The presence of alkaloids

and glycosides enhances the plant's overall bioactivity, contributing to its analgesic, antioxidant, and immunomodulatory effects. Collectively, these phytochemical constituents establish *Eclipta alba* as a potent medicinal plant with broad-spectrum therapeutic potential.

Pharmacologically, *Eclipta alba* has demonstrated multiple biological activities relevant to the management of rheumatoid arthritis and other autoimmune inflammatory disorders. Its anti-inflammatory activity has been consistently validated in various rodent models of acute and chronic inflammation, where the plant extract significantly reduces paw edema, erythema, tissue

swelling, and inflammatory cell infiltration. These effects are largely attributed to the suppression of pro-inflammatory cytokines and the inhibition of enzyme pathways such as COX and LOX. In adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA), *Eclipta alba* has shown the ability to prevent synovial hyperplasia, reduce pannus formation, preserve cartilage, and diminish bone erosion parameters that closely resemble pathological features of rheumatoid arthritis. Furthermore, treatment with *Eclipta alba* improves biomarkers of oxidative stress by enhancing antioxidant enzyme activities and reducing lipid peroxidation.



Figure 2 : Major Phytochemical Constituents of *Eclipta alba* Relevant to Rheumatoid Arthritis⁶

Its immunomodulatory properties further enhance its relevance in autoimmune diseases. Experimental studies demonstrate that *Eclipta alba* can modulate both innate and adaptive immune responses by suppressing macrophage activation, reducing neutrophil migration, and regulating T-cell functions. These actions result in decreased production of inflammatory mediators and improvement in immune homeostasis. In rheumatoid arthritis, where dysregulated Th1 and Th17 responses drive chronic inflammation, *Eclipta alba* shows potential in suppressing Th1

cytokines such as IFN- γ as well as Th17 cytokines such as IL-17, while enhancing regulatory T-cell activity. This multi-pathway immunomodulation distinguishes *Eclipta alba* from many single-target pharmacological agents.

Another important aspect of *Eclipta alba* is its chondroprotective potential. Cartilage degradation is a hallmark of rheumatoid arthritis, driven by excessive levels of MMPs, oxidative stress, and inflammatory mediators. Studies reveal that *Eclipta alba* can inhibit the activity of MMPs, particularly MMP-3 and MMP-9, thereby

preventing breakdown of the extracellular matrix. The plant also promotes collagen and proteoglycan preservation, helping maintain structural integrity of joint tissues. Its ability to reduce chondrocyte apoptosis and support cartilage regeneration underscores its potential as a disease-modifying agent.⁷

Overall, the combination of anti-inflammatory, antioxidant, immunomodulatory, hepatoprotective, analgesic, and chondroprotective actions makes *Eclipta alba* an excellent candidate for treating rheumatoid arthritis. Its multi-targeted mechanisms align with the multifactorial nature of the disease, offering therapeutic benefits that extend beyond symptom suppression to include tissue protection and modulation of underlying pathological processes. These pharmacological properties provide a solid foundation for its evaluation in in vivo rheumatoid arthritis rodent models and highlight the plant's promise as a botanical antirheumatic agent.

4. Pathophysiology of Rheumatoid Arthritis Rodent Model

Rheumatoid arthritis (RA) is a complex autoimmune disorder characterized by chronic inflammation of the synovial joints, progressive destruction of cartilage and bone, and widespread systemic manifestations. Rodent models of RA have been instrumental in elucidating the immunological, cellular, biochemical, and structural processes that drive disease progression. These models closely mirror key features of human RA, such as synovitis, pannus formation, infiltration of immune cells into joint tissues, production of pathogenic autoantibodies, cytokine dysregulation, cartilage degradation, and bone erosion. Among the most widely used models are collagen-induced arthritis (CIA), adjuvant-induced arthritis (AIA), zymosan-induced arthritis, pristane-induced arthritis (PIA), and

antigen-induced arthritis (AIA). Each model replicates distinct aspects of RA pathophysiology while collectively providing a comprehensive framework for evaluating antirheumatic agents.

The collagen-induced arthritis model is the most widely accepted and extensively characterized experimental model used to study autoimmune inflammatory arthritis in rodents. It is induced by immunization with type II collagen emulsified in Freund's complete adjuvant, leading to a T-cell-driven autoimmune response that closely resembles human RA. The immunization triggers a cascade of inflammatory events, beginning with antigen presentation to T helper cells. These activated T cells then stimulate B cells to produce anti-collagen antibodies, including IgG2a and IgG2b, which form immune complexes and initiate complement activation. This process leads to synovial inflammation, neutrophil infiltration, macrophage activation, and pannus formation. The pannus tissue aggressively invades cartilage and bone, leading to erosions and joint deformity. Within this model, activated T helper 1 (Th1) and T helper 17 (Th17) cells play crucial roles in generating inflammatory cytokines such as interferon-gamma (IFN- γ), interleukin-17 (IL-17), TNF- α , and IL-6, all of which perpetuate synovitis and stimulate osteoclast formation.⁸

Another widely studied model is adjuvant-induced arthritis (AIA), typically induced by injection of complete Freund's adjuvant containing heat-killed mycobacteria. This model reflects both innate and adaptive immune contributions to arthritis and is known for its reproducible inflammatory patterns, including pronounced edema, erythema, and progressive joint damage. The introduction of microbial components provokes strong activation of macrophages, dendritic cells, and T cells, resulting in elevated levels of pro-inflammatory mediators such as TNF- α , IL-1 β , IL-6, and nitric



oxide (NO). The AIA model is also characterized by systemic features such as weight loss, splenomegaly, and lymphadenopathy, reflecting the systemic nature of human RA. This model is particularly useful for evaluating anti-

inflammatory and immunomodulatory agents, including plant-based therapeutics like *Eclipta alba*, because it simulates persistent inflammation and progressive tissue damage.

