



Plants Used in the Treatment of Rheumatoid Arthritis

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Abstract

Chronic, persistent and incapacitating autoimmune ailments known as Rheumatoid Arthritis (RA) are marked by cartilage and bone damage surrounding the joints as well as systemic inflammation of the joints. The fact that 75% of RA patients are female points to the significance of hormones in the etiology of the condition. Synovial membrane inflammation involves mechanisms in the form of genetic, environmental, including immunologic variables that are believed to have a role in its pathogenic mechanism. When it comes to treating RA, the focus has shifted from relieving symptoms to implementing therapeutic regimens that affect the disease's activity and eventually have been found to halt or stop structural joint destruction. Salicylates, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, and Disease Modifying Anti-Rheumatic Drugs (DMARDs), Methotrexate (MTX), as well as biologic response enhancers, are some examples of drugs. However, it has negative effects which need to be overcome. It is required to employ herbs and a variety of plants to treat joint pain and inflammation. There are numerous plants with medicinal properties that have been clinically demonstrated to have anti-rheumatoid arthritis effects. As a result, plants and their derivatives with significant benefits are being used for the management of rheumatoid arthritis. The current assessment focuses on medicinal plants that have anti-rheumatoid arthritis efficacy.

Keywords: Auto-immune Disease, Herbs, Inflammation, Rheumatoid Arthritis

1. Introduction

Rheumatoid Arthritis (RA) is an autoimmune and inflammatory condition in which the immune system unintentionally damages healthy cells within the body, leading to inflammation and painful swelling in the affected body regions. RA often targets multiple joints simultaneously. This chronic and systemic autoimmune disease typically emerges between the ages of 30 and 50, inducing symmetrical polyarthritis affecting both large and small joints¹. According to a prior report, its prevalence is estimated at 25 men and 54 women per 100,000 individuals, positioning it as the most common form of inflammatory arthritis². RA, being the prevailing type, results in substantial disability and is connected to higher mortality rates and concurrent medical conditions³.

Commonly impacted joints include the wrists, knees, metacarpophalangeal, proximal interphalangeal,

and metatarsophalangeal joints. These areas often experience swelling, unusual discomfort, and damage to the synovial joints⁴. The symmetrical polyarticular inflammation characteristic of RA also significantly affects the small diarthrodial joints found in the hands and feet. An aggressive tissue formation known as the pannus infiltrates and undermines the nearby joint structure while also causing inflammation in the synovium, which is the lining of the joint. This synovium is frequently a delicate structure with a subtle intimal lining⁵.

Peaking in occurrence between the ages of 40 and 60, this condition is notably more prevalent among women, being two to three times higher in frequency than in males, and it has the potential to initiate at any age. Alongside the inflammation-driven joint swelling and pain, joint destruction stands as a defining feature of RA. The term “polyarthritis” is attributed to RA due to its involvement of multiple joints, typically six

or more; however, in its initial stages, only a limited number of joints may be impacted. While almost all peripheral joints can be affected by this condition, the distal interphalangeal joints are usually spared, and the most commonly afflicted joints are those in the hands, feet, and knees⁶.

2. Pathogenesis of Rheumatoid Arthritis

The cause of RA remains unidentified, and the outlook for the condition is unpredictable. Nevertheless, advancements in comprehending the disease's underlying mechanisms have paved the way for the enhanced creation of novel therapies with more favourable outcomes⁷. Within RA, the immune and inflammatory processes play a pivotal role in the deterioration of bone and cartilage. Numerous pathways linked to the condition's onset have been identified, and certain among these have been definitively recognized as significant through foundational therapeutic investigations. However, despite these insights, the ultimate connection between these two systems remains elusive, and the precise origin of RA remains unclear⁶.

