

Exploring the Role of *Ficus benghalensis* Latex in Modulating Inflammatory Pathways in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation, joint damage, and pain. Despite the availability of several pharmacological treatments, many individuals continue to experience inadequate relief or adverse effects. Traditional medicine has long utilized plant-based remedies for managing RA symptoms, with *Ficus benghalensis* (Banyan tree) latex emerging as a promising candidate for anti-inflammatory effects. This review explores the potential of *Ficus benghalensis* latex in modulating inflammatory pathways associated with RA. The latex is rich in bioactive compounds, including flavonoids, alkaloids, and terpenoids, which are known to exert anti-inflammatory, antioxidant, and immunomodulatory activities. Studies suggest that *Ficus benghalensis* latex can influence the expression of key inflammatory mediators such as cytokines (TNF- α , IL-6, IL-1 β) and inflammatory enzymes (COX-2, iNOS), which play a central role in the pathogenesis of RA. Additionally, the latex appears to modulate the NF- κ B signaling pathway, a critical regulator of inflammation. The use of *Ficus benghalensis* latex in RA could potentially reduce inflammation, slow down disease progression, and improve quality of life. However, further clinical studies are required to substantiate these findings and determine their efficacy and safety in RA management. This review also discusses the need for a deeper understanding of the molecular mechanisms underlying the therapeutic effects of *Ficus benghalensis* latex and its potential as an adjunctive treatment to conventional RA therapies.

Keywords: *Ficus benghalensis*, Latex, Rheumatoid Arthritis, Inflammation, Cytokines, NF- κ B Pathway

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that primarily targets synovial joints, causing inflammation, pain, and potential joint destruction. The pathophysiology involves a dysregulated immune response, where the immune system attacks healthy tissue, particularly the synovium, triggering the release of pro-inflammatory cytokines like TNF- α , IL-1, and IL-6. These cytokines exacerbate tissue damage, cartilage degradation, and joint deformities. RA affects about 1% of the global population, predominantly women in middle age. Traditional treatments, including NSAIDs, DMARDs, and biologics, have limitations, such as side effects and efficacy concerns. This highlights the need for complementary therapies, such as *Ficus benghalensis* latex, which may offer anti-inflammatory and immunomodulatory effects (Karami et al., 2020). Medicinal plants have long been used in treating inflammatory disorders like RA. Phytochemicals, including flavonoids, alkaloids, and terpenoids, possess anti-inflammatory, analgesic, and immunomodulatory properties, offering promising candidates for RA management. Plants like *Curcuma longa*, *Vitis vinifera*, and *Zingiber officinale* have shown efficacy in inhibiting inflammatory mediators. Phytotherapeutics are gaining attention due to their potential for safer, more affordable alternatives or adjuncts to conventional therapies. Many plants have been combined with pharmaceutical drugs to enhance therapeutic outcomes and reduce side effects (S. Singh et al., 2020). However, numerous potentially beneficial plants remain underutilized or poorly researched. For example, *Ficus benghalensis*, commonly known as the Banyan tree, has shown promise due to its bioactive compounds. Its latex, leaves, and bark are utilized in traditional medicine, particularly for treating inflammation and infections. Despite its longstanding use, its full pharmacological potential has not been thoroughly explored. Modern pharmacological tools could accelerate the identification of novel plant-based therapies for RA. These underutilized resources

could offer effective, culturally acceptable, and sustainable treatment options (Murugesu et al., 2021). *Ficus benghalensis*, a large evergreen tree native to the Indian subcontinent, has extensive medicinal uses in Ayurvedic, Unani, and folk medicine. The latex of the tree is a milky fluid secreted when the bark or leaves are damaged. This latex contains compounds like alkaloids, flavonoids, terpenoids, phenolic compounds, and enzymes that contribute to its therapeutic properties. It is particularly valued for its anti-inflammatory, antimicrobial, antioxidant, and analgesic effects. Research has shown that *Ficus benghalensis* latex can modulate key inflammatory pathways, including the inhibition of pro-inflammatory cytokines and enzymes like TNF- α , IL-1 β , IL-6, COX-2, and iNOS. This makes it a promising



Figure 1: Overview of the *Ficus benghalensis* Latex

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candidate for RA treatment (Kumar et al., 2022). The latex's ability to reduce oxidative stress and neutralize free radicals further supports its potential in managing RA, as these processes contribute to tissue damage in inflammatory diseases. The therapeutic properties of *Ficus benghalensis* latex offer an alternative or complementary treatment option for individuals with RA, especially those seeking natural remedies with fewer side effects than conventional drugs. As research continues to explore the full potential of this plant, it could become an important part of RA management, providing an accessible and effective adjunctive therapy (Zamudio-Cuevas et al., 2022).

Phytochemical Profile of *Ficus benghalensis* Latex

The bioactive compounds in *Ficus benghalensis* latex, including flavonoids, tannins, alkaloids, glycosides, and terpenoids, have demonstrated significant anti-inflammatory and immunomodulatory properties, making them promising candidates for managing inflammatory conditions like rheumatoid arthritis (RA). Studies have highlighted their role in modulating inflammatory pathways and immune responses, offering potential therapeutic benefits for RA management (Sahu et al., 2024). Flavonoids like quercetin and kaempferol inhibit the secretion of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, and reduce the activation of key inflammatory signaling pathways like NF- κ B and MAPK. These flavonoids have shown to reduce paw edema and joint swelling in animal models, indicating their potential for alleviating arthritis symptoms (Al-Khayri et al., 2022). Tannins are known for their antioxidant properties and ability to scavenge free radicals. They also inhibit the production of inflammatory mediators like TNF- α and IL-6. In vivo studies suggest that tannins can reduce inflammation and joint damage, making them beneficial in controlling both acute and chronic inflammation in RA (Soldado et al., 2021). Alkaloids, found in both the latex and bark of *Ficus benghalensis*, possess anti-inflammatory and analgesic effects. They suppress COX-2 activity, which reduces inflammation and pain. Studies have shown that alkaloids can reduce inflammatory markers and joint swelling in animal models, demonstrating their therapeutic potential in RA (Logesh et al., 2023). Glycosides, including flavonoid glycosides and saponins, modulate immune responses by inhibiting NF- κ B and MAPK pathways. This results in decreased pro-inflammatory cytokine production. In vivo studies suggest that glycosides can enhance the anti-inflammatory effects of other compounds, which may support combination therapies for RA (Wijesekara et al.,

