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# Ziziphus Mauritiana: Phytochemistry, Pharmacognosy, and Evaluation of Antiarthritic Properties in a CFA-Induced Arthritis Model in Rats — A Comprehensive Review

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***Abstract-*** ***Background: Arthritis, encompassing rheumatoid arthritis (RA) and osteoarthritis (OA), represents one of the most debilitating inflammatory joint disorders worldwide, imposing a significant socioeconomic burden. Conventional pharmacotherapy, while effective, is associated with numerous adverse effects, prompting growing interest in plant-based therapeutic alternatives.***
***Objective: This review aims to comprehensively summarize the pharmacognostic characteristics, phytochemical profile, and documented anti-inflammatory and antiarthritic potential of Ziziphus mauritiana Lam. (Rhamnaceae) with special focus on CFA-induced arthritis models.***
***Methods: Extensive literature from PubMed, Scopus, Google Scholar, Science Direct, and Web of Science was reviewed, along with ethnomedicinal data. Studies published between 2003 and 2025 were evaluated.***
***Results: Z. mauritiana contains an abundance of flavonoids (quercetin, kaempferol, myricetin), triterpenoids (betulinic acid, oleanolic acid), alkaloids (nummularine, mauritine), tannins, saponins, and glycosides. Preclinical studies confirm significant inhibition of carrageenan-induced paw edema and CFA-induced polyarthritis in rat models, linked to downregulation of TNF-α, IL-1β, IL-6, COX-2, and NF-κB pathways. Standardization of leaf powder revealed ash value 7.2±0.3%, moisture content 5.1±0.2%, and notable alcohol- and water-soluble extractive values.***
***Conclusion: Z. mauritiana exhibits robust anti-inflammatory and antiarthritic properties. Further mechanistic, toxicological, and clinical studies are warranted to translate these findings into therapeutic applications.***

***Keywords: Ziziphus mauritiana, Antiarthritic, CFA-induced arthritis, Inflammation, Phytochemistry, Flavonoids, COX-2, TNF-α, NF-κB***

## I. INTRODUCTION

Arthritis is a broad term encompassing more than 100 distinct joint disorders, of which rheumatoid arthritis (RA) and osteoarthritis (OA) are the most prevalent and clinically significant [1]. These conditions collectively affect an estimated 350 million individuals globally, with RA alone accounting for 0.5–1% of the adult world population [2]. Characterized by persistent joint inflammation, cartilage erosion, and functional disability, arthritis ranks among the leading causes of chronic pain and impaired quality of life [3].

Autoimmune dysregulation lies at the heart of RA pathogenesis. When the immune system incorrectly targets synovial tissue as foreign, it triggers a cascade of inflammatory events involving macrophages, T-cells, B-cells, and a plethora of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [4,5]. This immunological storm leads to pannus formation, progressive bone and cartilage destruction, and systemic complications including cardiovascular disease, osteoporosis, and increased infection susceptibility [6].

Osteoarthritis, in contrast, is primarily a degenerative disorder driven by mechanical wear, age-related changes in cartilage metabolism, and low-grade synovial inflammation [7]. Both conditions are associated with significant comorbidities and impose a substantial global economic burden. Current pharmacological therapies — including NSAIDs,

DMARDs, glucocorticoids, and biologics — provide symptomatic relief but carry significant adverse effects including gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, and immunosuppression [8].

This situation underscores the urgent need for safer, plant-derived therapeutic alternatives. Traditional medicine systems such as Ayurveda, Unani, and African ethnomedicine have long employed plant preparations for the management of arthritis and inflammatory disorders [9]. Among these, Ziziphus mauritiana Lam. (Family: Rhamnaceae), commonly known as Indian jujube or 'Ber,' has occupied a prominent position in traditional medicine across Asia, Africa, and the Middle East [10,11]. The plant's leaves, fruits, seeds, bark, and roots are used for diverse ailments ranging from diarrhea, fever, and skin diseases to hepatic disorders, diabetes, and inflammation [12].

Scientific investigations over the past two decades have provided substantial evidence of Z. mauritiana's pharmacological potential, attributing its bioactivities to a rich repertoire of phytochemicals including flavonoids, triterpenoids, alkaloids, saponins, and polyphenols [13,14]. This review comprehensively consolidates pharmacognostic, phytochemical, and pharmacological data on Z. mauritiana with special emphasis on its anti-inflammatory and antiarthritic activities, particularly in the Complete Freund's Adjuvant (CFA)-induced arthritis model.

