

Mechanisms and Applications of Natural Medicines in the Treatment of Rheumatoid Arthritis

Zhuo Lu

*College of pharmacy, Xinjiang Medical University, Wulumuqi, China
gthota@my.bridgeport.edu*

Abstract: Rheumatoid arthritis (RA), a chronic autoimmune disorder characterized by persistent joint inflammation and bone destruction, has prompted the exploration of natural products and novel therapeutic strategies that integrate anti-inflammatory, immunomodulatory, and osteoprotective properties. This review delves into the bioactive components of *Capparis spinosa*, *Bupleurum* and *Ligusticum chuanxiong*, elucidating the mechanisms in RA management. The active constituents of *Capparis spinosa* alleviate synovitis and bone erosion by suppressing pro-inflammatory cytokines (e.g. $\text{TNF-}\alpha$, IL-6) and modulating signaling pathways such as HIF-1 and PI3K-Akt, while preclinical studies demonstrate their inhibitory effects on osteoclastogenesis. Saikosaponins, the core bioactive compounds in *Bupleurum*, restore immune equilibrium by blocking the TLR4/NF- κ B and STAT3 pathways, thereby inhibiting Th17 cell differentiation and IL-17 secretion, while enhancing regulatory T-cell functionality. Clinical evidence further supports the efficacy of compound formulations like Xiao Chaihu Tang in reducing serum inflammatory markers (e.g. IL-1 β , $\text{TNF-}\alpha$) among RA patients. Additionally, ligustrazine (tetramethylpyrazine), the primary component of *Ligusticum chuanxiong*, mitigates synovial inflammation and cartilage degradation through T-cell activation suppression, downregulation of IL-1 and $\text{TNF-}\alpha$ expression, and calcium homeostasis regulation. Notably, advancements in transdermal delivery systems have significantly enhanced its localized therapeutic efficiency, optimizing bioavailability and sustained release.

Keywords: Rheumatoid arthritis, *Capparis spinosa*, *Bupleurum*, *Ligusticum chuanxiong*, Immunomodulatory

1. Introduction

Rheumatoid Arthritis (RA), a chronic and systemic autoimmune disorder, affects 0.5%–1.0% of the global population [1,2]. Clinically, RA is characterized by progressive joint pain, stiffness, and swelling, primarily targeting the hands, feet, and knees, leading to symmetric inflammation, functional impairment, and potential irreversible joint deformity. Pathological hallmarks include synovial hyperplasia, inflammatory cell infiltration, cartilage destruction, and bone loss. Despite advancements in modern therapeutics, current RA medications predominantly focus on symptom alleviation and disease control, often failing to fundamentally alter disease progression or fully halt joint damage. With growing interest in traditional herbal medicine, natural plant-derived agents have gained prominence in RA research due to their multi-target mechanisms, favorable safety profiles, and efficacy in modulating immune responses, attenuating inflammation, and combating oxidative

stress. Notably, botanicals such as *Capparis spinosa*, *Bupleurum*, and *Ligusticum chuanxiong* have emerged as promising candidates. This review examines the pathogenesis of RA and explores the therapeutic potential of these herbal agents in disease management.

2. The precise etiology of RA

Remains the precise etiology of RA is incompletely understood. However, genetic predisposition, environmental triggers, and dysregulated immune activation are recognized as pivotal contributors to RA pathogenesis. Genetic factors constitute a major risk determinant, with over 100 susceptibility loci identified, including HLA-DRB1, PTPN22, TRAF1/C5, STAT4, and PADI4 [3]. Environmental exposures such as smoking, ultraviolet radiation, pharmaceuticals, and microbial dysbiosis synergize with genetic susceptibility to elevate disease risk [4]. Immunologically, RA is driven by aberrant activation of T cells, B cells, and macrophages, coupled with excessive cytokine production. These dysfunctions perpetuate synovial inflammation, marked by elevated levels of pro-inflammatory mediators (e.g. TNF- α , IL-6, IL-1 β), which facilitate immune cell migration, activation, and tissue infiltration [5]. Pathologically, RA manifests as synovial hyperplasia, progressive cartilage degradation, and bone erosion, exacerbated by the synergistic action of inflammatory cytokines and proteolytic enzymes (e.g. matrix metalloproteinases) [6]. Consequently, therapeutic strategies focus on three pillars: immunomodulation, anti-inflammatory intervention, and preservation of joint integrity, reflecting a mechanistic understanding of RA progression.

3. *Capparis spinosa*

Capparis spinosa, traditional medicinal herb with a long history of use in regulating Qi-Blood homeostasis and alleviating pain and inflammatory conditions, has garnered significant attention in recent years for its potential in RA management. Phytochemical analyses reveal that *Capparis spinosa* is rich in diverse bioactive constituents, including flavonoids, saponins, and steroidal compounds, which collectively exhibit anti-inflammatory, antioxidant, and immunomodulatory properties.

