

An Overview of Selected Medicinal Plants for Reducing the Clinical Symptoms of Rheumatoid Arthritis

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Abstract

There are several contributing factors that lead to joint pain, and among them, osteoarthritis (OA) and rheumatoid arthritis (RA) are prominent. RA is an autoimmune disease characterized by chronic inflammation that affects joints, tissues, and the whole body. This inflammatory disease results in synovial inflammation and hyperplasia, leading to the breakdown of articular cartilage, bone erosion, and long-term deformities. RA significantly impairs people's mobility and quality of life worldwide. The conventional treatments for this condition include NSAIDs, DMARDs, corticosteroids, and biologics. However, due to the high incidence of adverse reactions, alternative medicine is gaining popularity. Medicinal plants are considered a precious alternative source for treating RA. Medicinal plants have been used traditionally to treat arthritis globally, which addresses the limitations associated with current treatments, particularly in developing countries. The aim of this study is to find effective medicinal plants that can help reduce RA symptoms.

Keywords: Rheumatoid Arthritis, Herbal Medicine, Traditional Medicinal, Inflammatory Disease, Inflammation, Natural Product

Introduction

The immune system is responsible for keeping our body safe from harmful organisms and diseases. However, if it becomes too active, it can lead to hypersensitivity or allergic reactions, causing disruptions.¹ This excessive activity can result in autoimmune diseases, where the immune system mistakenly attacks our own cells and tissues. Unfortunately, medical and pharmaceutical professionals face significant challenges as the causes of common autoimmune disorders remain unknown, such as myasthenia gravis, serum sickness, pernicious anemia, and reactive arthritis.² Joint pain can have various causes, with OA and RA being the most common. OA is the most widespread form of arthritis, causing pain, stiffness, and disability in adults.³ Radiographic evidence of OA is present in most individuals aged 65 and above, which increases to almost 80% in those aged 75 and older. Clinical manifestations of OA typically involve pain, stiffness, swelling, and inflammation.⁴ Rheumatoid arthritis is a long-lasting and inflammatory disease caused by the

growth of abnormal synovial tissue. This condition can cause damage to bones and cartilage, leading to joint deformities and reduced functionality.⁵ The immune system attacks the tissues around the joints, causing the release of chemicals and enzymes that break down bones and cartilage. Rheumatoid arthritis can also affect internal organs such as the eyes, lungs, heart, and nerves. The symptoms of this condition may differ from person to person and may start in a few joints before gradually spreading to others over time.⁶ The progression of rheumatoid arthritis can be severe and fast, and it can affect many joints, including the spine, hips, and knees. If left untreated, it can cause irreversible joint damage and disability. RA is a health condition that can cause various complications, such as stroke, neurological problems, heart disease, breathing difficulties, depression, and, in severe cases, disability or death.⁷ Patients may suffer significant physical, mental, and financial stress if they do not receive adequate treatment. Unfortunately, there are around 24.5 million

RA patients worldwide, with 5 to 50 diagnoses per 100,000 individuals per year. RA mostly affects women, accounting for more than 80% of cases.⁸ Although its exact cause is unknown, genetic factors, immunostimulatory agents, and sex hormones are all believed to be involved in its development. RA is a medical condition that affects many people, but its origin is still unknown despite ongoing research. One theory suggests that the body produces certain free radicals, like nitric oxide

and superoxide radicals, during cellular metabolism.⁹ These free radicals may stimulate the release of interleukins and tumor necrosis factor from T cells. As a result, these chemicals may influence the production of cytokines, adhesion molecules, and growth factors in immune cells, leading to inflammation and tissue damage.¹⁰ The objective of this project is to discover and recommend medicinal plants that can effectively alleviate the symptoms of RA in patients.