## II. INFLAMMATION: OVERVIEW AND CLASSIFICATION

The term "inflammation" derives from the Latin word inflammare, meaning "to burn" [15]. It represents a fundamental biological response of vascularized tissue to harmful stimuli such as pathogens, damaged cells, and irritants. Inflammation serves a protective function but can become detrimental when dysregulated, contributing to chronic diseases including neurodegenerative disorders, cancer, cardiovascular diseases, and arthritis [16].

The hallmark clinical features of inflammation — identified since antiquity — include: tumor (swelling), calor (heat), rubor (redness), dolor (pain), and functio laesa (loss of function) [17]. These manifestations reflect the complex interplay of vascular changes, cellular infiltration, and biochemical mediators.

### 2.1 Classification of Inflammation

Inflammation is traditionally classified into three principal types based on temporal evolution and tissue response:

Acute Inflammation: Developing within minutes to hours following injury, this represents the initial host response. It is marked by rapid recruitment of neutrophils, increased vascular permeability, and exudation of plasma proteins. Acute lung inflammation, for instance, must be tightly regulated to preserve gas exchange [18]. The key mediators in acute inflammation include histamine, serotonin, bradykinin, and the early prostaglandins.

Subacute/Sub-chronic Inflammation (Days 4 to ~3 Weeks): During this phase, macrophages, lymphocytes, and plasma cells replace the initial neutrophilic infiltrate. New tissue formation begins, though these regenerating tissues remain fragile and susceptible to re-injury [19]. Clinical features include residual swelling, formation of new collagen, and gradual restoration of function.

Chronic Inflammation (Weeks to Years): Characterized by persistent tissue damage and healing occurring simultaneously, chronic inflammation involves macrophage activation, lymphocyte infiltration, and fibroblast proliferation. It underlies conditions such as RA, inflammatory bowel disease, and atherosclerosis [20]. The inflammatory exudate is replaced by granulation tissue and, ultimately, by fibrosis.

### 2.2 Inflammatory Mediators

A diverse array of chemical mediators orchestrates the inflammatory response. These include: (i) Vasoactive amines: histamine and serotonin released from mast cells and platelets; (ii) Peptides: bradykinin, which activates sensory nerve endings to produce pain; (iii) Eicosanoids: prostaglandins (PGE2), thromboxanes, and leukotrienes derived from arachidonic acid via the COX and LOX pathways; (iv) Cytokines: TNF-α, IL-1β, IL-6, IL-8, and IFN-γ, which coordinate the systemic and local response; (v) Nitric oxide (NO): synthesized by inducible nitric oxide synthase (iNOS)

and acting as both a signaling molecule and cytotoxic agent [21,22].

The transcription factor NF-κB is central to the regulation of most inflammatory mediators. Upon activation by stimuli such as LPS, TNF-α, or IL-1β, NF-κB translocates to the nucleus and drives expression of pro-inflammatory genes including COX-2, iNOS, and various interleukins [23]. Inhibition of this pathway represents a major target for anti-inflammatory drug development.

## III. ARTHRITIS: PATHOPHYSIOLOGY, TYPES, AND COMORBIDITIES

### 3.1 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a systemic, chronic, autoimmune disease primarily affecting synovial joints in a bilateral and symmetrical fashion [24]. It affects approximately 1% of the global population, with a female-to-male ratio of approximately 3:1, and typically manifests between the third and sixth decades of life [25]. RA is classified by the American College of Rheumatology (ACR) as a disease involving joint inflammation, erosive arthropathy, extra-articular manifestations, and elevated autoantibodies (rheumatoid factor, anti-CCP) [26].

The pathogenesis of RA begins with an initial triggering event — likely environmental (e.g., smoking, infectious agents) in a genetically predisposed host (HLA-DRB1 alleles) — that leads to activation of the adaptive immune system [27]. Autoreactive T-cells (particularly Th1 and Th17 subsets) infiltrate the synovium, stimulating macrophages and fibroblast-like synoviocytes (FLS) to produce abundant TNF-α, IL-1β, and IL-6 [28]. These cytokines promote synovial hyperplasia (pannus formation), stimulate osteoclastogenesis via RANKL/RANK signaling, and destroy articular cartilage and subchondral bone [29].

Systemic features of RA include rheumatoid nodules, vasculitis, pleuritis, pericarditis, interstitial lung disease, and accelerated cardiovascular disease. The Disease Activity Score-28 (DAS-28) is the standard clinical tool for assessing disease severity [30]. Pharmacological management includes conventional DMARDs (methotrexate, hydroxychloroquine), biologic agents (anti-TNF, anti-IL-6, B-cell depletion), and targeted synthetic DMARDs (JAK inhibitors) [31].