3.1. The chemical components and pharmacological effects of *Capparis spinosa*

3.1.1. Flavonoids

Flavonoids are pivotal bioactive constituents in *Capparis spinosa*. Phytochemical studies demonstrate that flavonoids are distributed across all plant parts, with the highest concentration in young leaves harvested in May, followed by mature leaves, fruits, and flower buds, while stems and roots exhibit comparatively lower levels. Key flavonoid derivatives identified include quercetin; quercetin 3'-glucoside; quercetin 3'-rhamnoglucoside; quercetin 7-o- β -D-glucopyranoside- β -L-rhamnopyranoside; quercetin 3-o-glucoside; quercetin 3-o-glucoside-7-o-rhamnoside; quercetin 3-o- α -L-rhamnosyl- β -D-glucosyl- β -D-glucoside; 3-hydroxyl-kaempferol; kaempferol 3-rhamnopyranoside; kaempferol 3-rutinoside; kaempferol 3-o-rhamnorutinoside; kaempferol 3,7-dirhamnoside; kaempferol 3-rhamnosyl-rutinoside [7]. These compounds exhibit marked pharmacological activities, including antioxidant, anti-inflammatory, and antitumor effects.

Mechanistically, flavonoids such as quercetin attenuate RA-associated inflammation by modulating the NF- κ B signaling pathway, thereby suppressing the secretion of pro-inflammatory cytokines (e.g. TNF- α , IL-6, IL-1 β) [8,9]. This immunomodulatory action disrupts synovial inflammation and alleviates clinical symptoms in RA. Additionally, flavonoids mitigate oxidative stress—a critical driver of RA pathogenesis—by scavenging free radicals and inhibiting reactive oxygen species (ROS) production. Through these mechanisms, flavonoids protect articular cartilage from oxidative damage, preserving joint integrity.

Collectively, the dual anti-inflammatory and antioxidant properties of *Capparis spinosa* flavonoids underscore their therapeutic potential in managing immune-mediated inflammation and oxidative injury in RA, highlighting their clinical applicability.

3.1.2. Saponin compounds

Saponins represent another critical class of bioactive constituents in *Capparis spinosa*, demonstrating potent immunomodulatory properties. Widely distributed in plants, saponins comprise diverse glycosidic structures, including triterpenoid and steroidal glycosides, which mitigate rheumatoid arthritis (RA) symptoms through systemic immune regulation.

Mechanistically, saponins bind to immune cell receptors, suppressing overactivation of immunocytes and attenuating immune-mediated inflammatory responses. Experimental studies reveal that caper-derived saponins significantly inhibit T-cell hyperproliferation and reduce cytokine secretion (e.g. IL-2, IL-4, TNF- α), thereby preventing autoimmune-driven joint damage in RA [10].

Furthermore, saponins ameliorate synovial inflammation by downregulating key inflammatory mediators (e.g. IL-6, TNF- α), alleviating clinical manifestations such as joint swelling and pain [11]. Notably, these compounds enhance immune tolerance by modulating immunological memory pathways, rebalancing effector and regulatory immune subsets (e.g. Th17/Treg), which is pivotal for mitigating RA progression.

3.1.3. Steroid compounds

Steroidal compounds, another vital class of bioactive constituents in *Capparis spinosa*, exhibit anti-inflammatory and immunomodulatory pharmacological activities. Widely distributed in plants, these compounds share structural and mechanistic similarities with synthetic steroids but demonstrate enhanced safety profiles due to reduced off-target effects.

Mechanistically, phytosteroids attenuate joint degradation by suppressing the expression of pro-inflammatory cytokines (e.g. TNF- α , IL-1 β , IL-6) in synovial tissues [12]. They bind to intracellular hormone receptors (e.g. glucocorticoid receptors), inhibiting the release of inflammatory mediators and modulating immune cell hyperactivation. This dual action restores immune homeostasis, mitigating autoimmune-driven joint damage.

RA-associated complications, such as osteoporosis and cartilage erosion, are further addressed by phytosteroids. These compounds inhibit osteoclastogenesis by downregulating RANKL signaling while promoting osteoblast differentiation and bone formation. Concurrently, they upregulate osteoprotective factors (e.g. osteoprotegerin), thereby decelerating RA-induced bone loss.

3.2. The clinical application of *Capparis spinosa* in RA

The collagen-induced arthritis mouse model, a predominant experimental system for rheumatoid arthritis research, has been widely utilized to assess the anti-inflammatory efficacy of caper extracts. Studies reveal that administration of *Capparis spinosa* extracts to CIA mice markedly alleviates joint swelling, erythema, and pain, reduces serum levels of TNF- α , IL-6, and anti-cyclic citrullinated peptide antibodies, and attenuates synovitis and bone erosion in histopathological evaluations. Furthermore, in rat arthritis models, caper-derived total flavonoids suppress Th17 cell differentiation, promote Treg cell proliferation, decrease the RANKL/OPG ratio in joint tissues, inhibit osteoclastogenesis, and significantly downregulate expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in synovial membranes [13].