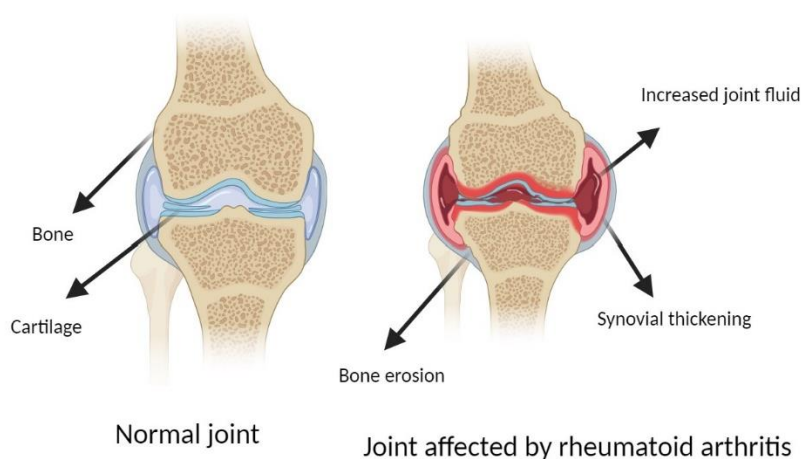


Figure 1. A Normal Knee Joint and a Knee Joint Affected by RA

Treatment of RA

In recent times, the treatment of RA has undergone significant changes. The traditional use of nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) has been replaced by new biological agents like TNF monoclonal antibodies. To manage RA, there are five main strategies to consider.¹¹ The first involves using NSAIDs, followed by moderate doses of glucocorticoids to reduce inflammation and prevent the disease from worsening. In chronic cases, treatment plans may include DMARD drugs like methotrexate, sulfasalazine, gold salts, or D-penicillamine. In addition, the treatment regimen may involve drugs like infliximab or etanercept, which neutralize TNF- α , anakinra, which neutralizes IL-1, or abatacept, which interferes with T-cell activation.¹² Finally, drugs like cyclosporine, azathioprine, and cyclophosphamide are used to manage chronic conditions by reducing inflammation and preventing joint damage. However, the potential risks of these drugs over the long term are not yet fully understood.¹³ Certain medications used to treat RA have the potential

to cause various harmful effects on the body, such as ulcers in the digestive system, complications with the heart, toxicity in the blood, kidneys, or lungs, bone marrow suppression, liver damage, and more. Patients may also experience additional side effects, such as fibrosis, inflammation of the mouth, liver scarring, diarrhea, immune responses, or reactions at the injection site.¹⁴ These medications are expensive and require careful monitoring due to their high costs and the risk of infections and cancer. The conventional healthcare approach to treating RA involves using NSAIDs, steroids, and DMARDs, in addition to auxiliary tools such as stents and splints, to improve overall body function. In severe cases, joint surgery may be necessary to prevent disease progression.¹⁵ However, the long-term use of these pharmaceuticals can lead to adverse effects like gastrointestinal bleeding, dyspepsia, and other reactions induced by NSAIDs. To overcome these challenges, researchers have explored the potential benefits of natural ingredients and medicinal herbs for alleviating RA symptoms.¹⁶ Our study conducted a comprehensive

review that included the use of databases such as Google Scholar, PubMed, Scopus, and Web of Science, with keywords such as RA, herbal medicine, traditional medicine, inflammatory disease, inflammation, and natural product. We present a list of plants that have shown effectiveness in improving symptoms among individuals with RA.

Alstonia scholaris Linn

The tree known as *Alstonia scholaris* Linn (AS) is commonly found in dry forests throughout India, including the Western Himalayas, Western Ghats, and Southern regions. It can grow up to 40 meters high and has a corky bark that is grey or grey-white and somewhat tessellated. The bark of AS has been used for medicinal purposes for a long time and is traditionally used to treat various ailments such as rheumatism, malarial fevers, abdominal disorders, leprosy, asthma, bronchitis, pruritis, and chronic ulcers. The traditional use of this tree in medicine highlights its potential to treat a wide range of health issues.¹⁷

Curcumin

Curcumin is a substance that comes from *Curcuma longa* and has several health benefits, including anti-inflammatory, hepatoprotective, antibacterial, antidiabetic, antidepressant, analgesic, and anticarcinogenic properties. Curcumin's anti-inflammatory effects come from its ability to inhibit lipoxygenase, suppress the activation of certain molecules, and prevent the upregulation of matrix metalloproteinase mRNA. In addition, curcumin can suppress the expression of MMP-13 in chondrocytes.¹⁸ Many studies have been conducted in vivo and in vitro to explore the possible antiarthritic effects of curcumin. In vivo assessments of curcuminoids have shown a significant decrease in both acute and chronic inflammation. Furthermore, curcumin has been shown to provide symptomatic relief for exercise-induced muscle damage due to its anti-inflammatory properties. These findings highlight the potential of curcumin as a treatment for various health conditions.¹⁹