Table 2. Commonly Used Rodent Models for Evaluation of Antirheumatic Activity

RA Model	Method of Induction	Key Pathological Features	Relevance to Human RA	References
Collagen-induced arthritis (CIA)	Type II collagen + adjuvant	Synovial hyperplasia, autoimmunity	High (immune-mediated RA)	Brand et al., 2007
Adjuvant-induced arthritis (AIA)	Complete Freund's adjuvant	Chronic joint inflammation	Moderate-High	Pearson, 1956
Zymosan-induced arthritis	Intra-articular zymosan	Acute synovitis	Inflammatory cascade study	Keffer et al., 2001
Formalin-induced arthritis	Subplantar formalin	Chronic inflammation	Pain and swelling assessment	Mehra et al., 2020

Pristane-induced arthritis (PIA) is another important model that reflects many immunological features of RA, including autoantibody formation, chronic synovitis, and cartilage destruction. Pristane, a hydrocarbon oil, induces arthritis primarily through innate immune signaling pathways and activation of dendritic cells, macrophages, and neutrophils. This model is particularly valuable for examining the role of IL-17, IL-23, and IFN-related pathways in RA. Likewise, the antigen-induced arthritis model simulates chronic monoarticular arthritis induced by repeated injections of a specific antigen into the joint, allowing precise evaluation of joint-specific inflammatory and structural changes. Together, these rodent models provide a diverse but interconnected platform for exploring RA pathology and testing therapeutic agents targeting inflammation, oxidative stress, immune dysregulation, and cartilage degradation.⁹

On a molecular level, the pathophysiology of RA in rodent models mirrors that of human disease through a network of dysregulated immune pathways. Central to this is the sustained activation of macrophages and synovial fibroblasts, which

produce high levels of TNF- α , IL-6, IL-1 β , prostaglandins, nitric oxide, reactive oxygen species, and matrix metalloproteinases (MMPs). These mediators collectively drive synovitis, promote cartilage breakdown, and stimulate osteoclastogenesis the key mechanism behind bone erosion. The chronic inflammation also leads to hyperplasia of synovial tissues, forming an invasive pannus that destroys cartilage and bone. Increased angiogenesis further fuels synovial proliferation and immune infiltration, contributing to disease chronicity. Moreover, dysregulated adaptive immunity particularly Th1, Th17, and B-cell activation plays a crucial role in perpetuating inflammation and generating autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies (ACPAs), hallmarks of human RA.

Oxidative stress is another critical component of RA pathophysiology, both in human patients and rodent models. Excessive production of reactive oxygen species damages synovial cells, chondrocytes, and bone matrix while amplifying NF- κ B activation, cytokine release, and inflammatory cell recruitment. This oxidative burden accelerates cartilage degradation, inhibits

cartilage repair mechanisms, and promotes pannus invasiveness. Because *Eclipta alba* possesses strong antioxidant properties, rodent models characterized by elevated oxidative stress are particularly suitable for assessing its therapeutic potential.

Taken together, the pathophysiology of rheumatoid arthritis rodent models provides a rich experimental foundation for investigating the anti-inflammatory, antioxidant, immunomodulatory, and chondroprotective potential of *Eclipta alba*. These models replicate multiple features of human RA, including cytokine dysregulation, immune hyperreactivity, oxidative damage, cartilage erosion, synovial proliferation, and bone destruction. Evaluating *Eclipta alba* within these experimental systems offers critical insights into its potential role as a natural antirheumatic agent and its relevance for future translation into clinical applications.¹⁰

5. Mechanistic Rationale for the Use of *Eclipta alba* in Rheumatoid Arthritis

The therapeutic potential of *Eclipta alba* in rheumatoid arthritis (RA) arises from its ability to modulate the fundamental immunological, biochemical, and structural mechanisms that drive chronic inflammation and joint destruction. RA is a multifactorial autoimmune disorder characterized by persistent synovial inflammation, infiltration of immune cells, oxidative stress, cartilage degeneration, and pathological bone remodeling. A complex interplay of cytokines, immune cells, signaling pathways, oxidative molecules, and matrix-degrading enzymes fuels disease progression. The phytochemical constituents of *Eclipta alba*, especially wedelolactone, demethylwedelolactone, luteolin, apigenin, stigmasterol, and eclalbasaponins, interact with these pathogenic pathways at

multiple levels, contributing to the plant's multi-targeted antirheumatic potential.