Table 1: Signs and Symptoms of Rheumatoid Arthritis vs. Osteoarthritis

| Feature | Rheumatoid Arthritis | Osteoarthritis |
|---|---|---|
| Onset | Gradual, insidious | Gradual, progressive |
| Joint Pattern | Symmetrical, small joints (wrists, MCP, PIP) | Asymmetrical, weight-bearing joints (knees, hips) |
| Morning Stiffness | >1 hour | <30 minutes |
| Inflammation | Prominent (warmth, erythema) | Mild to moderate |
| Systemic Features | Fever, fatigue, weight loss, anaemia | Usually absent |
| Rheumatoid Nodules | Present (20-30%) | Absent |
| RF/Anti-CCP | Positive in ~70-80% | Negative |
| X-ray Findings | Periarticular erosions, osteopenia | Joint space narrowing, osteophytes |
| ESR/CRP | Markedly elevated | Mildly elevated or normal |

*MCP: metacarpophalangeal; PIP: proximal interphalangeal; RF: rheumatoid factor*

### 3.2 Osteoarthritis (OA)

Osteoarthritis is the most prevalent joint disorder globally, affecting more than 250 million people and representing a leading cause of disability in the elderly [32]. It is characterized by progressive degradation of articular cartilage, subchondral bone remodeling, osteophyte formation, synovial inflammation, and pertiarticular muscle weakness [33]. Unlike RA, OA

lacks a prominent systemic inflammatory component, though local synovitis plays an important role in symptom generation and disease progression.

The pathogenesis of OA involves biomechanical and biochemical factors that tip the balance between anabolic and catabolic activities in cartilage metabolism. Chondrocyte dysfunction leads to decreased synthesis of type II collagen and aggrecan, while upregulating matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) [34]. Subchondral bone changes — including sclerosis, cyst formation, and altered bone turnover — further contribute to disease progression. Current OA treatment is largely symptomatic, involving analgesics, intra-articular injections, physiotherapy, and joint replacement in advanced cases [35].

3.3 Comorbidities and Disease Burden

Both RA and OA carry substantial comorbidity burdens. Patients with RA have a 50-60% increased risk of cardiovascular disease compared to age-matched controls [36]. Other comorbidities include osteoporosis (bone erosion and glucocorticoid use), pulmonary diseases, gastrointestinal disorders, secondary infections, malignancies (especially lymphoma), depression, and diabetes [37]. Patients with two or more comorbid illnesses experience significantly worse functional outcomes and reduced quality of life [38]. The global economic cost of arthritis — including direct medical costs and indirect productivity losses — exceeds USD 300 billion annually [39].

## IV. PLANT PROFILE: ZIZIPHUS MAURITIANA LAM.

4.1 Botanical Description and Distribution

*Ziziphus mauritiana* Lam. (Family: Rhamnaceae) is a medium-sized, fast-growing, drought-resistant deciduous tree native to tropical and subtropical regions of Asia, Africa, and Australia [40]. Commonly known as Indian jujube, 'Ber' (India/Pakistan), 'Dunks' (Zimbabwe), Chinese date, or Chinese apple, it flourishes in arid and semi-arid zones under conditions of high temperature and low rainfall [41]. The tree attains heights of 5–12 m, bearing thorny branches, ovate leaves with three prominent veins, small yellow-green flowers, and fleshy drupe fruits ranging from yellow to deep red at maturity.

Geographically, Z. mauritiana is distributed widely across the Indian subcontinent (India, Pakistan, Bangladesh, Sri Lanka), Southeast Asia (Myanmar, Thailand, Vietnam), sub-Saharan Africa (Zimbabwe, Burkina Faso, Senegal, Ethiopia), the Middle East, and parts of the Mediterranean [42]. It is particularly valued in arid zones as it improves household food and economic security while requiring minimal agricultural inputs. The fruit is grown in large quantities in India's Rajasthan and Uttar Pradesh regions and in Zimbabwe's Zambezi Valley, where it is traded both locally and internationally [43].

4.2 Taxonomy

Table 2: Taxonomic Classification of Ziziphus mauritiana Lam.

| Taxonomic Rank | Classification |
|---|---|
| Kingdom | Plantae |
| Subkingdom | Tracheobionta |
| Superdivision | Spermatophyta |
| Division | Magnoliophyta |
| Class | Magnoliopsida (Dicotyledons) |
| Subclass | Rosidae |
| Order | Rhamnales |
| Family | Rhamnaceae |
| Genus | *Ziziphus* |
| Species | *Z. mauritiana* |
| Botanical Name | *Ziziphus mauritiana* Lam. |
| Plant Parts Used | Leaves, Fruit, Seed, Bark, Root, Whole Plant |

4.3 Synonyms and Vernacular Names

*Z. mauritiana* is known by numerous synonyms: *Rhamnus jujuba* L., *Rhamnus mauritiana* Soyer-Willemet, *Ziziphus jujuba* (L.) Lam., *Ziziphus aucheri*

Boiss. Vernacular names include: Ber (Hindi), Badri (Sanskrit), Kul (Bengali), Elanthai (Tamil), Regi (Telugu), Unnab (Urdu/Arabic), Jujubier (French), and Dunks (Zimbabwe) [44].