Aconitum kusnezoffii Reichb

The dried root of *Aconitum kusnezoffii* Reichb, commonly known as cows, has been utilized for numerous years for treating RA and joint pain due to its anti-inflammatory properties. Studies have found that the main active components in *A. kusnezoffii* are

diterpenoid alkaloids, including aconitine, mesaconitine, hyaconitine, neoline, talatizamine, beiwutine, and deoxy-aconitine. Recently, researchers have focused on the anti-inflammatory properties of benzoyl aconitine (BAC), which is a derivative of the root of *A. kusnezoffii*. BAC has been found to effectively inhibit the production of IL-6 and IL-8 in human synovial cells, thus offering a promising strategy for treating RA.²⁰ Encapsulating BAC in mPEG-PLGA NPs (NP/BAC) increases its bioavailability and cytocompatibility for activated macrophages. NP/BAC has been shown to significantly inhibit the secretion of pro-inflammatory cytokines TNF- α and IL-1 β by impeding the NF- κ B signaling pathway. Caowu, which is derived from *A. kusnezoffii* is an essential component in the treatment of RA due to its role in relieving arthralgia and pain associated with RA by reducing painful obstruction syndrome and alleviating pain.²¹

Camellia sinensis

Tea has numerous health benefits, including reducing the risk of cancer and heart disease and having antimicrobial effects. Theophylline, a compound found in tea, has been used to treat respiratory diseases such as asthma. Tea contains polyphenols, like epigallocatechins, which work as antioxidants. In experiments with rats that had arthritis, green tea was found to have significant anti-inflammatory effects, which resulted in a reduction in the levels of the inflammatory cytokines TNF- α and γ -interferon and cyclooxygenase-2 (COX-2).²² Green teas also contributed to a decrease in total IgG antibodies and collagen-specific antibodies. Recent studies show that black tea extract has antiarthritic activity in both experimental and clinical studies. Black tea water extract showed antiarthritic effects in rats with Freund's complete adjuvant-induced arthritis, which was accompanied by a decrease in serum levels of prostaglandin E2 (PGE2), TNF α , IL-1 β , and IL-6. Tea's health-promoting properties, including its anti-inflammatory and antioxidant features, highlight its potential therapeutic value in addressing various health conditions, such as arthritis.²³

Piper nigrum

The objective of the research was to examine how piperine can help reduce inflammation in fibroblast-like synoviocytes that are stimulated by IL-1 β , which is derived from patients with RA. The study also

investigated the antiarthritic and analgesic properties of piperine using rat models with carrageenan-induced acute paw pain and arthritis. The findings revealed that piperine significantly reduced nociceptive and arthritic symptoms in rats on days 8 and 4, respectively.²⁴ The histological staining of ankle joints supported these results, showing that piperine had the potential to decrease the inflammatory area, suggesting its potential to reduce inflammation associated with arthritis. These results suggest that piperine has promising anti-inflammatory, analgesic, and antiarthritic activities, which could be utilized for therapeutic interventions in RA.²⁴

Shagoal

Ginger, which is scientifically known as *Zingiber officinale*, has been traditionally used to treat various ailments such as pain, arthritis, cough, oxidative stress, hepatotoxicity, and cardiovascular problems. Ginger contains several phytochemical constituents, including 6-, 8-, and 10-gingerol, 6-, 8-, and 10-shagaol, and zingiberine. One of these compounds, shagaol, is known for its ability to reduce arthritis symptoms by suppressing the production of inflammatory cytokines such as IL-1 β , IL-6, TNF- α , and interferon- γ (INF- γ).²⁵ Studies have shown that ginger powder can significantly alleviate knee joint pain by reducing the production of NO and C-reactive protein. Among the various shagaols and gingerols present in ginger, 6-shagaol is identified as the most potent antioxidant and anti-inflammatory agent. The secondary metabolite of ginger, which is ginger essential oil, has been found to have preventive effects against chronic joint inflammation and granuloma formation. It is important to mention that ginger's antirheumatic properties are not exclusively due to phenolic compounds such as gingerol and shagaol but also to other secondary metabolites present in ginger. These observations show that ginger has numerous therapeutic benefits for managing arthritis and other inflammatory conditions.²⁶

Boerhaavia diffusa Linn.