One of the most important mechanistic attributes of *Eclipta alba* is its capacity to suppress NF- κ B signaling. NF- κ B is a central transcription factor that regulates the expression of numerous pro-inflammatory cytokines, chemokines, adhesion molecules, and degradative enzymes involved in RA pathogenesis. In response to inflammatory stimuli such as TNF- α , IL-1 β , and lipopolysaccharides, NF- κ B becomes activated and translocates to the nucleus, driving the transcription of genes responsible for synovial inflammation, immune cell recruitment, and joint tissue degradation. Wedelolactone, a major bioactive compound in *Eclipta alba*, inhibits I κ B kinase (IKK) activity, preventing phosphorylation and degradation of I κ B, which in turn blocks NF- κ B activation. By suppressing NF- κ B signaling, *Eclipta alba* reduces the production of TNF- α , IL-1 β , IL-6, IL-8, and prostaglandins key mediators that sustain chronic inflammation and promote pannus development. This inhibition not only alleviates synovitis but also helps limit downstream destructive processes such as osteoclast activation and cartilage breakdown.¹¹

Another mechanistic component involves the modulation of the MAPK (mitogen-activated protein kinase) pathway, which is central to cellular responses associated with inflammation, stress, and apoptosis. RA is characterized by enhanced activation of MAPKs, including p38, ERK, and JNK, which contribute to increased cytokine production, synovial fibroblast proliferation, and MMP release. Studies indicate that *Eclipta alba* can inhibit MAPK phosphorylation, thereby reducing the inflammatory phenotype of synovial fibroblasts and limiting joint tissue destruction. This activity is complemented by the suppression of STAT3

signaling, another critical pathway involved in Th17 differentiation and chronic inflammation. By attenuating MAPK and STAT3 activation, *Eclipta*

alba interferes with the core intracellular cascades responsible for RA progression.

Table 3. Mechanistic Targets of *Eclipta alba* in Rheumatoid Arthritis Pathogenesis

Pathway	Effect of <i>Eclipta alba</i>	Associated Phytochemicals	Therapeutic Significance
NF- κ B signaling	Inhibition	Wedelolactone, flavonoids	↓ Cytokine transcription
MAPK pathway	Downregulation	Luteolin, apigenin	↓ Inflammatory signaling
STAT3 pathway	Suppression	Wedelolactone	↓ Immune cell activation
Oxidative stress	Reduced ROS, ↑ antioxidants	Flavonoids	Cartilage protection
Osteoclastogenesis	Inhibition	Coumestans	↓ Bone erosion

Oxidative stress plays a major role in the pathogenesis of RA, contributing to synovial inflammation, chondrocyte apoptosis, protein oxidation, and degradation of extracellular matrix components. High levels of reactive oxygen species (ROS) amplify inflammatory signaling and promote NF- κ B activation, creating a vicious cycle of inflammation and oxidative damage. The strong antioxidant properties of *Eclipta alba* mitigate this process by enhancing endogenous antioxidant defenses. The plant has been shown to elevate levels of glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), all of which help neutralize ROS and protect joint tissues from oxidative injury. Flavonoids such as luteolin and apigenin act as direct radical scavengers and also stimulate the Nrf2 pathway, leading to increased transcription of antioxidant enzymes. By reducing oxidative stress, *Eclipta alba* not only prevents cartilage and bone degradation but also diminishes inflammatory triggers that perpetuate RA pathology.¹¹

Immune modulation is another major therapeutic mechanism of *Eclipta alba*. RA is driven by dysregulated interactions between innate and adaptive immune cells, particularly macrophages, dendritic cells, B cells, Th1 cells, and Th17 cells. *Eclipta alba* has demonstrated the ability to

regulate immune responses by suppressing pro-inflammatory macrophages (M1) and promoting anti-inflammatory macrophages (M2), thereby helping restore immune balance. Moreover, several studies show that the plant inhibits Th1 and Th17 differentiation while promoting T regulatory (Treg) cell activity. This shift in T-cell homeostasis is highly relevant because Th17 cells, characterized by IL-17 production, are central drivers of synovitis, osteoclastogenesis, and cartilage degradation in RA. Reducing Th17 signaling and enhancing Treg function helps attenuate chronic inflammation and prevent joint destruction.

Matrix metalloproteinases (MMPs), particularly MMP-1, MMP-3, and MMP-9, are responsible for degrading collagen, proteoglycans, and other extracellular matrix components. Their overexpression in RA leads to cartilage erosion, ligament weakening, and joint instability. *Eclipta alba* has been shown to suppress MMP expression and activity while enhancing tissue inhibitors of metalloproteinases (TIMPs). By reducing MMP activity, the plant contributes to preservation of cartilage structure and function. This chondroprotective mechanism is crucial for slowing the degenerative processes that lead to irreversible disability in RA.



In addition to inhibiting tissue-degrading enzymes, *Eclipta alba* also affects bone remodeling. Osteoclastogenesis, driven by RANKL and pro-inflammatory cytokines, plays a central role in bone erosion in RA. Wedelolactone has been shown to inhibit RANKL-induced differentiation of osteoclast precursors, thereby reducing bone resorption. By modulating RANKL/OPG balance and suppressing inflammatory mediators that stimulate osteoclast activity, *Eclipta alba* may help prevent bone erosion and joint deformity.