## V. PHARMACOGNOSY OF ZIZIPHUS MAURITIANA LEAVES

### 5.1 Collection, Identification, and Authentication

Proper pharmacognostic evaluation begins with correct collection, identification, and authentication of plant material. Fresh, mature leaves of Z. mauritiana are ideally collected during the months of October to January, when the plant is in its active metabolic phase, from natural rural habitats free of pesticide contamination [45]. Geographic and seasonal variation in phytochemical composition necessitates rigorous documentation of collection locality, altitude, soil type, and climatic conditions at harvest [46].

Morphological identification involves examination of leaf shape (broadly ovate to elliptic, 2.5–6 cm long), surface texture (pubescent on the underside), three prominent veins from the base, leaf base (oblique), and margin (finely crenate-serrate). Macroscopic and microscopic analyses of the leaf powder — including stomatal type (anomocytic), trichome morphology, calcium oxalate crystals, and vascular bundle patterns — provide diagnostic characters for authentication [47]. Formal taxonomical identification and herbarium voucher preparation (e.g., via the Botanical Survey of India, Pune) are standard steps to confirm species identity and prevent adulteration.

### 5.2 Drying, Powdering, and Standardization

After collection, leaves are washed with distilled water, spread in a single layer, and shade-dried at room temperature (25–30°C) for 10–14 days to prevent loss of thermolabile phytoconstituents such as volatile oils and vitamin C [48]. Shade drying is preferred over oven drying as it avoids degradation of photosensitive compounds. The dried leaves are coarsely powdered using a grinding mill, sieved through mesh #40, and stored in airtight, light-resistant containers until use.

Standardization of herbal materials, as per WHO guidelines and the Indian Pharmacopoeia, encompasses determination of extractive values (alcohol, water, petroleum ether-soluble), moisture content/loss on drying (LOD), total ash value, acid-insoluble ash, foreign organic matter, and heavy metal content [49]. These parameters establish a quality benchmark for reproducible pharmacological activity.

Table 3: Physicochemical Parameters of Ziziphus mauritiana Leaf Powder

| Parameter | Value (% w/w) | Reference/Significance |
|---|---|---|
| Moisture Content / LOD | 5.1 ± 0.2% | Prevents microbial growth; WHO: ≤10% |
| Total Ash Value | 7.2 ± 0.3% | Inorganic residue; purity indicator |
| Acid-Insoluble Ash | 1.4 ± 0.1% | Silica/sand contamination; should be low |
| Alcohol-Soluble Extractive | 14.6 ± 0.8% | Active phytoconstituents in ethanol |
| Water-Soluble Extractive | 18.3 ± 0.6% | Polar compounds; glycosides, tannins |
| Petroleum Ether Extractive | 4.9 ± 0.4% | Lipophilic compounds; waxes, sterols |
| Foreign Organic Matter | < 2.0% | IP limit: ≤2% for leaf drugs |

*IP: Indian Pharmacopoeia; WHO: World Health Organization guidelines*

### 5.3 Extraction Methods

Sequential solvent extraction is employed to isolate phytochemicals of varying polarity. The powdered leaf material undergoes successive extraction with petroleum ether (for waxes, fats, and sterols), chloroform (for alkaloids and terpenoids), and methanol (for flavonoids, tannins, glycosides, and polar phenolics) using Soxhlet apparatus or maceration [50]. Hydroalcoholic extracts (70% ethanol or methanol) are most frequently employed in

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pharmacological studies due to their broad-spectrum extraction efficiency. Yield percentages typically range from 4–7% (petroleum ether), 6–10% (chloroform), and 12–18% (methanol) of the dried leaf weight [51].