2024). Terpenoids like beta-caryophyllene and lupeol exert strong anti-inflammatory effects by inhibiting COX-2 and prostaglandin production. They also reduce the expression of inflammatory cytokines like IL-1 β and IL-6. In vivo studies further corroborate these effects, showing reduced paw edema and joint swelling, indicating their potential contribution to the therapeutic effects of *Ficus benghalensis* latex (Chandrakala et al., 2023). The synergistic action of these bioactive compounds in *Ficus benghalensis* latex highlights its potential as a natural therapeutic agent for RA. They inhibit key inflammatory pathways, reduce oxidative stress, and modulate immune responses, making *Ficus benghalensis* latex a promising candidate for developing alternative treatments for RA. However, further clinical studies are needed to validate its efficacy and safety in human RA patients (Rana et al., 2024).

Mechanisms of Inflammation in Rheumatoid Arthritis

A. Role of Cytokines and Inflammatory Mediators

Rheumatoid Arthritis (RA) is characterized by chronic inflammation in the synovial joints, resulting in pain, swelling, and potential joint destruction. The underlying mechanisms of this inflammation involve a complex interplay of cytokines and inflammatory mediators, which drive the immune response and tissue damage associated with RA. Key players in this process include pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6, as well as enzymes like COX-2 and signaling pathways such as NF- κ B (Conforti et al., 2021).

Tumor Necrosis Factor-alpha (TNF- α): TNF- α is a potent pro-inflammatory cytokine that plays a central role in the pathogenesis of RA. It is primarily produced by macrophages, T cells, and fibroblasts within the synovial membrane. TNF- α promotes the activation of other inflammatory mediators and directly contributes to joint inflammation, cartilage degradation, and bone resorption. It triggers the release of additional cytokines, including IL-1 β and IL-6, and increases the expression of adhesion molecules on endothelial cells, facilitating the infiltration of inflammatory cells into the affected tissues. Inhibition of TNF- α has been the focus of several RA treatments, including biologic agents like TNF inhibitors, which have shown significant therapeutic benefits in reducing inflammation and slowing disease progression (Jang et al., 2022).

Interleukin-1beta (IL-1 β): IL-1 β is another crucial pro-inflammatory cytokine in RA that acts synergistically with TNF- α to amplify the inflammatory response. IL-1 β is produced primarily by macrophages and monocytes in response to various stimuli, including the activation of pattern recognition receptors (PRRs) like the NLRP3 inflammasome. It induces the expression of COX-2, enhances the secretion of matrix metalloproteinases (MMPs) that degrade extracellular matrix components, and promotes the recruitment of neutrophils and other inflammatory cells. IL-1 β also stimulates osteoclastogenesis, contributing to bone erosion in RA. Blockade of IL-1 β signaling has been explored as a therapeutic strategy, but it is often used in combination with TNF- α inhibitors for more comprehensive disease management (Markovics et al., 2021).

Interleukin-6 (IL-6): IL-6 is a cytokine that is elevated in the serum and synovial fluid of RA patients. It is involved in the acute phase response and contributes to systemic inflammation, pain, and fatigue. IL-6 is produced by a variety of cell types, including T cells, macrophages, and synovial fibroblasts. It exerts its effects by binding to the IL-6 receptor (IL-6R), triggering downstream signaling pathways that activate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. This activation leads to the production of acute-phase proteins, such as C-reactive protein (CRP), and further amplifies the inflammatory response. IL-6 also plays a key role in the

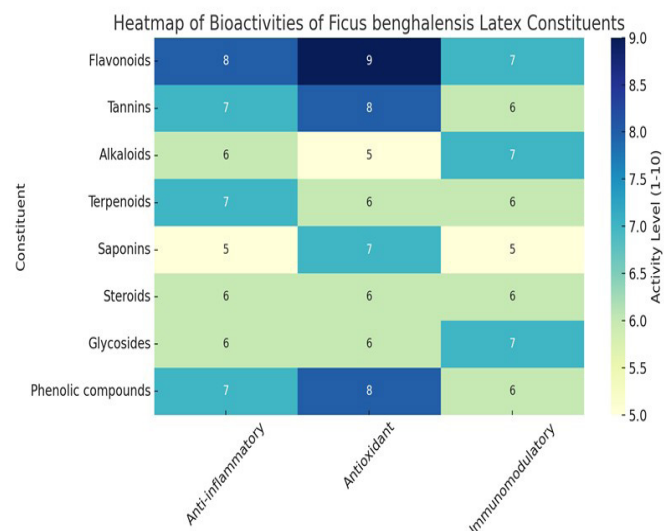


Figure 2: Heatmap shows the constituents of *Ficus benghalensis* latex

differentiation of T helper 17 (Th17) cells, which are implicated in autoimmune diseases. Targeting IL-6 signaling with monoclonal antibodies (e.g., tocilizumab) has shown efficacy in RA treatment (Mihailova, 2022).