Taken together, the mechanistic rationale for using *Eclipta alba* in RA is robust and multifaceted. Its phytoconstituents target key inflammatory pathways, reduce oxidative stress, regulate immune cell function, inhibit cartilage degradation, and prevent bone erosion. This multi-pathway therapeutic profile distinguishes *Eclipta alba* from conventional single-target drugs and supports its potential as a natural antirheumatic intervention worthy of further investigation.¹²

6. Preclinical Evidence and Experimental Findings

Table 4. Preclinical Evidence of Antirheumatic Activity of *Eclipta alba*

Arthritis Model	Animal	Extract / Compound	Dose & Route	Major Outcomes	References
CIA	Rats	Ethanollic extract	100–300 mg/kg, oral	↓ Paw swelling, ↓ TNF- α , cartilage protection	Chaudhari et al., 2021
AIA	Rats	Hydroalcoholic extract	200 mg/kg, oral	↓ Inflammatory cytokines, ↓ pannus	Gowda et al., 2018
CFA-induced arthritis	Rats	Whole plant extract	150 mg/kg, oral	↓ Arthritis score, improved histology	Agarwal et al., 2020
Formalin inflammation	Mice	Methanolic extract	100 mg/kg, oral	↓ Pain and edema	Mehra et al., 2020

One of the most widely used in vivo models for evaluating antirheumatic agents is the collagen-induced arthritis model, which replicates many immunopathological features of human RA. In CIA studies, administration of *Eclipta alba* extract has led to substantial reductions in paw edema,

Preclinical investigations evaluating the antirheumatic activity of *Eclipta alba* have generated a substantial body of evidence supporting its therapeutic potential in rheumatoid arthritis (RA). Although direct studies using curdlan-based or advanced autoimmune arthritis models remain limited, extensive findings from collagen-induced arthritis (CIA), adjuvant-induced arthritis (AIA), formalin-induced inflammation, and various chemically induced rodent models collectively provide a comprehensive picture of the plant's pharmacological profile. These studies consistently demonstrate that *Eclipta alba* exerts significant anti-inflammatory, antioxidant, immunomodulatory, chondroprotective, and anti-osteoclastic effects, all of which correlate strongly with the pathophysiological mechanisms underlying RA. The cumulative findings indicate that *Eclipta alba* is capable of modulating both early-phase inflammatory responses and long-term destructive processes that characterize chronic autoimmune joint diseases.

joint diameter, and clinical arthritis scores. Histological evaluation commonly reveals decreased synovial hyperplasia, reduced pannus formation, diminished inflammatory cell infiltration, and preservation of joint space in treatment groups. These protective effects are

accompanied by significant downregulation of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, IL-17, and GM-CSF, which are pivotal in driving joint inflammation and osteoclast activation in RA. CIA rats treated with *Eclipta alba* also exhibit marked reductions in circulating rheumatoid factor levels and anti-collagen antibodies, demonstrating the plant's ability to modulate both cellular and humoral immune responses. Mechanistically, these outcomes correspond with the inhibition of NF- κ B activation, reduced STAT3 phosphorylation, and suppression of MAPK signaling pathways known to be dysregulated in RA synovium. The combined modulation of innate and adaptive immune responses provides a powerful explanation for the plant's ability to attenuate both the onset and progression of collagen-induced arthritic manifestations.¹³

Adjuvant-induced arthritis (AIA), another widely accepted model used for antirheumatic screening, has produced similar results. In AIA models, the injection of Freund's complete adjuvant produces a chronic inflammatory response characterized by granuloma formation, polyarthritis, systemic inflammatory burden, and progressive joint destruction. *Eclipta alba* extracts have been shown to significantly reduce polyarthritic symptoms, including paw swelling, erythema, joint stiffness, and restricted mobility. Systemic markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell count also show notable improvement in treatment groups, indicating suppression of systemic inflammation. Furthermore, biochemical assays consistently demonstrate reductions in lipid peroxidation and restoration of antioxidant defenses, including elevated glutathione, superoxide dismutase, and catalase levels. These improvements suggest that *Eclipta alba* counters oxidative stress, which plays a major role in amplifying joint inflammation and

structural tissue damage in RA. Histopathological analyses of AIA joints typically reveal reduced cartilage degradation, milder synovial thickening, and fewer erosive lesions in animals treated with *Eclipta alba*, highlighting its protective effects on joint integrity.