Boerhaavia diffusa, commonly found in India during the rainy season, has two varieties: red and white. Its root is the most important part of the plant with medicinal properties and has been traditionally used as a laxative, diuretic, expectorant, diaphoretic, and emetic. A mixture of BD roots with other herbs is used

to relieve joint pain. Furthermore, the root is used in powder form or as a decoction or infusion to manage inflammatory disorders such as arthritis. This traditional use of *Boerhaavia diffusa* demonstrates its potential as a therapeutic agent for various inflammations.²⁷

Strychnos nux-vomica

Strychnos nux-vomica, which is also called nux-vomica, is a natural drug that has been traditionally used to treat inflammatory disorders and rheumatoid conditions. The plant is thought to have a soothing effect on rheumatic pain. Studies have shown that the seeds of *S. nux-vomica* have anti-inflammatory properties by reducing vascular permeability and suppressing the production of PGE2. Two natural alkaloids, brucine and brucine N-oxide, which are extracted from the seeds of *S. nux-vomica*, are believed to contribute to the plant's anti-inflammatory effects. These findings suggest that *S. nux-vomica* could be a natural solution for managing inflammatory conditions such as rheumatoid pain.²⁸

Althaea officinalis L.

The flowers of the marshmallow plant, also known as *Althaea officinalis*, have been traditionally used to treat inflammatory diseases and chronic pain. In Persian medicine, it is used to treat respiratory diseases, colitis, and joint pains. Scientific research has shown that the anti-inflammatory effect of marshmallow flowers is due to their ability to reduce capillary permeability and inhibit the release of prostaglandin E (PGE) from inflamed tissues. Scopoletin, an important component found in marshmallow leaves, is believed to have potential benefits in the treatment of RA.²⁹ Scopoletin works by suppressing the release of pro-inflammatory cytokines such as PGE2, TNF- α , IL-1 β , and IL-6 and inhibiting the expression of COX-2. According to scientific research, scopoletin has the ability to regulate the expression of pro-inflammatory cytokines by acting on the nuclear factor, which is a transcription factor that binds to specific genes' promoter regions. Additionally, scopoletin has been found to have a positive impact on the histological structure of arthritic joints by reducing synovial hyperplasia, preventing the formation of new blood vessels in synovial tissues, and inhibiting erosive changes in bone and cartilage. These findings suggest that marshmallow, and particularly scopoletin, could

be a natural solution for managing inflammatory conditions, including RA.³⁰

Guggulosterone

Guggul is a resin obtained from various *Commiphora* species, which has several bioactive components, including guggulsterone, diterpenes, Gallic acid, and flavonoids. Guggulsterone is noteworthy for its pharmacological effects, including the inhibition of MAP kinase and cytokines such as IFN- γ , IL-12, IL-1 β , and NO. These actions contribute to the anti-inflammatory properties of guggul. In vivo studies have shown that guggulsterone has anti-inflammatory activity comparable to phenylbutazone and ibuprofen in rats, suggesting that it may be a potential therapeutic option for managing inflammatory conditions.³¹

Paeonia lactiflora Pallas

Paeonia lactiflora Pallas, also known as Chinese peony, has been used as a traditional medicinal plant in China for thousands of years due to its pain-relieving, anti-inflammatory, and immune-boosting properties. The therapeutic effects of this plant have been recognized in ancient Chinese medical texts. Total glycoside of paeony is an extract obtained from the root of the *P. lactiflora* plant, which contains beneficial components such as paeoniflorin, hydroxy-paeoniflorin, paeonin, albiflorin, and benzoyl-paeoniflorin.³² Clinical trials have shown that TGP can be used as a disease-modifying drug for RA, and a combination treatment of TGP and methotrexate has fewer side effects. TGP-treated RA patients have shown a reduction in erythrocyte sedimentation rate, C-reactive protein levels, and a decrease in the population of IFN- γ - and IL-17-producing cells. These findings suggest that *P. lactiflora* and TGP may be useful therapeutic options for managing RA, based on both traditional use and modern clinical trials.³³

Aristolochia bracteata Lam.