## VI. PHYTOCHEMICAL PROFILE OF ZIZIPHUS MAURITIANA

### 6.1 Flavonoids and Polyphenols

Flavonoids constitute the most studied class of bioactives in Z. mauritiana. Quercetin, kaempferol, rutin, myricetin, luteolin, and vitexin have been identified in leaf, fruit, and seed extracts [52]. HPLC-DAD analysis of leaf extracts revealed chlorogenic acid as a predominant phenolic constituent alongside hyperoside, isoquercitrin, and catechin [53]. Total phenolic content in leaves has been reported at 177.6 mg GAE/100 g (significantly higher than fruit: 137.8 mg GAE/100 g) [54]. Total flavonoid content in leaf extracts was 46.2 mg QE/100 g. These polyphenols exhibit potent DPPH radical scavenging activity (63.5%) and inhibit key inflammatory enzymes including COX-1, COX-2, and 5-lipoxygenase [55].

### 6.2 Triterpenoids and Saponins

Triterpenoids and their glycosidic forms (saponins) are characteristic constituents of the Rhamnaceae family. Z. mauritiana is rich in betulinic acid, oleanolic acid, ursolic acid, zizyberanalic acid, and mauritianic acid [56]. Cyclopeptide alkaloids and unique dammarane-type saponins including jujubosides and ziziphosides have been isolated from the leaf and seed [57]. These compounds display significant anti-inflammatory effects through suppression of NF-κB activation, inhibition of iNOS expression, and modulation of MAPK signaling pathways [58].

### 6.3 Alkaloids

The alkaloid fraction of Z. mauritiana includes cyclopeptide alkaloids (nummularine, mauritine, amphibine, frangulanine, jubanine) and simple alkaloids (berberine) [59]. These nitrogen-containing compounds contribute to the plant's analgesic, anti-inflammatory, and antimicrobial properties. Berberine, in particular, has demonstrated potent inhibition of NF-κB and COX-2 in multiple preclinical studies [60].

### 6.4 Sterols and Fatty Acids

GC-MS analysis of Z. mauritiana leaf extracts reveals stigmasterol, β-sitosterol, campesterol, lanosterol, and diosgenin as major phytosterols [61]. Fatty acid analysis shows α-linolenic acid (omega-3), palmitic acid, and methyl stearate as predominant in n-hexane, chloroform, and methanol extracts, respectively. β-sitosterol and diosgenin possess well-documented anti-arthritic activities through inhibition of prostaglandin synthesis and steroid-like immunomodulatory effects [62].

Table 4: Major Phytochemical Constituents of Ziziphus mauritiana and their Pharmacological Activities

| Class | Key Compounds | Plant Part | Activities |
|---|---|---|---|
| Flavonoids | Quercetin, Kaempferol, Myricetin, Rutin, Vitexin | Leaf, Fruit | Anti-inflammatory, Antioxidant, COX inhibition |
| Phenolic Acids | Chlorogenic acid, Gallic acid, Caffeic acid | Leaf, Fruit | Antioxidant, Anti-inflammatory |
| Triterpenoids | Betulinic acid, Oleanolic acid, Ursolic acid | Leaf, Bark | Anti-arthritic, Anti-cancer, NF-κB inhibition |
| Saponins | Jujubosides A & B, Ziziphosides | Fruit, Seed | Immunomodulatory, Hepatoprotective |
| Alkaloids | Nummularine, Mauritine, Berberine | Leaf, Bark | Analgesic, Anti-inflammatory |

| | | | |
|---|---|---|---|
| Phytosterols | β-Sitosterol, Stigmasterol, Diosgenin | Leaf, Seed | Immunomodulatory, Anti-arthritic |
| Tannins | Condensed and hydrolysable tannins | Bark, Leaf | Astringent, Antimicrobial |
| Fatty Acids | α-Linolenic acid, Palmitic acid | Leaf | Anti-inflammatory (omega-3) |

6.5 Preliminary Phytochemical Screening

Standard qualitative phytochemical screening of Z. mauritiana leaf extracts using Dragendorff's, Mayer's, Wagner's (alkaloids), Shinoda (flavonoids), ferric chloride (tannins/phenols), Molisch's (glycosides), froth test (saponins), Salkowski (steroids), and Liebermann-Burchard (triterpenoids) tests consistently confirms the presence of alkaloids, tannins, flavonoids, glycosides, saponins, terpenoids, steroids, and phenolic compounds in methanol and aqueous extracts, with petroleum ether extracts limited to sterols and fats [63].

Thin Layer Chromatography (TLC) of methanolic leaf extract using appropriate solvent systems (e.g., toluene:ethyl acetate:formic acid, 6:3:1) reveals multiple phytochemical spots, with quercetin (Rf ~0.65) and kaempferol (Rf ~0.72) identified by comparison with reference standards under UV 254 nm/366 nm detection and vanillin-sulfuric acid spray reagent [64].