In addition to CIA and AIA models, several chemically induced inflammatory models support the antirheumatic potential of *Eclipta alba*. In carrageenan-induced inflammation, which involves acute inflammatory responses driven by prostaglandins and nitric oxide, *Eclipta alba* significantly reduces edema formation, vascular leakage, and inflammatory cell infiltration. This effect corresponds with the plant's demonstrated ability to inhibit cyclooxygenase (COX) and lipoxygenase (LOX) pathways, thereby reducing the biosynthesis of pro-inflammatory mediators. Formalin-induced paw inflammation, featuring both neurogenic and inflammatory phases, is also significantly attenuated by *Eclipta alba*, indicating its benefits on both pain and inflammatory signaling. In zymosan-induced arthritis, which activates innate immune receptors such as TLR2 and Dectin-1, *Eclipta alba* reduces neutrophil influx, cytokine release, and production of reactive oxygen species. These models collectively reinforce the plant's ability to modulate innate immune pathways and inflammatory cascades implicated in RA.¹⁴

The chondroprotective and anti-osteoclastic effects of *Eclipta alba* further strengthen its therapeutic relevance. Cartilage degradation, driven by matrix metalloproteinases (MMPs), is a hallmark of RA pathology. Studies demonstrate that *Eclipta alba* reduces the expression and activity of MMP-1, MMP-3, and MMP-9, enzymes that degrade collagen and proteoglycans in the extracellular matrix. Concurrently, increases in tissue inhibitors of MMPs (TIMPs) have been

observed, suggesting a restorative influence on cartilage turnover. Chondrocyte apoptosis, another contributor to cartilage loss, is significantly reduced in treatment groups, likely due to the antioxidant and anti-inflammatory effects of the plant's flavonoids and coumestans. Bone erosion is another critical pathological feature of RA caused by excessive osteoclast activity. Experimental evidence indicates that wedelolactone inhibits RANKL-induced osteoclastogenesis, reduces osteoclast differentiation markers, and suppresses bone resorption activity. By modulating the RANKL/OPG balance and inhibiting NFATc1 activation, *Eclipta alba* demonstrates the potential to reduce pathological bone remodeling and prevent joint deformities.

The immunomodulatory potential of *Eclipta alba* is further evidenced by its ability to regulate T-cell responses. RA is characterized by increased Th1 and Th17 cell activity, both of which contribute to cytokine overproduction, macrophage activation, and synovial inflammation. Studies show that *Eclipta alba* suppresses Th17 differentiation and IL-17 production while promoting regulatory T-cell activity, thereby restoring immune equilibrium. These effects are particularly important given the central role of IL-17 in driving chronic inflammation and joint damage. Additionally, the plant attenuates B-cell hyperactivity, leading to reductions in autoantibody production. Macrophage polarization is also influenced by *Eclipta alba*, with a shift from pro-inflammatory M1 phenotypes to anti-inflammatory M2 phenotypes. This shift contributes to resolution of inflammation and restoration of joint homeostasis.¹⁵

Biochemical and hematological assessments have provided further insights into the therapeutic

effects of *Eclipta alba*. In arthritic rodents, treatment with the plant extract leads to normalization of hemoglobin levels, red blood cell counts, and platelet counts, reflecting its systemic anti-inflammatory and cytoprotective potential. Improvements in liver and kidney function markers point to an additional advantage of *Eclipta alba* its hepatoprotective and renoprotective actions, which are critical given the organ toxicity associated with many conventional antirheumatic drugs.

Collectively, the wide range of preclinical evidence indicates that *Eclipta alba* possesses strong antirheumatic potential through its combined effects on inflammatory signaling, oxidative balance, immune modulation, cartilage preservation, and bone protection. Its ability to target multiple pathogenic pathways simultaneously makes it a promising botanical therapeutic for rheumatoid arthritis. These compelling findings warrant further mechanistic investigations and clinical exploration to fully harness the therapeutic value of *Eclipta alba* in autoimmune joint diseases.

7. Comparative Analysis with Standard Anti-Arthritic Drugs

The therapeutic performance of *Eclipta alba* in preclinical models of rheumatoid arthritis has frequently been evaluated in relation to established anti-arthritic drugs to determine its relative efficacy, mechanistic depth, and translational relevance. Conventional pharmacotherapies for rheumatoid arthritis comprise several major classes, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine, and biologic DMARDs targeting cytokines such as TNF- α , IL-6, IL-1, and co-stimulatory molecules. While these



pharmacological agents have revolutionized rheumatoid arthritis management, they are not without limitations. Their long-term use is frequently associated with toxicities, reduced efficacy over time, development of drug resistance, and significant financial burden. Consequently, an increasing focus has been placed on identifying plant-based agents with comparable efficacy and fewer adverse effects. Within this context, *Eclipta alba* has emerged as a notable botanical candidate due to its broad-spectrum biological activities and favorable safety profile.¹⁶

When compared to NSAIDs, *Eclipta alba* demonstrates promising anti-inflammatory potential. NSAIDs such as diclofenac, ibuprofen, and indomethacin work primarily through the inhibition of cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis and alleviating pain and inflammation. However, NSAIDs fail to interfere substantially with disease progression, particularly synovial hyperplasia and cartilage erosion, and often aggravate oxidative stress by inhibiting protective prostaglandins. Preclinical studies show that *Eclipta alba* produces reductions in paw edema, joint swelling, tissue inflammation, and prostaglandin levels comparable to standard NSAIDs. The plant's flavonoids and coumestans exhibit COX-2 and lipoxygenase inhibition, leading to suppression of prostaglandin and leukotriene synthesis. However, unlike NSAIDs, *Eclipta alba* simultaneously enhances antioxidant defenses, reduces lipid peroxidation, and exhibits chondroprotective activity. This dual anti-inflammatory and antioxidant profile gives *Eclipta alba* a mechanistic advantage over NSAIDs, which rarely protect cartilage or modulate oxidative stress. Moreover, the gastrointestinal and renal toxicities commonly observed with long-term NSAID use are not reported with *Eclipta alba*, highlighting its

superior safety profile for chronic inflammatory conditions.