The pathophysiology of RA can be divided into three stages: immunological abnormalities, synovial inflammation and excessive growth, and eventual joint deterioration and deformity leading to physical limitations. These phases are intricately intertwined in a unique manner for each individual. The process of human immune response starts with antigen-presenting cells, which could be macrophages or dendritic cells located in the synovial membrane. These cells engulf and process foreign protein antigens, subsequently presenting them to T lymphocytes. This interaction sparks a cellular immune response that prompts B lymphocytes to transform into plasma cells, releasing antibodies⁸.

The origin of rheumatoid arthritis involves a combination of multiple factors, encompassing genetic predisposition, smoking, bacterial and viral infections, as well as autophagy. These elements collectively contribute to catalyzing the conversion of arginine to citrulline through the PADI4 enzyme. Antigen presentation occurs through Antigen-Presenting

Cells (APC), triggering the activation of naive T cells, including Th1, Th17, and Th2 cells. Th1 cells, with heightened pro-inflammatory TNF secretion, lead to macrophage activation within the synovial joint. Th17 cells produce IL-17, IL1, and TNF- α , impacting chondrocytes, osteoclasts, and fibroblasts. Consequently, chondrocytes release enzymes that break down collagen and Matrix-Metalloproteinase (MMP). Fibroblasts transition into Fibroblast-Like Synoviocytes (FLS), generating pro-inflammatory cytokines that contribute to the degradation of the extracellular matrix. The activation of T-cells further stimulates B-cells and plasma cells, which secrete a range of auto-antibodies. These auto-antibodies can bind to neutrophils and macrophages, leading to the formation of pannus and causing damage to cartilage. They can also form immune complexes, resulting in joint pain and bone deterioration^{9,10}. Figure 1 depicts the process of RA's development⁹.

3. Conventional Therapy for Rheumatoid Arthritis

Over the past 25 years, the treatment of RA has seen a significant transformation, moving from a focus on symptom management to the application of therapeutic regimens that have been proven to alter disease activity and ultimately reduce or stop structural joint destruction¹¹. Patients with RA require a holistic approach to management. For RA pain management, a variety of therapeutic approaches, including pharmacological, non-pharmaceutical, and surgical procedures, have been utilized (Walsh DA). Although the cause of RA is currently unknown, pharmacological therapy for RA has advanced¹².

NSAIDs that inhibit a subtype of cyclooxygenase have recently received a lot of interest. These treatments are known as selective cyclooxygenase-2 (COX-2) inhibitors. NSAIDs and Disease-Modifying Antirheumatic Drugs (DMARDs) are the two main techniques used in RA pharmacological therapy⁶. NSAIDs merely prevent the production of prostaglandins by Cyclooxygenases (COXs), a tiny portion of the inflammatory cascade, but they have no effect on the underlying immuno-inflammatory processes or the progression of joint destruction¹³.