4. Bupleurum

The genus *Bupleurum* encompasses medicinal species such as *Bupleurum chinense*, commonly known as Northern Bupleurum, and *Bupleurum scorzonerifolium*, referred to as Southern Bupleurum. These herbs are characterized by a bitter and pungent flavor with a slightly cold nature, traditionally associated with the liver, gallbladder, and lung meridians in Traditional Chinese Medicine.

4.1. The chemical components and pharmacological effects of Bupleurum

Saikosaponins, the core active components of *Bupleurum*, play a critical role in autoimmune disease treatment by multi-target regulation of inflammatory signaling pathways and immune cell functions. Their anti-inflammatory mechanisms primarily involve inhibiting the release of pro-inflammatory factors and blocking inflammatory signal transduction. In lipopolysaccharide (LPS)-induced macrophage inflammation models, saikosaponin D dose-dependently inhibits the gene expression of iNOS and COX-2, reducing the synthesis of inflammatory mediators such as nitric oxide and prostaglandin E₂, while significantly decreasing the levels of pro-inflammatory cytokines including tumor necrosis factor- α and interleukin-6. Additionally, saikosaponins inhibit the activation of Toll-like receptor 4 (TLR4) and phosphorylation of I κ B kinase, thereby blocking nuclear translocation of nuclear factor- κ B and reducing the transcription of downstream inflammation-related genes. This inhibitory effect on the TLR4/NF- κ B pathway demonstrates significant anti-inflammatory efficacy in LPS-induced RAW264.7 murine macrophage models.

In terms of immunomodulation, saikosaponins balance autoimmune responses by intervening in T-cell functions. For example, saikosaponin D specifically binds to the SH2 domain of signal transducer and activator of transcription 3, inhibiting its phosphorylation and transcriptional activity, thereby reducing the differentiation of helper T cells 17 and the secretion of interleukin-17A. The overactivation of Th17 cells is a key driver of autoimmune diseases such as RA, and elevated IL-17A levels are closely associated with joint inflammation and bone erosion. Concurrently, saikosaponins interfere with the membrane translocation of protein kinase C θ , suppressing abnormal activation mediated by T-cell receptors, promoting the functional recovery of Tregs, and re-establishing the dynamic balance between Treg and Th17 cells. This dual regulatory mechanism not only inhibits attacks by autoreactive T cells but also enhances immune tolerance, providing a pivotal strategy for controlling autoimmune disease progression.

Flavonoids in *Bupleurum* further enhance anti-inflammatory effects through pathways such as free radical scavenging and macrophage function modulation. For instance, *Bupleurum* flavonoids reduce macrophage phagocytic activity and decrease reactive oxygen species release, alleviating inflammation-related oxidative damage. This multi-component synergy endows *Bupleurum* with broader pharmacological activity in compound formulations.

In summary, saikosaponins demonstrate multi-dimensional and multi-target therapeutic potential in RA treatment by suppressing inflammatory mediator synthesis, regulating key signaling pathways (e.g. NF- κ B, STAT3), and restore immune cell balance. These findings provide a robust scientific foundation for clinical translation.

4.2. The clinical application of *Capparis spinosa* in Bupleurum

Clinical studies demonstrate that compound formulations containing *Bupleurum*—such as Da Chaihu Tang and Xiao Chaihu Granules—significantly reduce serum levels of IL-1 β and TNF- α in RA patients. These formulations also improve acute inflammatory markers, including procalcitonin and cystatin C, thereby validating their synergistic anti-inflammatory and immunomodulatory effects.

5. *Ligusticum chuanxiong*

Ligusticum chuanxiong Hort., a perennial herbaceous plant of the *Ligusticum* genus in the Apiaceae family, is primarily cultivated in Sichuan, Yunnan, and Guizhou provinces of China. Its dried rhizome is used medicinally. In TCM, this herb is described as having a warm nature, pungent flavor, and affinity for the Liver, Gallbladder, and Pericardium meridians. Recognized as a classical remedy for blood stasis and qi stagnation syndrome, it exhibits therapeutic effects in activating blood circulation, promoting qi movement, dispelling wind, and alleviating pain. The primary bioactive constituents of *Ligusticum chuanxiong* include ligustrazine (tetramethylpyrazine), ferulic acid, volatile oils, and phenolic compounds.