Aristolochia bracteata, which is also known as worm killer or kidamari, is a type of shrub that grows in various regions, including Deccan Gujarat, western and southern India, and Bengal. It has been used traditionally for medicinal purposes to treat different ailments, such as gonorrhea, syphilis, inflammation, ulcers, amenorrhea, skin diseases, dermatitis, leprosy, jaundice, and helminthiasis. AB contains a diverse

range of chemical constituents, such as alkaloids, triterpenoids, steroids, flavonoids, saponins, carbohydrates, proteins, and cardiac glycosides.³⁴

Citrus medica L. (Rutaceae)

Citrus medica, commonly known as citron, is a plant grown and cultivated globally. Its peel, leaves, and root have been traditionally used in Asian folk medicine, especially in India and Iran, to treat various ailments like arthritis, hepatitis, and rheumatism. Studies have confirmed that *Citrus medica* fruits have antioxidant and anti-inflammatory properties. Additionally, research has shown that the peels of *Citrus medica* and the fruits of *Citrus unshiu* (Swingle) Marcow can reduce inflammatory responses in rheumatoid conditions. These natural remedies have anti-inflammatory properties that work by suppressing the production of inflammatory cytokines like TNF- α , PGE2, IL-1 β , and IL-6.³⁵ These cytokines play a significant role in regulating various intercellular and vascular cell adhesion agents, which attract leukocytes to the sites of inflammation. Citrus fruits can hinder the release of NO by suppressing the iNOS enzyme's expression. Limonene, an active component present in *Citrus medica*, has been found to be an effective NO production inhibitor. Furthermore, it reduces the expression of iNOS and COX-2 proteins. Limonene is also known to lessen the expression of pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6. These discoveries suggest that *Citrus medica* and its constituents, especially limonene, may naturally work as anti-inflammatory agents. They may be beneficial in treating inflammatory illnesses such as RA.³⁶

Colchicum autumnale L. (Colchicaceae)

The corm of *Colchicum autumnale* is a natural drug that has been used for a long time to treat inflammatory disorders like gout, hemorrhoids, hepatitis, and rheumatism. Recent studies have shown that the hydroalcoholic extract from the corm of *Colchicum luteum* Baker can be an effective anti-arthritic agent. The extract is better than indomethacin in reducing joint swelling over time and has a powerful therapeutic effect on complete Freund's adjuvant-induced arthritis, which is similar to human RA. The extract's effectiveness in treating arthritis is due to its ability to prevent the production of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-

1β and reduce the expression of TNF-R1 in the synovium.³⁷ The text above explains that TNF-R1 is a subtype of receptor that contributes to arthritis development through the effects of TNF- α . Colchicine is a natural ingredient found in *Colchicum luteum* that can inhibit pro-inflammatory cells like macrophages by interacting with cellular tubulin protein. This interaction helps relieve symptoms such as rat paw edema and granuloma formation by suppressing inflammatory cytokines TNF- α , IL-6, and IL-1 β in inflamed tissue, as well as inhibiting COX-2 proteins. These findings suggest that *Colchicum luteum* may be a natural remedy for managing inflammatory conditions, especially RA.³⁸

Ligusticum chuanxiong Hort

Ligusticum chuanxiong Hort, also known as Chuanxiong Rhizoma, is a type of medicinal herb that belongs to the Umbelliferae family. It has been widely used for treating various diseases in traditional medicine. The herb contains several compounds like ligustilide, 3-butyrolactone, and cypressene, as well as other compounds such as ferulic acid, tetramethylpyrazine, palmitic acid, carotene, and β -sitosterol. Many biomedical and clinical studies have proved that *Ligusticum chuanxiong* has several positive effects, like antioxidant, neuroprotective, anti-fibrotic, antinociceptive, anti-inflammatory, and antineoplastic effects. In 2014, a study by Chuan-Xian Mu et al. found that ligustrazine, one of the compounds found in *Ligusticum chuanxiong*, significantly reduced swelling