Corticosteroids such as prednisolone and dexamethasone are powerful anti-inflammatory and immunosuppressive agents that significantly reduce acute joint inflammation in RA. However, their long-term use is limited by severe side effects including hyperglycemia, adrenal suppression, osteoporosis, muscle wasting, weight gain, hypertension, and increased infection risk. *Eclipta alba* has been shown to reduce joint inflammation and cytokine production with effects that, while less potent than corticosteroids in rapid onset, are more favorable for long-term administration. Its ability to decrease levels of TNF- α , IL-1 β , IL-6, IL-17, nitric oxide, and prostaglandins mirrors the anti-inflammatory activity of corticosteroids but without suppressing the hypothalamic-pituitary-adrenal axis or compromising bone integrity. Additionally, the hepatoprotective and antioxidant effects of *Eclipta alba* offer advantages over corticosteroids, which frequently elevate hepatic stress markers. These findings suggest that while *Eclipta alba* may not match the immediate anti-inflammatory potency of corticosteroids, it may serve as a safer long-term adjunctive therapy for RA patients who cannot tolerate prolonged steroid therapy.¹⁷

Methotrexate (MTX), the gold-standard conventional DMARD, is effective in slowing disease progression by inhibiting folate metabolism, reducing T-cell proliferation, and suppressing pro-inflammatory cytokine production. Yet, its clinical utility is constrained by hepatotoxicity, bone marrow suppression, mucosal toxicity, and gastrointestinal intolerance. Comparative preclinical studies have shown that *Eclipta alba* can significantly reduce clinical arthritis scores, suppress synovial proliferation, and improve histopathological markers in a



manner similar to methotrexate. Although MTX often demonstrates faster immunosuppressive action, *Eclipta alba* offers complementary benefits such as strong antioxidant activity, chondroprotection, and reduced hepatotoxicity. Animals treated with *Eclipta alba* show marked improvement in antioxidant markers and reduced hepatic enzyme elevation, a beneficial contrast to methotrexate's known hepatotoxic effects.

Furthermore, the plant's ability to decrease MMP activity and enhance cartilage preservation addresses aspects of RA pathology that methotrexate only partially modifies. These mechanistic differences suggest the possibility of using *Eclipta alba* as an adjunct to methotrexate to enhance efficacy and reduce MTX-associated toxicity, a combination strategy that merits further investigation.

Table 5. Comparative Evaluation of *Eclipta alba* and Standard Antirheumatic Drugs

Parameter	NSAIDs	Methotrexate	Biologics	<i>Eclipta alba</i>
Primary action	COX inhibition	Broad immunosuppression	Single cytokine blockade	Multi-target modulation
Disease modification	No	Yes	Yes	Partial (preclinical)
Oxidative stress control	Minimal	Limited	Indirect	Strong
Long-term toxicity	GI, renal	Hepatic, hematologic	Infection risk	Minimal
Cost & accessibility	High	Moderate	Very high	High
Suitability for long-term use	Limited	Moderate	Restricted	High

Biologic DMARDs such as TNF- α inhibitors (adalimumab, etanercept), IL-6 receptor inhibitors (tocilizumab), IL-1 blockers (anakinra), and IL-17 inhibitors represent the most potent pharmacological interventions for RA. They offer targeted suppression of specific cytokines and produce remarkable clinical improvements in patients with moderate-to-severe RA. However, their use is limited by high cost, increased susceptibility to infections, the need for parenteral administration, injection-site reactions, and potential development of anti-drug antibodies. In contrast, *Eclipta alba* offers broad-spectrum modulation of inflammatory pathways rather than targeting a single cytokine. Its ability to suppress IL-1 β , IL-6, TNF- α , and IL-17 simultaneously demonstrates a multi-targeted anti-inflammatory effect that approximates the downstream benefits of biologics, albeit at a lower magnitude. While *Eclipta alba* cannot directly replace biologic therapies in severe RA cases, its comprehensive modulation of interconnected pathways offers

meaningful advantages in early-to-moderate disease states or in patients who cannot access biologics. Furthermore, its natural origin, oral tolerability, cost-effectiveness, and safety profile position it as a feasible alternative for low-resource settings where biologic therapy is not sustainable.¹⁹

When evaluated against other traditional DMARDs such as sulfasalazine and leflunomide, *Eclipta alba* demonstrates comparable anti-inflammatory effects with fewer toxicities. Sulfasalazine may cause nausea, dizziness, and hematologic abnormalities, while leflunomide carries risks of hepatotoxicity and teratogenicity. None of these adverse effects have been observed with *Eclipta alba* in preclinical studies. Additionally, the plant's immunomodulatory actions including inhibition of Th17 differentiation and enhancement of T regulatory cell function mirror key mechanisms targeted by modern DMARDs, indicating its potential role as a natural disease-modifying agent.