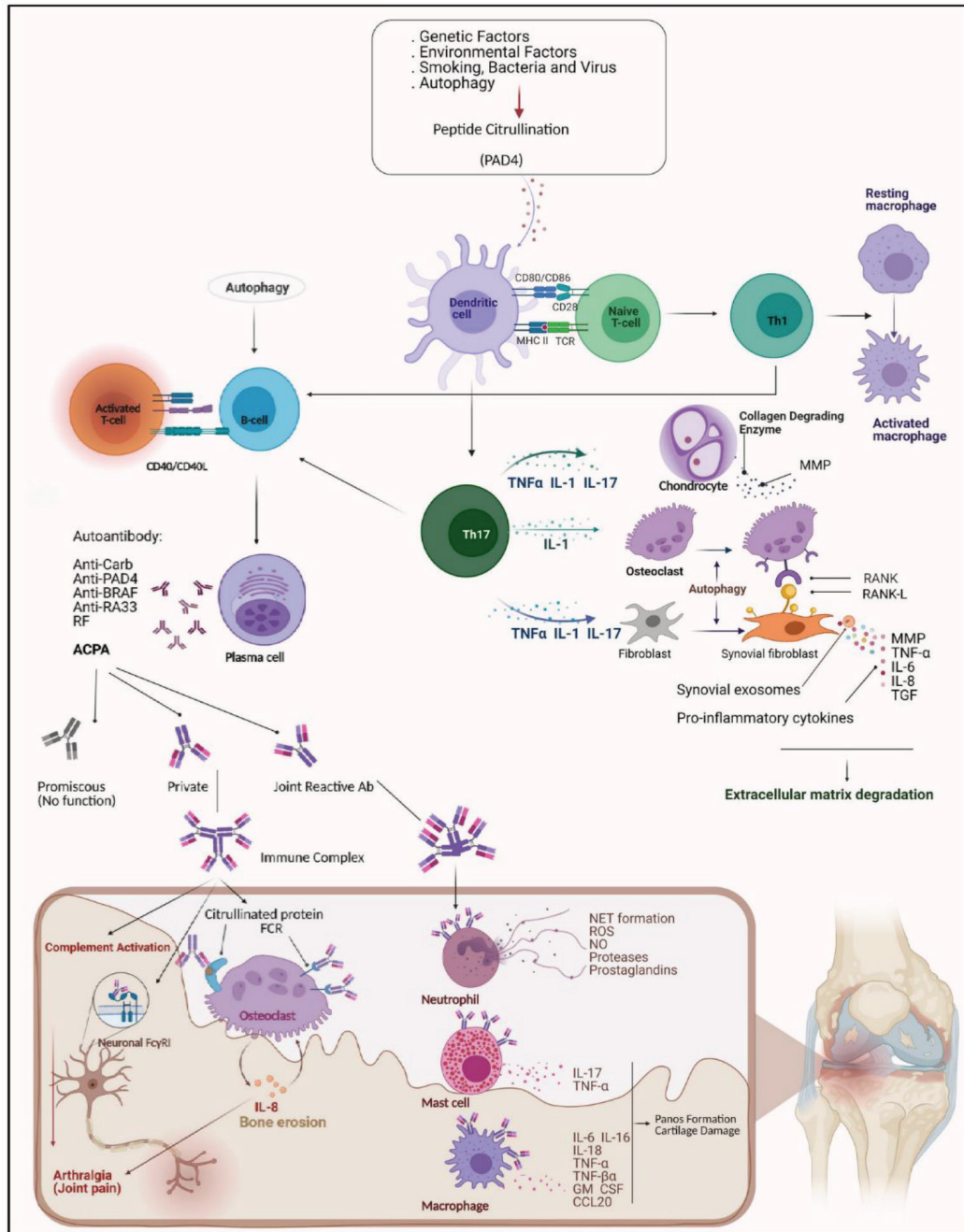


Figure 1. Pathogenesis of rheumatoid arthritis.

The American College of Rheumatology has proposed recommendations for employing DMARDs to alleviate symptoms and enhance joint functionality¹⁴. Despite their effectiveness, these medications are associated with numerous well-known adverse effects. Surgical intervention is often suitable and carries the potential for significant complications such as bleeding and infection. Combining the use of DMARDs with

complementary medicine is also a viable approach¹⁵. The drawbacks of conventional pharmaceutical interventions have motivated individuals to explore alternative therapies. Among these supplementary methods, aromatherapy stands out. Additionally, there has been a reconsideration of whether low-dose glucocorticoid therapy can prevent articular damage in RA¹⁶.

4. Herbal Plants used in Treatment of Rheumatoid Arthritis

Plant-derived compounds possessing the capability to regulate the propagation of pro-inflammatory signals hold promise in the treatment of arthritis. These substances encompass various compounds reputed for their anti-inflammatory attributes, including alkaloids, flavonoids, quinones, terpenes, catechins, anthocyanins, and anthoxanthins. The subsequent discourse delves into several of these polyphenols that have been explored for their potential in addressing arthritis¹⁷. Medicinal plants have garnered considerable favour in multiple traditional medical systems due to their extensive array of pharmacological potentials, coupled with their relatively minimal adverse effects on biological systems¹⁸.