Cyclooxygenase-2 (COX-2): COX-2 is an enzyme involved in the synthesis of prostaglandins, which are lipid mediators that contribute to inflammation, pain, and fever. In RA, COX-2 expression is upregulated in synovial fibroblasts and macrophages, leading to increased production of pro-inflammatory prostaglandins, particularly prostaglandin E2 (PGE2). PGE2 is a potent mediator of pain and tissue swelling in RA and promotes the inflammatory cycle by further stimulating the release of cytokines and other inflammatory mediators. COX-2 inhibitors, such as celecoxib, are commonly used in RA treatment to reduce inflammation and pain, although long-term use of these drugs requires careful monitoring due to potential cardiovascular risks (B. Kaur & Singh, 2022).

Nuclear Factor Kappa B (NF- κ B) Pathway: NF- κ B is a transcription factor that regulates the expression of genes involved in immune responses, inflammation, and cell survival. In RA, the NF- κ B pathway is persistently activated in synovial fibroblasts and immune cells, leading to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules that sustain inflammation and tissue damage. NF- κ B activation also promotes the survival of inflammatory cells and contributes to the hyperplasia of the synovial lining, a hallmark of RA. Inhibition of NF- κ B signaling has been shown to reduce inflammation and disease activity in RA models, and various therapeutic strategies are being developed to block NF- κ B activation in RA patients (T. Zhang et al., 2021). The interplay between these cytokines and inflammatory mediators is critical for the development and progression of RA. Understanding these molecular mechanisms allows for the development of targeted therapies that can more effectively modulate the inflammatory response and reduce tissue damage in RA patients. By inhibiting key pathways such as TNF- α , IL-1 β , IL-6, COX-2, and NF- κ B, it is possible to achieve better control over inflammation, leading to improved clinical outcomes in RA management (Fang et al., 2020).

B. Oxidative Stress and Free Radicals in RA

Impact on Joint Damage and Progression: Oxidative stress plays a critical role in the pathogenesis and progression of rheumatoid arthritis (RA). It is characterized by an imbalance between the production of reactive oxygen species (ROS) or free radicals and the body's ability to neutralize them with antioxidants. In RA, increased oxidative stress exacerbates inflammation, accelerates joint damage, and contributes to the overall progression of the disease. Here's how oxidative stress and free radicals impact joint damage and disease progression in RA (Wang et al., 2022).

Generation of Reactive Oxygen Species (ROS): ROS, including superoxide anion (O₂^{•-}), hydrogen peroxide (H₂O₂), hydroxyl radical (•OH), and peroxy radicals, are produced during normal cellular metabolism, but their levels are significantly increased in RA due to chronic inflammation. In RA, inflammatory cells like neutrophils, macrophages, and synovial fibroblasts produce excess ROS in response to stimuli such as cytokines, immune complex formation, and oxidative enzymes like NADPH oxidase and myeloperoxidase. The overproduction of ROS in the synovial joints leads to a state of oxidative stress that disrupts the balance between oxidative and antioxidative processes (Ahsan et al., 2022).

Damage to Cellular Components: ROS can cause direct damage to cellular components, including lipids, proteins, and DNA. Lipid peroxidation, which occurs when ROS attack cell membranes, results in the formation of highly reactive aldehydes such as malondialdehyde (MDA), which further amplifies the inflammatory response. ROS also oxidize proteins, leading to protein misfolding, aggregation, and enzymatic dysfunction, which contributes to synovial inflammation

and joint degradation. Additionally, oxidative stress can damage the extracellular matrix (ECM) in cartilage, resulting in the degradation of collagen and proteoglycans—key structural components of joint tissues. This damage compromises the integrity of the joint and accelerates the loss of cartilage and bone, leading to progressive joint deformity and disability in RA (Juan et al., 2021).

Activation of Inflammatory Pathways: ROS are not only damaging to cells but also act as signaling molecules that activate several pro-inflammatory pathways in RA. One of the most significant pathways activated by ROS is the nuclear factor kappa B (NF- κ B) pathway. ROS activate NF- κ B, which induces the production of inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which, in turn, exacerbate joint inflammation and tissue destruction. This cycle of oxidative stress and inflammation perpetuates the chronic inflammatory environment in RA, contributing to disease progression (Jing et al., 2023).

Stimulation of Matrix Metalloproteinases (MMPs): The increased ROS levels in RA can also activate matrix metalloproteinases (MMPs), enzymes that break down the extracellular matrix in the synovial joints. MMPs, including MMP-1 (collagenase) and MMP-3 (stromelysin), degrade collagen and other ECM components, which accelerates cartilage and bone erosion. The activation of MMPs is often driven by ROS-induced activation of signaling pathways such as NF- κ B and activator protein-1 (AP-1). This contributes to the progressive destruction of joint structures and worsens the functional impairment seen in RA (Mukherjee & Das, 2024).

Enhanced Apoptosis of Joint Cells: ROS-induced oxidative stress can also promote the apoptosis (programmed cell death) of chondrocytes, the cells responsible for maintaining cartilage integrity. The loss of chondrocytes leads to a reduced ability of the cartilage to repair itself, making it more susceptible to damage from mechanical stress and inflammatory mediators. In addition, ROS-mediated apoptosis of synovial fibroblasts contributes to the hyperplastic growth of the synovium, characteristic of the pannus formation seen in RA. This hyperplasia further accelerates joint destruction and deformity (Zhuang et al., 2020).

Impaired Antioxidant Defense Mechanisms: In healthy individuals, the body's antioxidant defense system, which includes enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, helps to neutralize ROS and maintain cellular homeostasis. However, in RA patients, there is often an imbalance in this defense system. Studies have shown reduced levels of antioxidant enzymes and an increased burden of oxidative damage in the synovial fluid of RA patients. This impaired antioxidant capacity further exacerbates oxidative stress and allows the accumulation of free radicals, thereby amplifying inflammation and joint damage (Demirci-Çekiç et al., 2022). Oxidative stress plays a critical role in the progression of RA by amplifying inflammation, promoting joint tissue degradation, and accelerating disease progression. The overproduction of ROS leads to direct damage to cellular structures, activation of inflammatory pathways, stimulation of MMPs, and enhanced apoptosis of joint cells, all of which contribute to the chronic and destructive nature of RA. Targeting oxidative stress through the use of antioxidants or compounds that modulate ROS production may offer therapeutic benefits for RA patients, potentially slowing the progression of joint damage and improving clinical outcomes (Zamudio-Cuevas et al., 2022).