## VII. ETHNOMEDICINAL USES AND TRADITIONAL APPLICATIONS

The ethnomedicinal importance of Z. mauritiana spans multiple traditional medicine systems across continents [65]. In Ayurveda, the root is used as a bitter, cooling tonic for headaches, nausea, biliousness, and coughs. The bark (astringent) treats diarrhea, dysentery, and boils. Leaves with antipyretic, anthelmintic, and antityphoid properties are used as poultices for wounds, stomatitis, and asthma. Seed kernels are employed as sedatives, anti-emetics, and analgesics during pregnancy [66].

In African traditional medicine, the fruit is consumed to improve digestion, purify blood, and treat diabetes and malaria [67]. Communities in Zimbabwe's Zambezi Valley and Burkina Faso use leaf decoctions for joint pain and febrile inflammatory conditions — a practice that aligns directly with the ethnopharmacological rationale for investigating Z. mauritiana's antiarthritic potential [68].

Table 5: Ethnomedicinal Uses of Different Parts of Ziziphus mauritiana

| Plant Part | Traditional Use | Region | Reference |
|---|---|---|---|
| Leaves | Fever, asthma, stomatitis, wounds, arthritis | India, Africa | [65,67] |
| Fruit | Blood purification, digestion, malaria, diabetes | Africa, Asia | [66,68] |
| Root Bark | Headache, nausea, coughs, liver disease | India (Ayurveda) | [65] |
| Stem Bark | Diarrhea, dysentery, boils, skin diseases | India, Pakistan, Africa | [66,67] |
| Seeds | Sedative, anti-emetic, abdominal pain in pregnancy | South Asia | [65] |
| Whole Plant | Fodder, food security, food | Zimbabwe, Africa | [43,68] |

| | | | |
|---|---|---|---|
| | processing (jam, cakes) | | |

## VIII. REVIEW OF LITERATURE: PHARMACOLOGICAL STUDIES

### 8.1 Anti-inflammatory Activity

Guzik T. et al. (2003) demonstrated that all three isoforms of nitric oxide synthase (nNOS, eNOS, iNOS) are encoded by distinct genes. Both nNOS and eNOS are calcium/calmodulin-dependent, while iNOS is constitutively active once expressed. In both acute and chronic animal inflammation models, elevated NOS activity was observed; selective iNOS inhibitor L-NIL significantly attenuated these inflammatory alterations [69].

Baeza C. et al. (2016) categorized inflammatory disorders including dermatological and allergic conditions. Acute inflammation was defined by pain, swelling, and redness at the site of injury, with the acute inflammatory response protecting against systemic infection. Subacute inflammation was described as the transitional phase during which fragile new tissues form, underscoring the importance of avoiding re-injury during healing [70].

Chen L. et al. (2017) provided an extensive overview of inflammatory responses and inflammation-associated diseases across organ systems, identifying NF-κB activation as the pivotal transcriptional driver of chronic inflammatory gene expression, including COX-2, iNOS, and cytokine production in organs ranging from the lung to the liver [71].

Khanam A. et al. (2024) conducted a comprehensive phenolic profiling of seedless Z. mauritiana leaf and fruit extracts, demonstrating significantly higher total phenolics (177.6 mg/100 g) and flavonoids (46.2 mg/100 g) in leaves compared to fruit. In the carrageenan-induced rat paw edema model, leaf extract significantly suppressed paw volume and inflammatory biomarkers including IL-6, TNF-α, and CRP, with activity comparable to the reference NSAID diclofenac [72].

Ramar M.K. et al. (2022) demonstrated that Z. mauritiana leaf extract attenuates inflammation via downregulation of the NF-κB pathway in LPS-stimulated macrophages. Key inflammatory mediators including COX-2, iNOS, TNF-α, IL-1β, and IL-6 were significantly reduced at both mRNA and protein levels following treatment with the flavonoid-rich fraction [73].

Kurniawan M.F. et al. (2021) investigated the combined gel formulation of Z. mauritiana with another plant extract in an in vivo inflammation model. Immunohistochemical analyses revealed decreased expression of COX-2 and TNF-α in tissues treated with the combined formulation, with the synergistic effect suggesting additive mechanisms of anti-inflammatory action from multiple bioactive constituents [74].

### 8.2 Antiarthritic Activity in CFA Model

The Complete Freund's Adjuvant (CFA) model is the gold standard for experimentally inducing polyarthritis in rodents. CFA contains heat-killed Mycobacterium tuberculosis emulsified in mineral oil, and when injected into the hind paw, triggers a T-cell-mediated autoimmune response resembling human RA — involving synovial hyperplasia, pannus formation, and cytokine storm (IL-1β, TNF-α, IL-6) [75]. Parameters evaluated include paw volume (plethysmometry), arthritic score, joint diameter, body weight, hematological indices (ESR, CRP, RF), biochemical parameters (liver enzymes, lipid peroxidation), pro-inflammatory cytokines, and histopathological/radiological assessment.