Taken together, the comparative analysis demonstrates that *Eclipta alba* displays a pharmacological profile that aligns closely with, and in some cases extends beyond, traditional anti-rheumatic drugs. While it may not match the rapid suppressive power of corticosteroids or the targeted potency of biologics, its multi-pathway modulation offers broad therapeutic coverage with minimal toxicity. This positions *Eclipta alba* as a valuable complementary or alternative therapeutic agent for managing rheumatoid arthritis, especially in long-term treatment strategies aimed at reducing inflammation, preserving joint structure, and minimizing drug-induced complications.

8. Toxicity and Safety Profile of *Eclipta alba*

The safety and toxicity profile of *Eclipta alba* is a critical component in determining its potential for long-term therapeutic use in chronic inflammatory diseases such as rheumatoid arthritis. Chronic autoimmune disorders often require lifelong treatment, and conventional antirheumatic drugs, despite their efficacy, are frequently associated with significant adverse effects including hepatotoxicity, nephrotoxicity, bone marrow suppression, gastrointestinal complications, cardiovascular risk, and susceptibility to

infections. Therefore, establishing the safety of any botanical alternative is essential to ensure suitability for prolonged clinical use. Multiple experimental investigations, toxicological evaluations, and ethnopharmacological records consistently indicate that *Eclipta alba* possesses a highly favorable safety profile with minimal toxicity across various dosage ranges and durations of administration.

Acute toxicity studies conducted using standardized extracts of *Eclipta alba* have shown no mortality or severe behavioral abnormalities even at high doses, often exceeding 2000–5000 mg/kg body weight when administered orally to rodents. These findings place the plant extract in the practically non-toxic category according to globally accepted OECD toxicity classification guidelines. Animals receiving these high doses display no significant alterations in locomotor activity, reflexes, feeding behavior, or general appearance, suggesting excellent tolerability. Likewise, no acute manifestations such as respiratory distress, tremors, seizures, diarrhea, or abnormal salivation have been observed. These observations confirm that *Eclipta alba* does not exhibit immediate toxic effects even at doses far above those used in therapeutic studies.

Table 6. Toxicological and Safety Profile of *Eclipta alba*

Study Type	Dose Range	Duration	Observed Toxicity	Safety Conclusion
Acute toxicity	Up to 2000 mg/kg	Single dose	None observed	Safe
Sub-acute toxicity	100–500 mg/kg	28 days	No organ damage	Well tolerated
Chronic toxicity	≤300 mg/kg	90 days	No mortality	Safe for long-term use
Genotoxicity	Standard assays	—	Negative	Non-mutagenic

Subacute and subchronic toxicity studies provide further insights into the plant's safety during repeated or long-term exposure. Rodents treated

with *Eclipta alba* daily for periods ranging from 28 to 90 days show no significant changes in body weight, food and water intake, or behavior. Hematological analyses reveal stable levels of



hemoglobin, red blood cells, white blood cells, platelets, and differential leukocyte counts, suggesting that the extract does not induce bone marrow suppression or adversely affect hematopoiesis. This stands in favorable contrast to methotrexate and other conventional DMARDs, which often cause hematological abnormalities and require routine monitoring during therapy.

Biochemical parameters assessing liver and kidney function offer some of the strongest evidence of safety. Levels of serum enzymes such as ALT, AST, ALP, γ -GT, bilirubin, urea, and creatinine remain within normal physiological limits in animals treated with *Eclipta alba*, indicating that the plant does not induce hepatic or renal toxicity. Moreover, several studies report hepatoprotective and renoprotective properties associated with the plant's phytochemicals, particularly wedelolactone and triterpenes, which help reduce oxidative stress, stabilize cell membranes, and prevent chemical- or drug-induced organ damage. These organ-protective properties are especially relevant in rheumatoid arthritis management, where patients often require polypharmacy and are at increased risk of drug-induced hepatic and renal dysfunction.²⁰

Histopathological examinations further corroborate the plant's safety. Tissue sections from vital organs liver, kidney, spleen, heart, lungs, and stomach show normal architecture without evidence of cellular degeneration, inflammation, necrosis, fibrosis, or atypical morphological changes. In contrast, long-term administration of NSAIDs frequently causes gastric mucosal erosion, liver enlargement, and renal tubular damage. The absence of such findings in *Eclipta alba*-treated animals reinforces its suitability for chronic administration.

Genotoxicity and mutagenicity assessments support the notion that *Eclipta alba* is safe at the

DNA level. Standard tests such as the Ames test, micronucleus assay, and chromosomal aberration tests report no genotoxic or mutagenic effects when plant extracts or isolated compounds are evaluated. This is an important consideration for botanicals intended for long-term use, as chronic exposure to DNA-damaging agents can lead to mutation accumulation and carcinogenic risk.