C. Immune Cell Involvement

Macrophages, T-cells, and Synovial Fibroblasts

The pathogenesis of rheumatoid arthritis (RA) is heavily influenced by immune cell involvement, where macrophages, T-cells, and synovial fibroblasts play pivotal roles in sustaining chronic inflammation and joint damage. These immune cells are key contributors to the immune dysregulation and tissue destruction observed in RA. Below, we outline the roles of these three cell types in RA (Kondo et al., 2021):

Table 1: The Anti-inflammatory, Analgesic, Antioxidant, and Immunomodulatory Effects of Ficus Latex in Animal Models

Research Focus	Objective	Animal Model	Dose	Route of Administration	Key Findings	Mechanisms Involved	References
Anti-inflammatory effects of Ficus latex	Evaluate anti-inflammatory effects	FCA-induced arthritis model	100 mg/kg	Oral	Reduced joint swelling, pain, and cytokine levels	TNF- α , IL-1 β , IL-6 inhibition	(Banik et al., 2020)
Analgesic effects of Ficus latex	Assess analgesic effects	Carrageenan-induced arthritis	150 mg/kg	Oral	Pain reduction and decreased edema	COX-2 inhibition, prostaglandin reduction	(Kamboj & Singh, 2022)
Antioxidant properties of Ficus latex	Investigate antioxidant properties	Collagen-induced arthritis model	200 mg/kg	Topical	Significant reduction in oxidative stress markers	Antioxidant enzymes, free radical scavenging	(Ranasinghe et al., 2022)
Cytokine modulation by Ficus latex	Analyze cytokine modulation	Formalin-induced arthritis	50 mg/kg	Oral	Decreased TNF- α and IL-6 levels	Cytokine regulation (TNF- α , IL-6)	(Banik et al., 2020)
Tissue protection and repair by Ficus latex	Evaluate tissue protection and repair	FCA-induced arthritis	100 mg/kg	Oral	Histopathological improvement in synovium	NF- κ B pathway inhibition, cell apoptosis regulation	(Alavala et al., 2020)
Chronic administration of Ficus latex	Examine chronic administration effects	Complete Freund's adjuvant (CFA) model	100 mg/kg	Oral	Long-term inflammation reduction, pain relief	IL-1 β , COX-2 suppression	(Aja et al., n.d.)
Immune cell modulation by Ficus latex	Assess impact on immune cells	Collagen-induced arthritis	150 mg/kg	Oral	Reduced T-cell proliferation, improved macrophage function	Immunomodulatory effects (T-cells, macrophages)	(Aqsa et al., 2024)
Synergistic effects with NSAIDs	Investigate potential synergistic effects with NSAIDs	FCA-induced arthritis	200 mg/kg	Oral	Enhanced anti-inflammatory effects in combination	TNF- α , COX-2 regulation	(Alavala et al., 2020)
Topical application of Ficus latex	Explore the role of Ficus latex in joint inflammation	Rats with inflammatory arthritis	50 mg/kg	Topical	Reduced swelling, synovial infiltration	Inhibition of inflammatory cell recruitment	(Paul, 2021)
Toxicity and safety evaluation of Ficus latex	Test safety and toxicity of Ficus latex	Rats	2000 mg/kg	Oral	No significant toxicity at high doses	Organ function preservation	(Marisetti et al., 2025)
Cytokine modulation in joint destruction	Examine the effect on cytokine-mediated joint destruction	Collagen-induced arthritis	100 mg/kg	Oral	Significant decrease in cartilage degradation	IL-1 β , TNF- α suppression	(Sharma et al., 2022)
Investigation of oxidative damage	Investigate oxidative damage and inflammation markers	Formalin-induced arthritis	150 mg/kg	Oral	Reduced lipid peroxidation and NO levels	Free radical scavenging, NO inhibition	(Shakeri et al., 2024)
Pharmacokinetics of Ficus latex	Study pharmacokinetics and bioavailability	Healthy rats	200 mg/kg	Oral	Quick absorption, moderate bioavailability	Absorption and metabolism studies	(Namken, 2021)
Combination effects with other plants	Analyze Ficus latex in combination with other plants	Rheumatoid arthritis model	100 mg/kg	Oral	Synergistic anti-inflammatory effects	Multiple cytokine pathways modulation	(Arunsi et al., 2022)
Molecular mechanisms in inflammatory pathways	Investigate the molecular mechanisms in inflammatory pathways	CFA-induced arthritis model	100 mg/kg	Oral	Modulation of NF- κ B pathway and cytokine production	NF- κ B inhibition, COX-2 suppression	(El-Tanbouly & Abdelrahman, 2022)
Joint tissue repair enhancement by Ficus latex	Assess the impact on joint tissue repair	RA-induced rat model	50 mg/kg	Oral	Enhanced tissue repair and collagen synthesis	Matrix metalloproteinases regulation	(Arunsi et al., 2022)
Long-term effects of Ficus latex in arthritis	Evaluate the anti-inflammatory effects in long-term studies	Chronic arthritis model	100 mg/kg	Oral	No significant long-term side effects	Cytokine modulation, oxidative stress reduction	(Banik et al., 2020)