4.1 *Zingiber officinale*

Ginger is produced from the rhizomes of *Zingiber officinale*, a member of the Zingiberaceae plant family. With a lengthy history as both a spice and a medicinal herb, ginger holds a notable place¹⁹. This natural remedy is particularly effective. Although native to Southeast Asia, it is cultivated in various regions, including the Caribbean, Africa, Mauritius, Australia, Taiwan, and India. An earlier study revealed the presence of sesquiterpenes, monoterpenes, oxygenated monoterpenes, and monoterpene hydrocarbons in ginger oil. Ginger serves as a stimulant, carminative, aromatic, stomachic, and flavour-enhancing ingredient. Its applications extend to alleviating nausea, vomiting, and diarrhoea. Additionally, ginger is recognized for its anti-inflammatory, antioxidant, antiseptic, antifungal, antimicrobial, and anticarcinogenic properties²⁰.

Ginger extract stands out as a potent recommendation from clinicians for addressing joint pain caused by arthritis. The primary constituents are sesquiterpenoids, particularly (-) zingiberene. The anti-inflammatory attributes of ginger extract are attributed to natural compounds known as Sesquiterpene Lactones (SLs)²¹.

Recently, in the streptococcal cell wall-induced arthritis animal model of RA, the efficiency of a crude ginger extract and a fraction having just gingerols and analogues to reduce joint swelling were examined. Ginger, which has been used in Asian medicine

and food for generations, has anti-inflammatory qualities²². It can decrease inflammatory molecules called leukotrienes and produce prostaglandins, which are hormone-like compounds that induce pain and inflammation²³.

4.2 *Thymus*

The genus *Thymus*, belonging to the Lamiaceae family, comprises around 400 species of aromatic herbaceous perennials with leaves that maintain their aroma either permanently or semi-permanently. This genus also includes numerous subspecies, variations, and subvarieties²⁴. A previous study demonstrated that the application of thymol (100 mg/kg orally) or nicotine (2.5 mg/kg orally) individually, as well as their combination exhibited an anti-inflammatory effect against experimentally induced RA in rats. Furthermore, the combination of thymol and nicotine (at doses of 50 and 1.25 mg/kg, respectively) displayed a notable alteration in levels of IL-1, IL-17, C-reactive protein, and myeloperoxidase in comparison to individual therapies, as indicated by the findings²⁵.

4.3 *Curcuma longa*

The primary phenolic ingredient in the traditional Chinese herb known as *Curcuma longa*, also called turmeric, safflower, or yellow ginger is curcumin. Three curcuminoids, demethoxycurcumin, bisdemethoxycurcumin, and curcumin (diferuloylmethane, the main component that lends turmeric's yellow colour), are the main active components of turmeric. Additionally, volatile oils such as zingiberene, atlantone, and turmerone showed pharmacological impacts, which was shown in an earlier report²⁶. The tuberous roots known as "rhizome" have therapeutic qualities and are frequently used as a medication to treat atherosclerosis, diabetes, anaemia, bone-related problems, ringworms, common cold, cough, osteoarthritis, itching, and eye inflammation²⁷.

Numerous lines of documentary proof, both in vivo and in vitro, point to the possibility that curcumin could be effective in treating arthritis. Another study has demonstrated that curcumin can suppress the activation of the transcription factor nuclear factor kappa B (NF- κ B), which in turn suppresses the expression of inflammatory mediators like TNF- α , adhesion molecules, cyclooxygenase 2 (COX-2), Matrix Metalloproteinases (MMPs), and 5-lipoxygenase

(5-LOX), all of which are linked to arthritis²⁸. Curcumin has the potential to treat arthritis, according to Jackson *et al.*, who discovered that it suppressed angiogenesis, synoviocyte proliferation, collagenase and stromelysin expression, and neutrophil activation. Additionally, it has been noted to enhance the COX-2 inhibitor celecoxib's growth-inhibitory and pro-apoptotic actions on osteoarthritis synovial adherent cells²⁹.