in rats with collagen-induced arthritis.³⁹ Ligustrazine, a medication used in the treatment of RA, has been found to effectively lower the levels of inflammatory cytokines, such as IL-1 and IL-6, in the blood and increase the levels of the anti-inflammatory cytokine IL-2. This indicates that ligustrazine can help prevent RA by balancing the inflammatory cytokine network. In addition, ligustrazine and leflunomide, another medication used for treating RA, have been found to effectively stop bone degradation in RA patients. These results suggest that *Ligusticum chuanxiong*, specifically ligustrazine, could be a promising therapeutic option for managing RA. A diagram, Figure 2, demonstrates the effectiveness of medicinal plants in improving the symptoms of RA.⁴⁰

Peiminine

Peiminine, an active substance extracted from *Fritillaria thunbergii*, is widely utilized in Asian countries due to its numerous health benefits. According to previous research, peiminine has anti-inflammatory, anti-cancer, and antioxidant properties. It's been found to suppress the release of inflammatory cytokines such as IL-1 β and TNF α , which cause inflammation, in a dose-dependent manner by blocking NF- κ B signaling pathways and suppressing cytokines. *Peiminine* has been shown to be effective in alleviating the symptoms of rheumatoid arthritis, which is characterized by joint inflammation. Figure 2 shows some other medicinal plants that can be used to improve the symptoms of RA.⁴¹



Figure 2. Medicinal Plants Effective on RA

Discussion and Conclusion

Arthritis is a disease that affects people worldwide and is becoming more common due to modern lifestyles. Unhealthy diets and a lack of exercise make younger people more susceptible to developing arthritis. While traditional medicines like NSAIDs and steroids can alleviate pain and somewhat control the disease, they have severe side effects.⁴² Therefore, people are increasingly interested in exploring alternative treatments, such as natural compounds from medicinal plants.⁴³ This study reported the potential therapeutic properties of various plants, including *Alstonia scholaris*, *curcumin*, *Aconitum kusnezoffii* Reichb., *Camellia sinensis*, *piper nigrum*, *Boerhaavia diffusa*, *Strychnos nux-vomica*, *Althaea officinalis*, *Paeonia lactiflora* Pallas, *Aristolochia bracteata*, *Citrus medica*, *Ligusticum chuanxiong* Hort, and *Colchicum autumnale*. Many studies suggest that these natural compounds have anti-inflammatory and anti-arthritic properties, which can reduce inflammatory cytokines and alleviate joint swelling.⁴⁴ It has been observed that certain compounds, such as ligustrazine from *Ligusticum chuanxiong*, when used in conjunction with conventional drugs such as *leflunomide*, may help reduce bone erosion in patients with rheumatoid arthritis. While these findings are encouraging, it is essential to emphasize the need for further research and clinical trials to establish the safety and effectiveness of natural remedies in treating RA in humans.⁴⁵ It is highly recommended that individuals always seek the advice of healthcare professionals before considering new treatments for medical conditions.⁴⁶ This review article draws on over twenty references and offers valuable insights that can guide further research in the field of phytopharmacology. Researchers can use this information to advance their studies on the potential applications of plants for treating arthritis. With the current scientific understanding, the development of combination drugs and herbal formulations utilizing medicinal plant resources holds promise for the creation of effective medicines to address the needs of RA patients.⁴⁸ To treat RA, combining certain natural compounds like *ligustrazine* from *Ligusticum chuanxiong* with conventional drugs such as *leflunomide* has shown promise in reducing bone erosion. However, further research and clinical trials are necessary to confirm their safety and effectiveness. Consulting healthcare professionals before trying new treatments is highly recommended.⁴⁵ This review article provides valuable

insights from over twenty references that can guide further research in the field of phytopharmacology. Researchers can use this information to explore the potential of using plants for treating arthritis. The development of combination drugs and herbal formulations using medicinal plant resources is a promising area for creating effective medicines to help RA patients.⁴⁸

Conflict of Interest

The authors declare no conflicts of interest.

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