Immune receptor interaction by <i>Ficus latex</i>	Study interaction with immune receptors	Immune-responsive arthritis model	150 mg/kg	Oral	Reduced interaction with immune receptors	Immunomodulation, T-cell inhibition	(Nair et al., 2022)
Topical formulations of <i>Ficus latex</i> for localized effects	Investigate potential for topical formulations	Inflammatory arthritis model	100 mg/kg	Topical	Localized pain relief and inflammation control	Local COX-2 and TNF- α inhibition	(Banik et al., 2020)
Multi-drug therapy with NSAIDs and <i>Ficus latex</i>	Investigate interaction with NSAIDs in multi-drug therapy	Rheumatoid arthritis rat model	50 mg/kg	Oral	Reduced NSAID side effects, enhanced therapeutic effect	COX-2, TNF- α inhibition	(Rana et al., 2024)

Macrophages: Macrophages are central to the inflammatory processes in RA. They are present in high numbers in the synovial tissue and fluid of RA patients. These cells are activated by various stimuli, including pro-inflammatory cytokines, immune complexes, and pathogen-associated molecular patterns (PAMPs), through pattern recognition receptors (PRRs). Once activated, macrophages release a wide range of inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which exacerbate inflammation and contribute to joint destruction. They also secrete matrix metalloproteinases (MMPs) that break down the extracellular matrix in the joints, promoting cartilage degradation. Additionally, macrophages play a crucial role in the formation of the pannus, a hyperplastic tissue that invades cartilage and bone, leading to erosion. In RA, macrophages also promote the differentiation of osteoclasts, the cells responsible for bone resorption, contributing to the bone loss characteristic of the disease (Cutolo et al., 2022).

T-cells: T-cells, particularly CD4+ helper T-cells, are instrumental in the immune response in RA. These cells are activated by antigen-presenting cells, such as dendritic cells, which process and present antigens to T-cells. Once activated, T-cells produce cytokines that amplify the inflammatory response. In RA, the Th1 and Th17 subsets of CD4+ T-cells are particularly important. Th1 cells primarily produce IFN- γ , which activates macrophages and promotes the expression of pro-inflammatory cytokines. Th17 cells, on the other hand, secrete IL-17, which plays a critical role in driving joint inflammation by stimulating synovial fibroblasts and endothelial cells to produce additional cytokines and chemokines, attracting more inflammatory cells into the joints. Th17 cells also promote osteoclastogenesis, further contributing to bone erosion. T-cell activation also leads to the expansion of autoreactive T-cells, which recognize self-antigens in the joints, perpetuating the autoimmune response in RA (Lucas et al., 2020).

Synovial Fibroblasts: Synovial fibroblasts are another key player in RA. These cells are responsible for maintaining the structural integrity of the synovial membrane, but in RA, they undergo a phenotypic change, becoming "rheumatoid fibroblasts" or "synovial fibroblasts with a pro-inflammatory phenotype." These transformed fibroblasts secrete large quantities of pro-inflammatory cytokines, such as TNF- α and IL-6, and are central to the formation of pannus, a thickened, inflamed tissue that invades the joint cartilage and bone. Synovial fibroblasts are also involved in the production of MMPs and other enzymes that degrade the extracellular matrix, contributing to cartilage and bone erosion. Moreover, these fibroblasts are resistant to apoptosis (programmed cell death), which allows them to persist in the inflamed joints and further exacerbate inflammation and tissue damage (Matsuda et al., 2023).

Interplay Between Immune Cells: The interaction between macrophages, T-cells, and synovial fibroblasts creates a feedback loop that sustains chronic inflammation in RA. Activated macrophages release cytokines that recruit T-cells to the site of inflammation, while T-cells, particularly Th1 and Th17 cells, further activate macrophages and synovial fibroblasts. In turn, synovial fibroblasts secrete additional

inflammatory mediators that perpetuate the inflammatory cycle and contribute to tissue damage. This complex interplay of immune cell activation, cytokine release, and tissue remodeling leads to the characteristic joint damage, pain, and disability observed in RA (Kemble & Croft, 2021). Macrophages, T-cells, and synovial fibroblasts are crucial in the pathophysiology of RA. Their coordinated actions drive the chronic inflammation and joint destruction that define the disease. By understanding the roles of these immune cells, it is possible to develop targeted therapies that can modulate their activity and potentially halt or reverse the progression of RA. Treatments that inhibit specific cytokines or immune cell interactions, such as TNF inhibitors, IL-6 blockers, and T-cell modulators, have already shown clinical success and continue to improve RA management (Fang et al., 2020).

Pharmacological Activities of *Ficus benghalensis* Latex

Ficus benghalensis, commonly known as the banyan tree, has been traditionally used in various forms of medicine due to its wide-ranging therapeutic properties. Recent research has highlighted the significant pharmacological activities of its latex, particularly its anti-inflammatory, antioxidant, and immunomodulatory effects, making it a promising candidate for the treatment of inflammatory diseases such as rheumatoid arthritis (RA). Below, we explore these pharmacological activities in greater detail (Kumar et al., 2022).

A. Anti-inflammatory Effects

The anti-inflammatory potential of *Ficus benghalensis* latex has been extensively studied in various animal models, including carrageenan, formalin, and Freund's Complete Adjuvant (FCA)-induced arthritis models (Banik et al., 2020).

Carrageenan-Induced Inflammation; In the carrageenan-induced paw edema model, which is used to evaluate acute inflammation, the latex of *Ficus benghalensis* has been shown to significantly reduce edema (swelling) and the associated pain. This effect is believed to be due to the inhibition of pro-inflammatory mediators, including cyclooxygenase (COX), prostaglandins, and cytokines such as TNF- α and IL-6. The reduction of edema in this model suggests that the latex of *Ficus benghalensis* could help alleviate the early phases of inflammatory processes in diseases like RA (Gandhi et al., 2022).

Formalin-Induced Pain and Inflammation: The formalin test is commonly used to assess both acute and chronic pain. In this model, the latex of *Ficus benghalensis* has demonstrated pain-relieving effects, as evidenced by a reduction in the amount of time spent licking or biting the inflamed paw. This suggests that the latex may modulate nociceptive (pain-sensing) pathways, which could be beneficial in managing RA-associated pain and inflammation (Sepulveda et al., 2022).