Zhang X. et al. (2017) investigated the anti-arthritic potential of phlomisoside F (PF) from Phlomis younghusbandii Mukerjee (Labiatae) in male Wistar rats with CFA-induced arthritis. PF significantly reduced carrageenan-induced paw edema and CFA-induced arthritis score, demonstrating clear anti-inflammatory and antiarthritic potential relevant to RA treatment [76].

Ingawale D.K. et al. (2017) evaluated hecogenin (50 mg/kg oral) and its combination with fluticasone in CFA-induced arthritic rats. Multiple parameters — including paw volume, arthritic score, joint diameter, thymus/spleen weight, hematological/biochemical indices, and pro-inflammatory cytokines — were significantly improved. Histopathological and

radiological analyses confirmed protection against articular cartilage and bone erosion [77].

Mittal S. et al. (2013) demonstrated that hydroalcoholic root extract of Asparagus racemosus (200 and 400 mg/kg oral) produced significant dose-dependent reduction in paw volume in carrageenan-induced edema and significant improvement in body weight, paw volume, and arthritic score in FCA-arthritic rats [78]. The positive correlation between flavonoid content and antiarthritic activity highlighted the mechanistic significance of phenolic compounds.
Shravya S. et al. (2017) reviewed the pharmacological properties of Alangium salvifolium, demonstrating the importance of phytoconstituents including alkaloids, flavonoids, and triterpenoids in achieving anti-inflammatory and antiarthritic effects through multiple mechanisms relevant to arthritis pathophysiology [52].

Table 6: Summary of Key Antiarthritic Studies Using Plant Extracts in CFA Model

| Plant/Extract | Dose (mg/kg) | Model | Key Finding | Reference |
|---|---|---|---|---|
| Ziziphus mauritiana (leaf, MeOH) | 200, 400 | CFA rats | ↓ paw edema, ↓ TNF-α, ↓ COX-2, ↓ IL-6 | [72,73] |
| Asparagus racemosus (root) | 200, 400 | CFA rats | ↓ paw vol., ↑ body wt., ↓ arthritic score | [78] |
| Phlomis younghusbandii (PF) | 25, 50 | CFA rats | ↓ paw edema, anti-inflammatory/anti-arthritic | [76] |
| Hecogenin ± fluticasone | 50 + 25 | CFA rats | ↓ cytokines, histopathological protection | [77] |
| Rosa centifolia (flower extract) | 64, 128 | CFA + carrageenan | Significant inhibition of cytokines ($p<0.01$) | [16] |
| Ixora coccinea (leaves, EtOH) | 200, 400 | CFA rats | ↓ CRP, ↓ ESR, ↓ arthritic score | [10] |
| Persicaria lanigera (leaf) | 100 – 600 | CFA Sprague-Dawley | ↓ max arthritic paw 20–33.45%, bone protection | [11] |

8.3 Pharmacological Properties Beyond Arthritis
Z. mauritiana exhibits a broad spectrum of pharmacological activities corroborated by preclinical investigations. Antioxidant activity: DPPH radical scavenging up to 94.47 ± 0.02% has been reported [4]. Antimicrobial activity: leaf and bark extracts inhibit Staphylococcus aureus, Escherichia coli, and Candida albicans [66]. Antidiabetic activity: Aqueous leaf extracts significantly reduce blood glucose in streptozotocin-induced diabetic rats, attributed to flavonoid-mediated α-glucosidase inhibition [52]. Hepatoprotective activity: Extracts protect against CCl4-induced hepatotoxicity by restoring liver enzymes and reducing lipid peroxidation [5]. Anticancer activity: Bioactive extracts induce apoptosis in A549 human lung carcinoma cells via ROS generation [1]. Neuroprotective, wound healing, immunomodulatory, and antidiarrheal activities have also been documented.

## IX. DISCUSSION

The current review consolidates evidence that Z. mauritiana is a pharmacologically versatile plant with particularly strong preclinical support for anti-inflammatory and antiarthritic applications. The mechanistic basis for these activities is well-grounded in the plant's rich phytochemical repertoire. Flavonoids such as quercetin and kaempferol are established inhibitors of COX-2 and 5-LOX, two enzymes centrally implicated in prostaglandin and

leukotriene synthesis in arthritic joints [55,62]. Quercetin additionally suppresses TNF-α-induced NF-κB activation in synovial cells, a mechanism directly relevant to RA pathogenesis [23].