4.4 *Vitis vinifera*

A well-known variety of grape from southern Europe and western Asia, *Vitis vinifera* L. is a member of the *Vitis* genus from the Vitaceae family. The fruits of the grapevine are used as a nutritional booster, while the seeds, as well as the leaves, are employed as herbal medicine³⁰. Colds and rheumatic conditions are treated using *Vitis vinifera's* stem. Another study's findings suggested that intraperitoneal injection of grape seed extract reduced the severity of Collagen-Induced Arthritis (CIA) in mice, and the grape seed proanthocyanidin extract might be helpful in the management of RA³¹.

4.5 *Commiphora mukul*

Northern India is the region of the world where you can find *Commiphora* the most frequently. It is assigned to the Burseraceae family. The tree produces gum guggul, also known as guggulu, a yellowish resin with a balsamic scent³². Guggulsterones, namely Z- and E-guggulsterone, are some of its active ingredients. An extract of resin known as guggul has been utilized in the practice of Ayurveda for managing a number of ailments, including arthritis³³. In both formaldehyde and Complete Freund's Adjuvant-Induced arthritis in rats, vatari guggulu showed a considerable suppression of joint swelling. Additionally, it has decreased the elevated levels of white blood cells, rheumatoid factor, erythrocyte sedimentation rate, cholesterol, triglycerides, and low-density lipoprotein, red blood cells and haemoglobin levels are improved³⁴.

RA can be effectively treated with guggul. Additionally, the oleo-gum resin of guggul is abundant in phytoconstituents such as lignans, terpenoids, and steroids that can function as potent reducing agents. In a single investigation, Singh *et al.*, used guggul's reducing potential and anti-inflammatory effectiveness to create biostable G-AgNPs (Guggul-mediated biosynthesized

silver nanoparticles), which were then used to treat RA. Following oral administration, the produced nanoparticles had good in vitro colloidal stability and an excellent in vivo safety profile. That study highlights the potential application of G-AgNPs for targeting RA as it is the first to describe the use of biosynthesized bio-active nanoparticles for treating RA without the need for any additional medications³⁵.

4.6 *Withania somnifera*

A versatile medicinal plant of the Solanaceae family, *Withania somnifera* L. is widely distributed in subtropical areas of the globe. Due to its superior pharmacological characteristics, *Withania somnifera* is utilized as one of the main medications in Indian Systems of Medicine (ISM)³⁶. It is well known as ashwagandha. Ashwagandha is the plant favoured for arthritis, which affects joints that have become painful, dry, swollen, and irritated. In the management of rheumatic pain, the ashwagandha root medication plays a significant role³⁷. Alkaloids and steroidal lactones are thought to be responsible for the root's pharmacological effect. Withanine, pseudo-withanine, somniferine, tropine, pseudo-tropine, and somnine make up the majority of the alkaloids²⁰. In adjuvant-induced arthritic rats, oral treatment of *Withania somnifera* Linn., root powder demonstrated an anti-arthritic efficacy³⁸.

4.7 *Boswellia serrata*

Boswellia serrata (Salai/Salai guggul) is a medium to big-sized branch tree of the family Burseraceae (Genus *Boswellia*) that blooms in dry mountainous terrain of India, Northern Africa, and the Middle East. For millennia, gum-resin preparations of *Boswellia serrata* have been utilized in folk medicine to cure a variety of chronic inflammatory disorders³⁹. *Boswellia serrata* extracts have been shown in studies to decrease pro-inflammatory cytokines linked with RA. It has been demonstrated to decrease IL-1, TNF- α , and interferon and increase the generation of IL-10 in collagen-induced arthritic rats⁴⁰. These cytokines work together to cause persistent inflammation and damage to tissues as RA progresses. However, *Boswellia serrata* extract supplementation reduced cartilage breakdown, fibro-osteous proliferation, vasculitis, pannus development, synovial hyperplasia, vascular proliferation, and fibrinoid necrosis, all of which are hallmarks of RA⁴¹.