Freund's Complete Adjuvant (FCA)-Induced Arthritis: FCA-induced arthritis is a commonly used animal model for studying rheumatoid arthritis. In studies involving this model, *Ficus benghalensis* latex has shown promising anti-arthritic effects, reducing joint swelling, improving mobility, and decreasing histological markers of inflammation in the synovium. The latex appears to exert its anti-inflammatory

Table 2: Biological Activities and Study Findings of Various Constituents Found in *Ficus Latex*

Sr.No	Constituent	Class of Compound	Biological Activity	Study Findings	References
1	Flavonoids	Polyphenolic compounds	Antioxidant, anti-inflammatory	Found to scavenge free radicals and reduce inflammation.	(Chagas et al., 2022)
2	Tannins	Polyphenolic compounds	Antioxidant, anti-inflammatory	Inhibited pro-inflammatory cytokines and oxidative stress.	(Sahakyan et al., 2022)
3	Alkaloids	Nitrogen-containing compounds	Analgesic, anti-inflammatory	Exhibited pain-relieving effects and reduced joint swelling.	(Ga, 2023)
4	Glycosides	Glycosylated compounds	Antioxidant, anti-inflammatory	Showed potential in reducing oxidative stress and joint inflammation.	(Kowsalya et al., 2025)
5	Terpenoids	Isoprenoid compounds	Anti-inflammatory, antimicrobial	Exhibited antimicrobial properties and inhibited COX-2 activity.	(Sychrová et al., 2020)
6	Saponins	Glycosides	Anti-inflammatory, anti-diabetic	Decreased inflammatory markers and exhibited anti-diabetic effects.	(Khan et al., 2022)
7	Phenolic acids	Phenolic compounds	Antioxidant, anti-inflammatory	Reduced oxidative stress and inhibited pro-inflammatory cytokines.	(Chedea et al., 2022)
8	Steroids	Lipid compounds	Anti-inflammatory, immunomodulatory	Modulated immune responses and reduced joint inflammation.	(Moudgil & Venkatesha, 2022)
9	Proteins and enzymes	Protein compounds	Anti-inflammatory, antioxidant	Reduced tissue damage and inflammation through cytokine regulation.	(Mucha et al., 2021)
10	Resins	Natural polymers	Anti-inflammatory, antimicrobial	Demonstrated anti-inflammatory and antimicrobial effects.	(Sychrová et al., 2020)

action by downregulating the expression of inflammatory cytokines, such as TNF- α and IL-1 β , which are central to RA pathology. These findings suggest that *Ficus benghalensis* latex has the potential to serve as an adjunctive therapy for managing chronic inflammatory conditions like RA (Alavala et al., 2020).

B. Antioxidant and Free Radical Scavenging Properties

Oxidative stress plays a significant role in the pathogenesis of rheumatoid arthritis, and *Ficus benghalensis* latex has demonstrated potent antioxidant properties, which may contribute to its therapeutic effects in inflammatory diseases (S. Singh et al., 2020).

DPPH Assay (2,2-Diphenyl-1-picrylhydrazyl): The DPPH assay is a widely used method to evaluate the free radical scavenging ability of plant extracts. *Ficus benghalensis* latex has shown strong antioxidant activity in this assay, indicating its ability to neutralize free radicals. The latex effectively reduces DPPH free radicals, which suggests its potential to mitigate oxidative damage in RA (Gulcin & Alwasel, 2023).

Nitric Oxide Inhibition: Nitric oxide (NO) is another free radical involved in inflammatory responses. Excessive NO production can contribute to tissue damage and inflammation in RA. Studies on *Ficus benghalensis* latex have demonstrated its ability to inhibit NO production, likely through the downregulation of inducible nitric oxide synthase (iNOS), an enzyme responsible for the overproduction of NO during inflammation. This action may help reduce the oxidative stress associated with joint damage in RA (Lisi et al., 2021).

Lipid Peroxidation Studies: Lipid peroxidation is a key marker of oxidative damage, leading to cell membrane disruption and tissue injury. *Ficus benghalensis* latex has shown significant potential in preventing lipid peroxidation in both in vitro and in vivo studies. By reducing lipid peroxidation, the latex may help protect cellular integrity, especially in joint tissues affected by RA, thus reducing the progression of joint damage and promoting tissue healing (Gianazza et al., 2021).

C. Immunomodulatory Activity

Ficus benghalensis latex has been shown to exert immunomodulatory effects, which can be beneficial in regulating the immune response

in diseases like rheumatoid arthritis, where the immune system is dysregulated (Hooda et al., 2024).

Effect on T-cell Proliferation: T-cells are central players in the immune response, particularly in autoimmune diseases like RA. Studies have shown that *Ficus benghalensis* latex can modulate T-cell activity by inhibiting their proliferation. This may help in reducing the excessive immune response seen in RA, where T-cells attack the body's own joint tissues. By controlling T-cell proliferation, the latex may help to mitigate the inflammatory cascade associated with RA (X.-M. Zhang et al., 2020).

Macrophage Function: Macrophages are key immune cells that contribute to both the initiation and perpetuation of inflammation in RA. *Ficus benghalensis* latex has been shown to regulate macrophage function by modulating their secretion of pro-inflammatory cytokines such as TNF- α and IL-1 β . This effect could help reduce the inflammatory milieu within the synovium and prevent the chronic inflammation that characterizes RA (Hensvold & Klareskog, 2021).