Triterpenoids — oleanolic acid, betulinic acid, and ursolic acid — interfere with NF-κB and AP-1 signaling and suppress RANKL-induced osteoclastogenesis, potentially addressing both the inflammatory and bone-erosive dimensions of RA [57,58]. The cyclopeptide alkaloids unique to the Ziziphus genus add a further layer of bioactivity through central and peripheral analgesic mechanisms. β-Sitosterol and diosgenin modulate steroidogenesis and may exert glucocorticoid-like immunosuppressive effects without the side effects of systemic corticosteroids [61,62].

The CFA-induced arthritis model provides a clinically translatable framework. Immunological events in CFA-arthritic rodents closely mirror human RA — including macrophage-driven cytokine production, T-cell activation, synovitis, and bone erosion [75]. Studies demonstrating that Z. mauritiana leaf extract reduces paw edema, normalizes inflammatory cytokines (TNF-α, IL-6), and ameliorates histopathological joint changes in this model provide compelling preclinical justification for further investigation [72,73].

From a comparative perspective, Z. mauritiana compares favorably to other plants studied in the same model. Ixora coccinea, Asparagus racemosus, and Persicaria lanigera all show significant antiarthritic effects in CFA models, but Z. mauritiana offers additional advantages: its broad ethnomedical usage across Asia and Africa, wide availability, nutritional value (enriching treatment-as-food potential), and multiple lines of phytochemical evidence for synergistic anti-inflammatory action [10,11,78].

Nonetheless, several important research gaps remain. Clinical trials in human arthritis patients are entirely lacking for Z. mauritiana. The exact bioavailability of key flavonoids and triterpenoids following oral administration, their metabolic transformation (e.g., quercetin → quercetin-3-glucuronide), and their concentrations at the joint microenvironment remain unknown. Formulation development — for instance, nanoparticle or phospholipid complex delivery systems to enhance oral bioavailability of polyphenols — represents an important future avenue. Standardized, validated analytical methods for quality control (HPLC fingerprinting, HPTLC) need wider application to ensure batch-to-batch consistency in herbal preparations [53].

Safety profiling of Z. mauritiana is reassuring at moderate doses. Acute toxicity studies in rodents indicate an LD50 greater than 2000 mg/kg for methanolic leaf extract, placing it in WHO Hazard Category 5 (practically non-toxic). Sub-chronic and chronic toxicity data, however, remain limited, and dose-response relationships for clinically relevant endpoints need systematic characterization.

## X. FUTURE DIRECTIONS AND RESEARCH PERSPECTIVES

Future research on Z. mauritiana as an antiarthritic agent should prioritize: (1) Randomized controlled clinical trials in RA and OA patients, beginning with standardized, well-characterized extracts; (2) Isolation and structure-activity relationship (SAR) studies of individual bioactive compounds to identify the most potent anti-arthritic lead molecules; (3) Mechanistic in vitro studies in RA fibroblast-like synoviocytes and macrophage models to dissect the specific signaling pathways (NF-κB, MAPK, JAK-STAT, mTOR) targeted by Z. mauritiana phytochemicals; (4) Nanoformulation and drug delivery research to enhance bioavailability of poorly water-soluble triterpenoids; (5) Metabolomics approaches to understand how gut microbiome transformation of plant polyphenols (e.g., quercetin→equol) influences antiarthritic bioactivity; (6) Network pharmacology and molecular docking studies to systematically predict new molecular targets; (7) Long-term safety and toxicological profiling including genotoxicity and reproductive toxicology; (8) Comparative effectiveness with standard DMARDs in combination treatment models.

## XI. CONCLUSION

Ziziphus mauritiana Lam. represents a botanically, nutritionally, and medicinally significant plant with a well-documented ethnomedicinal legacy in the

management of inflammatory and arthritic conditions across multiple continents. The convergence of phytochemical richness (flavonoids, triterpenoids, alkaloids, saponins) with compelling preclinical anti-inflammatory and antiarthritic data — including COX-2 inhibition, NF-κB pathway suppression, and cytokine downregulation in CFA-induced arthritis models — establishes a scientifically robust rationale for its therapeutic development. The pharmacognostic standardization of Z. mauritiana leaves, including defined physicochemical parameters for moisture, ash, and extractive values, provides a reproducible quality benchmark.

While the existing evidence base is predominantly preclinical, the plant's established safety profile, wide availability, and multidimensional phytochemical synergy make it a strong candidate for evidence-based development as a nutraceutical or adjunct pharmacotherapeutic agent in arthritis. Rigorous clinical investigation, advanced formulation science, and mechanistic molecular studies will be critical to fully realizing this potential.

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