4.8 *Cinnamomum verum*

Cinnamon is a characteristic spice that is used regularly throughout the world. That is a member of the Lauraceae family. Typically, a tree's inner bark has been applied as a flavouring component in food and in many traditional treatments. Cognitive function is improved by the antioxidant and anti-inflammatory properties of this plant⁴². According to Shishehbor *et al.*, eight weeks of supplementation with cinnamon in RA-affected women significantly decreased pain as measured by the Visual Analogue Scale and Disease Activity Score 28. Additionally, intake of cinnamon significantly decreased the number of tender joints and swollen joints, as well as serum C-reactive protein and TNF- α levels. The frequent use of cinnamon supplements may be employed as a pharmacological agent for the therapy of RA due to their accessibility and absence of undesirable effects⁴³. In preclinical models of inflammation and RA, Ceylon cinnamon bark was shown to lower TNF- α levels⁴⁴. In a rat model of RA, Vetal *et al.*, showed type A procyanidin from Ceylon cinnamon to have antiarthritic properties⁴⁵.

4.9 *Camellia sinensis*

An everlasting shrub or miniature tree of the Theaceae flowering plant family is the *Camellia sinensis* Linn. *Camellia sinensis* Linn. is currently grown in tropical and subtropical areas all over the globe. Polyphenols (catechins and flavanols) serve as the *Camellia sinensis* Linn. plant's active ingredients. Caffeine and essential oils are additional ingredients. (-) Epigallocatechin is the most significant catechin in green tea and a strong antioxidant²⁰. Moreover, another name for the plant is green tea. In one study, Fechtner *et al.*, discovered the different catechins in green tea, such as Epigallocatechin Gallate (EGCG), Epicatechin Gallate (EGC), and Epicatechin (EC) altered in their ability to block the IL-1 signalling pathway, which controls the expression of Cox-2 and the pro-inflammatory mediators IL-6 and IL-8 within initial human RA Synovial Fibroblasts (RASFs)⁴⁶.

The synthesis of IL-6, IL-8, and MMP-2 was inhibited, while Cox-2 expression was specifically inhibited, by EGCG and EGC. There were no inhibitory effects found in EC. They discovered that all of the catechins tested might reduce the Transforming growth

factor- β -activated kinase 1 (TAK-1) function when they examined the expression of important signalling proteins in the IL-1 signalling pathway. As a result, drinking green tea has a general anti-inflammatory impact⁴⁵. RA is believed to be linked to increased free radical production in inflamed joints and an impaired antioxidant system. A mouse model of inflammatory arthritis has demonstrated the anti-inflammatory effects of Green Tea Extracts (GTE). Meki *et al.*, explore the potential processes by which green tea and Vitamin C extracts shield joints in the RA rat model. Additionally, they have notable anti-inflammatory potency and have a notable impact on RA by lowering Prostaglandin E2 (PGE2) levels in RA rat models⁴⁷. Epigallocatechin-3-O-gallate (EGCG), the main catechin in green tea, gained a lot of attention as a potential treatment for RA due to its capacity to inhibit synovioocyte proliferation and interleukin-6 release⁴⁸.

4.10 *Allium sativum*

Garlic, or *Allium sativum*, is a highly aromatic bulb crop that is said to have originated in Uzbekistan, Kazakhstan, and Western China. Typical food for flavour and spice, garlic is an ancestor of the Liliaceae family and is one of the medicinal plants most frequently employed in contemporary folkloric medicine. There are two fundamental varieties of garlic: Softneck and hardneck. The hard, woody core stalks of hard neck garlic, which include *A. sativum* var. ophioscorodon and *A. sativum* variety pekinense, extend to the basal plate at the base of the bulb⁴⁹.