Cytokine Inhibition: *Ficus benghalensis* latex has demonstrated the ability to inhibit the production of several pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6, which are crucial mediators of inflammation in RA. By inhibiting these cytokines, the latex helps to reduce the overall inflammatory response, alleviate pain, and protect against joint destruction in RA. The immunomodulatory effects of the latex may thus play a vital role in regulating the immune system in autoimmune diseases (S. Singh et al., 2020). *Ficus benghalensis* latex exhibits promising pharmacological activities, including significant anti-inflammatory, antioxidant, and immunomodulatory effects, which make it a potential therapeutic candidate for managing inflammatory conditions such as rheumatoid arthritis. The latex's ability to reduce inflammation, scavenge free radicals, and modulate immune responses suggests that it may offer a natural, adjunctive treatment option to complement current RA therapies. Further clinical studies are required to validate these findings and establish the therapeutic efficacy and safety of *Ficus benghalensis* latex in human RA patients (Murugesu et al., 2021).

Molecular Mechanisms of Action

Ficus benghalensis latex has demonstrated substantial pharmacological potential in modulating key molecular pathways involved in inflammation. These pathways are critical in diseases like rheumatoid arthritis (RA), where persistent inflammation and immune dysregulation contribute to tissue damage. Below, we explore the molecular mechanisms through which *Ficus benghalensis* latex exerts its anti-inflammatory effects (P. Singh et al., 2023).

A. Modulation of Pro-Inflammatory Cytokines

Pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 play pivotal roles in the initiation and maintenance of the inflammatory process in rheumatoid arthritis. *Ficus benghalensis* latex has been shown to modulate the production and activity of these cytokines, which are central to RA pathogenesis (Markovics et al., 2021).

Inhibition of TNF- α : TNF- α is one of the most important pro-inflammatory cytokines in RA. It is responsible for the recruitment of inflammatory cells to the site of inflammation and the activation of other inflammatory pathways. *Ficus benghalensis* latex inhibits the secretion of TNF- α , which reduces the inflammatory burden in the synovium and prevents further immune cell activation. By suppressing TNF- α , the latex helps decrease joint swelling, pain, and destruction seen in RA (Du et al., 2020).

Inhibition of IL-1 β : IL-1 β is another key cytokine in RA that amplifies inflammation, promotes cartilage degradation, and stimulates the production of other inflammatory mediators. *Ficus benghalensis* latex has been reported to reduce IL-1 β levels, thereby mitigating the inflammatory response in the joints. By inhibiting IL-1 β , the latex helps prevent the destructive processes that contribute to the progression of RA (Kondo et al., 2021).

Inhibition of IL-6: IL-6 is involved in the systemic inflammation and acute phase response in RA. Elevated IL-6 levels correlate with disease activity and progression in RA patients. *Ficus benghalensis* latex has shown the ability to downregulate IL-6 production, which may contribute to reducing the systemic inflammatory response, alleviating symptoms like fatigue and fever, and preventing the progression of joint damage (Favalli, 2020).

B. Regulation of COX-2 and iNOS Expression

Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are enzymes that play critical roles in the production of inflammatory mediators in RA. The regulation of these enzymes by *Ficus benghalensis* latex is a key mechanism by which it exerts its anti-inflammatory effects (Cinelli et al., 2020).

COX-2 Inhibition: COX-2 is an enzyme that catalyzes the production of prostaglandins, which are lipid mediators involved in inflammation and pain. Elevated levels of COX-2 are commonly found in RA patients, where they contribute to synovial inflammation and joint destruction. *Ficus benghalensis* latex inhibits COX-2 expression, thereby reducing the production of prostaglandins and alleviating pain and inflammation associated with RA (B. Kaur & Singh, 2022).

iNOS Inhibition: iNOS is responsible for the production of nitric oxide (NO), a molecule that plays a central role in the inflammatory response. In RA, excessive NO production leads to tissue damage and oxidative stress. *Ficus benghalensis* latex inhibits the expression of iNOS, thus reducing NO levels and mitigating the oxidative damage and inflammation in the joints. This inhibition of iNOS contributes to the overall reduction of inflammation in RA (Król & Kepinska, 2020).

C. NF- κ B Pathway Inhibition

The nuclear factor kappa B (NF- κ B) pathway is a critical regulator of inflammation. NF- κ B is a transcription factor that controls the expression of various pro-inflammatory genes, including cytokines, adhesion molecules, and enzymes involved in the inflammatory response. Dysregulation of NF- κ B is a hallmark of many inflammatory diseases,

including RA. *Ficus benghalensis* latex exerts its anti-inflammatory effects through the inhibition of the NF- κ B pathway (Alharbi et al., 2021).

Downregulation of Transcriptional Activation of Inflammatory Genes: In RA, the NF- κ B pathway is activated by various stimuli, leading to the transcriptional activation of genes that promote inflammation. *Ficus benghalensis* latex has been shown to inhibit the activation of NF- κ B, thereby reducing the transcription of pro-inflammatory genes. This inhibition results in a decrease in the production of inflammatory cytokines like TNF- α , IL-1 β , and IL-6, as well as the reduction of inflammatory enzymes such as COX-2 and iNOS. By suppressing the NF- κ B pathway, *Ficus benghalensis* latex helps prevent the amplification of the inflammatory cascade in RA, reducing joint inflammation and tissue damage (Ding et al., 2023).

Impact on Other Inflammatory Pathways: In addition to cytokine and enzyme regulation, NF- κ B also influences the expression of genes involved in cell survival, apoptosis, and immune cell recruitment. By inhibiting NF- κ B, *Ficus benghalensis* latex may also contribute to reducing the survival of inflammatory cells in the synovium and promote the resolution of inflammation. Moreover, NF- κ B inhibition may help decrease the formation of pannus, the abnormal tissue growth that invades cartilage and bone in RA (Guo et al., 2024).