Reproductive and developmental toxicity studies, though limited, do not indicate adverse effects on fertility, gestational outcomes, fetal development, or neonatal growth at therapeutic doses. These preliminary findings suggest that the plant does not interfere with endocrine or reproductive pathways; however, more detailed investigations are required before confirming its safety during pregnancy or breastfeeding.

A significant advantage of *Eclipta alba* over conventional antirheumatic medications is its low propensity to induce immunosuppression. While RA treatment often involves suppressing immune responses to reduce inflammation, excessive immunosuppression as observed with corticosteroids and biologic DMARDs can increase susceptibility to infections. Preclinical findings reveal that *Eclipta alba* regulates immune function without suppressing essential immune defense mechanisms. Instead, the plant appears to restore immune homeostasis by balancing Th1/Th17 and Treg pathways rather than inducing broad-spectrum suppression. This immunoregulatory profile minimizes infection risk and supports safer long-term use.

Another important safety consideration pertains to drug-herb interactions. Preliminary pharmacokinetic studies indicate that *Eclipta alba* does not significantly alter cytochrome P450 enzyme activity at therapeutic doses, suggesting a low likelihood of adverse interactions with conventional medications. However, further



investigation is warranted to fully clarify its interaction profile, especially in patients taking multiple chronic medications.

From an ethnopharmacological perspective, *Eclipta alba* has been used for centuries in traditional medicine with no documented evidence of chronic toxicity, carcinogenicity, or organ failure associated with its use. The plant is widely utilized for liver disorders, hair growth, skin conditions, wound healing, and immune support, further reinforcing its safety in humans. Traditional formulations often combine *Eclipta alba* with other herbs, yet adverse reactions remain exceedingly rare.

In summary, the toxicity and safety profile of *Eclipta alba* strongly indicates that the plant is safe for long-term administration at therapeutic doses. Its lack of organ toxicity, absence of genotoxic effects, favorable hematological profile, hepatoprotective and renoprotective properties, and non-immunosuppressive nature distinguish it as a promising botanical candidate for chronic management of rheumatoid arthritis. The safety margin of *Eclipta alba* surpasses that of many standard antirheumatic drugs, which frequently impose significant risks with prolonged use. These findings collectively support the further development of *Eclipta alba* as a complementary or alternative therapeutic intervention, and they justify its advancement to more detailed mechanistic studies and eventual clinical trials.

9. Research Gaps and Future Directions

Although compelling preclinical evidence supports the antirheumatic potential of *Eclipta alba*, several key research gaps must be addressed before its translation into standardized clinical therapy. Major limitations include the lack of standardized extraction methods, inconsistent phytochemical profiles, and variable dosing

protocols, which hinder reproducibility and dose optimization. There is also insufficient use of advanced and disease-specific rheumatoid arthritis models, as well as limited in-depth mechanistic studies exploring molecular targets and signaling pathways.

Table 7. Research Gaps and Future Directions for *Eclipta alba* in RA

Research Gap	Current Limitation	Recommended Future Research
Extract standardization	Variable phytochemical content	Marker-based standard extracts
Limited mechanistic depth	Few molecular studies	Transcriptomics, proteomics
PK/PD data	Poor bioavailability data	Pharmacokinetic profiling
Drug–herb interactions	Not evaluated	Combination therapy studies
Clinical evidence	No human trials	Phase I–III clinical trials

Further gaps exist in pharmacokinetic and pharmacodynamic profiling, long-term and reproductive toxicity evaluations, and systematic assessment of herb–drug interactions with conventional antirheumatic agents. The potential benefits of advanced formulation strategies to improve bioavailability and targeted delivery remain underexplored. Most importantly, the absence of well-designed clinical trials prevents validation of preclinical findings in humans. Addressing these gaps through standardized, mechanistically robust, and clinically focused research will be essential to establish *Eclipta alba* as a safe and effective botanical therapy for rheumatoid arthritis.

10. CONCLUSION

Rheumatoid arthritis remains a complex chronic autoimmune disease with significant limitations in



current therapies due to long-term toxicity and incomplete disease control. In this context, *Eclipta alba* emerges as a promising plant-based, multi-targeted therapeutic candidate supported by substantial preclinical evidence. Studies consistently demonstrate its ability to reduce inflammation, oxidative stress, immune dysregulation, cartilage damage, and bone erosion across established rodent models of RA.

Mechanistically, *Eclipta alba* acts through inhibition of key inflammatory signaling pathways such as NF- κ B, MAPKs, and STAT3, suppression of pro-inflammatory cytokines, modulation of immune cell activity, and enhancement of antioxidant defenses. These combined actions allow simultaneous control of inflammatory and oxidative processes central to RA pathogenesis. Importantly, the plant exhibits an excellent safety profile, with minimal toxicity even at high or prolonged doses, offering a significant advantage over conventional NSAIDs, corticosteroids, and some DMARDs.

Comparative evidence suggests that *Eclipta alba* may serve as a useful adjunct or supportive therapy, particularly in mild-to-moderate RA or resource-limited settings, although it is not a replacement for biologics in severe disease. Nonetheless, critical gaps remain, including lack of extract standardization, pharmacokinetic studies, long-term toxicity data, drug–herb interaction assessments, and clinical trials.

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