5.1. The chemical components and pharmacological effects of *Ligusticum chuanxiong*

Tetramethylpyrazine (TMP), a monomeric compound extracted from the roots and stems of *Ligusticum chuanxiong*, is primarily utilized to enhance microcirculation, dilate blood vessels, and inhibit platelet aggregation, with demonstrated anti-inflammatory activity. As the principal bioactive component of *Ligusticum chuanxiong*, it exhibits multi-target regulatory properties in autoimmune disorders. Core pharmacological actions include immunomodulation, anti-inflammatory effects, antioxidant activity, and calcium homeostasis regulation.

Ligustrazine modulates immune dysregulation by suppressing aberrant T-cell activation and B-cell co-stimulatory signaling. Studies reveal that ligustrazine downregulates mRNA expression of B7-1 and B7-2 in peripheral blood mononuclear cells of RA patients during active phases, thereby reducing T-cell activation by autoantigens and inhibiting autoimmune responses. In collagen-induced arthritis rat models, ligustrazine significantly decreases IL-1, TNF- α , and IL-12 levels while suppressing serum anti-collagen antibody production, indicating its ability to mitigate pathological damage through Th1/Th2 balance regulation and humoral immune modulation. Furthermore, ligustrazine inhibits IgG and IgM synthesis, thereby attenuating hyperactive immune responses. Concurrently, it blocks inflammatory cascades by suppressing key inflammatory cytokines such as TNF- α , IL-6, and IL-17, as well as inflammatory mediator release. Additionally, ligustrazine exerts antioxidant effects by scavenging reactive oxygen species and inhibiting lipid peroxidation, thereby reducing oxidative stress-induced joint tissue damage.

Moreover, ligustrazine maintains intracellular calcium homeostasis by inhibiting pathological calcium influx. In knee osteoarthritis models, ligustrazine blocks TRPV4 calcium channels on chondrocyte membranes, reducing Ca²⁺ overload and alleviating mitochondrial dysfunction and oxidative stress, thereby preserving cartilage matrix metabolism. This mechanism parallels the function of mitochondrial calcium uptake protein 1 which suppresses vascular inflammation by regulating mitochondrial calcium homeostasis, suggesting ligustrazine may similarly target calcium signaling dysregulation in autoimmune diseases.

5.2. The clinical application of *Capparis spinosa* in *Ligusticum chuanxiong*

In vitro studies utilizing a pharmacokinetic/pharmacodynamic (PK/PD) model established through microdialysis and ELISA techniques demonstrate that the pharmacological efficacy of the Chuanxiong patch—such as inhibition of IL-1 β and TNF- α —exhibits a significant correlation with blood drug concentration, consistent with a first-order kinetic model [14]. Additionally, research indicates that the optimization of matrix formulations in transdermal drug delivery systems (e.g. gel patches) significantly enhances the percutaneous permeation efficiency of Chuanxiong extracts.

6. Conclusion

This review focuses on natural products for RA treatment, particularly *Capparis spinosa*, *Bupleurum*, and *Ligusticum chuanxiong*, exploring their multi-component, multi-target physicochemical properties and their anti-inflammatory, immunomodulatory, and osteoprotective effects. The flavonoids, saponins, and steroidal compounds in *Capparis spinosa* significantly alleviate joint inflammation and bone erosion by suppressing the NF- κ B pathway, modulating the Th17/Treg balance, reducing the RANKL/OPG ratio, and lowering pro-inflammatory cytokine levels, thereby ameliorating pathological damage. Saikosaponins from *Bupleurum* restore immune homeostasis by blocking the TLR4/NF- κ B and STAT3 signaling pathways, inhibiting Th17 differentiation and IL-17 secretion, while enhancing Treg functionality. Clinical compound formulations further validate their synergistic anti-inflammatory and immunomodulatory effects. Ligustrazine, the primary active component of *Ligusticum chuanxiong*, reduces synovitis and cartilage degradation through interventions in the cGAS-STING pathway, suppression of calcium overload, and regulation of Th1/Th2 balance. Additionally, optimized transdermal delivery systems provide novel strategies for localized precision therapy.

However, current research faces limitations, including a predominant focus on animal or cellular studies, limited clinical trials with small sample sizes, and a lack of standardized evaluation systems. Future studies should prioritize the development of advanced formulations, such as transdermal systems targeting RA-associated ion channels, to translate pharmacological pathway findings into clinical applications. Innovations in nanodelivery systems and structural modifications could enhance component targeting and stability. Multi-omics technologies—including single-cell sequencing and metabolomics—should be employed to decode the dynamic immune microenvironment regulated by natural products. Artificial intelligence-driven screening of compound combinations may optimize "component-target-pathway" synergies. Concurrently, expanding clinical sample sizes, strengthening evidence-based medical research, and establishing standardized evaluation criteria are critical. Through interdisciplinary integration and combined traditional Chinese-Western medical strategies, natural products hold promise as safer, long-acting therapeutic options for RA, advancing personalized precision medicine.

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