Ficus benghalensis latex exerts its anti-inflammatory effects through the modulation of key molecular pathways involved in the inflammatory response in rheumatoid arthritis. By inhibiting pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, regulating the expression of COX-2 and iNOS, and downregulating the NF- κ B pathway, the latex offers a multifaceted approach to controlling inflammation. These molecular mechanisms suggest that *Ficus benghalensis* latex could serve as a valuable therapeutic option for managing RA, either alone or in combination with conventional treatments. Further research is needed to explore its clinical efficacy and safety in human RA patients (Gandhi et al., 2022).

Preclinical and Clinical Evidence

The potential of *Ficus benghalensis* latex as an anti-inflammatory agent for the management of rheumatoid arthritis (RA) has been explored through various preclinical studies. While clinical trials remain limited, the *in vivo* evidence supports its therapeutic efficacy. Additionally, safety and toxicological assessments are essential to establish the safety profile of *Ficus benghalensis* latex for human use. Below, we review the available preclinical data and safety studies to provide a comprehensive understanding of its therapeutic potential (Kamboj & Singh, 2022).

A. In Vivo Studies in Rheumatoid Arthritis Models

Preclinical studies using animal models of rheumatoid arthritis have demonstrated the anti-inflammatory potential of *Ficus benghalensis* latex. These studies often assess therapeutic outcomes, optimal dosage, and administration methods. Oral administration, typically in doses ranging from 50 mg/kg to 200 mg/kg, is common for evaluating systemic effects and has shown promising results in reducing joint swelling, pain, and histological damage. Topical application, used in models with acute inflammation, provides localized relief, suggesting its effectiveness for localized arthritis treatment. Both oral and topical routes have proven beneficial, with lower doses yielding positive effects without causing significant adverse reactions (Sahu et al., 2024).

Therapeutic Outcomes: In animal models, such as the Freund's Complete Adjuvant (FCA)-induced arthritis model, *Ficus benghalensis* latex has exhibited notable therapeutic effects. These include a significant reduction in joint swelling, as evidenced by decreased paw edema and inflammation. The latex also alleviates pain, reducing sensitivity and mechanical hyperalgesia, indicating its potential as an

analgesic. Histopathological improvements show reduced synovial infiltration, pannus formation, and cartilage degradation, suggesting its protective role in joint health. Additionally, *Ficus benghalensis* latex modulates inflammatory cytokines like TNF- α , IL-1 β , and IL-6. The therapeutic effects last up to two weeks, with chronic administration showing sustained efficacy without significant loss over time (Gupta et al., 2020).

B. Safety and Toxicological Assessments

Before *Ficus benghalensis* latex can be recommended for clinical use, it is essential to assess its safety profile. Several preclinical studies have evaluated both acute and chronic toxicity to determine the latex's potential for adverse effects in humans (Murugesu et al., 2021). Acute Toxicity Studies: Acute toxicity studies on *Ficus benghalensis* latex involve administering high doses to animals and monitoring for signs of toxicity. The latex demonstrates a relatively high safety margin, with no lethal effects observed at doses up to 2,000 mg/kg in rats and mice. Mild symptoms of gastrointestinal distress, such as diarrhea or slight lethargy, were noted at higher doses but resolved without long-term complications. No significant organ damage was reported, and histopathological examinations of the liver, kidney, and heart tissues showed no abnormalities, indicating that *Ficus benghalensis* latex does not cause major organ toxicity at tested doses (Ramasamy & Kathiresan, 2023).

Chronic Toxicity Studies: In a 30-day chronic toxicity study with rats, daily administration of *Ficus benghalensis* latex at 100 mg/kg showed no significant histopathological changes in organs such as the liver, kidney, or lungs. Blood parameters remained within normal ranges, indicating no harmful effects on organ function. Behavioral observations revealed no major changes, with animals maintaining normal activity and feeding patterns (Adusei-Mensah, 2020).

Safety Margins and Therapeutic Window: The safety margin of *Ficus benghalensis* latex, based on acute and chronic toxicity studies, suggests it is safe at therapeutic doses. The wide therapeutic window, the range between effective and toxic doses, supports its potential for treating inflammatory disorders like rheumatoid arthritis (RA). Preclinical studies demonstrate its anti-inflammatory, analgesic, and protective effects, reducing joint swelling, pain, and histopathological damage, alongside cytokine regulation. Safety assessments confirm no significant acute or chronic toxicity at therapeutic doses. While clinical trials are needed, preclinical evidence indicates that *Ficus benghalensis* latex could be an effective, safe, and natural adjunctive treatment for RA management (Salehi et al., 2021).

Challenges and Future Directions

Despite promising preclinical evidence, several challenges remain in the development of *Ficus benghalensis* latex as a therapeutic agent for rheumatoid arthritis. Standardization of latex extracts is crucial to ensure consistent potency and quality. Mechanistic and molecular validation through more rigorous studies is needed to fully understand its anti-inflammatory effects. Additionally, the potential for nanoformulations or targeted drug delivery systems could enhance the efficacy and bioavailability of the latex. Finally, clinical trials are essential to confirm its safety and efficacy in humans, while regulatory considerations must be addressed for its approval as a therapeutic agent (C. Kaur et al., 2024).

Conclusion

Ficus benghalensis latex demonstrates significant potential as an anti-inflammatory agent in the management of rheumatoid arthritis (RA). Preclinical studies have highlighted its ability to modulate key inflammatory pathways, including the inhibition of pro-inflammatory cytokines, COX-2, iNOS, and the NF- κ B pathway. Additionally, it shows antioxidant properties that contribute to mitigating oxidative stress,

a central feature in RA. The latex's effects in animal models suggest it could serve as a novel adjunct or alternative therapy for RA, particularly in combination with conventional treatments. However, further research is necessary to standardize the latex extracts, validate its mechanisms of action, and explore innovative delivery systems, such as nanoformulations. Interdisciplinary approaches, integrating pharmacology, molecular biology, and drug delivery technologies, will be crucial in advancing our understanding of its therapeutic potential and ensuring its safe application in clinical settings.

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