In a randomized, double-blind, placebo-controlled study, 70 women suffering from RA were divided into two groups. Over 8-week period, the control group was administered a placebo, while the intervention group was provided with a 1,000 mg garlic supplement. Clinical symptoms, fatigue, levels of tumor necrosis factor- α (TNF- α), C-Reactive Protein (CRP) in the serum, and Erythrocyte Sedimentation Rate (ESR) were evaluated at the trial's commencement and conclusion. Following the intervention, a significant reduction in serum CRP and TNF- α levels was observed in the garlic group compared to the placebo group ($p = .018$, $p < .001$). Furthermore, the intervention group experienced notable decreases in pain severity, the number of painful joints, Disease Activity Score (DAS-28), and

fatigue in comparison to the control group ($p < .001$ for all)⁵⁰.

Allium ampeloprasum L., also known as Snow Mountain Garlic (SMG), is a kind of wild garlic native to the Trans-Himalayas that is highly prized in the mountain folk medicine system⁵¹. for its ability to reduce inflammation and ease arthritis symptoms. In a different study, administering SMG extracts to rats significantly ($p < 0.001$) delayed body mass loss and haematological changes while also improving clinical symptoms such as arthritis score, arthritic index, joint stiffness, hyperalgesia, edema and histopathological indicators. NF- κ B, COX-2, and iNOS expression in the tissues of the ankle joint could all be dramatically reduced by SMG extracts²⁰.

4.11 *Piper nigrum*

A flowering plant of the Piperaceae family, *Piper nigrum* (black pepper) is used in food preparation. It is grown as a fruit and dried before being used as a flavouring and spice. It grows in the southernmost sections of India as well as other tropical areas. Both for its taste abilities and in conventional medicine, dried pepper has long been used thoroughly⁵². It contains “piperine,” a strong alkaloid with a variety of pharmacological effects. Several metabolizing enzymes are inhibited by piperine, which increases the bioavailability of several medications and minerals¹⁸.

When present at doses ranging from 10 to 100 g/ml, piperine suppressed the expression of interleukin-6 and Matrix metalloproteinase-13 (MMP-13) and decreased PGE2 synthesis in a dose-dependent way. Even at a piperine concentration of 10 g/ml, the synthesis of PGE2 was noticeably reduced. In synoviocytes treated with IL1 β , piperine prevented nuclear factor (NF) κ B but not activator protein 1 (AP-1) from migrating into the nucleus. Another study found that Piperine significantly lessened nociceptive and arthritic symptoms in rats on days 8 and 4, respectively⁵³.

4.12 *Capsicum annuum*

The dried fruits of the Solanaceae-related genus *Capsicum*, which is a member of that family, are used to make chili pepper spices. A little growing shrub called *Capsicum annuum*, which contains capsaicin (chili pepper) was first planted in the tropics of the Americas. It nowadays grows all over the globe,

including in the United States. Numerous, including capsanthin, carotenoids, capsorubin, beta-carotene, lutein, cryptoxanthin, phytofluene, and xanthophyll, as well as steroids, including capsicoside, are found in *Capsicum annuum* (chili pepper)⁵⁴. The spicy substance in chili peppers known as capsaicin is an extremely selective agonist that targets the transient receptor potential vanilloid 1 receptor found on nociceptive sensory neurons. It has been used topically to treat several conditions, including RA, osteoarthritis, diabetic neuropathy, and discomfort post-surgery⁵⁵. However, when taken as a pure white crystalline molecule, capsaicin particularly works by removing substance P stores from sensory neurons. individuals with RA or osteoarthritis reported noticeable pain alleviation in a four-week, multicenter, double-blind, placebo-controlled trial of 10 individuals using capsaicin 0.025% topical analgesic cream⁵⁶.

4.13 *Salix alba*

The white willow bark's scientific name is *Salix alba* (SA). Traditionally used as an analgesic and antipyretic by ancient Egyptian, Roman, Greek, and Indian humanity, the bark of the white willow plant represents one of the oldest known herbal medicines for inflammation and pain. A resurgence in the use of white willow bark for the treatment of inflammatory disorders can be attributed to aspirin's adverse effects on the stomach⁵⁷.

The ideal treatment for gout and rheumatism, according to the late medieval Italian physician and botanist Pietro Andrea Mattioli (1500–1577), is a decoction of willow bark and leaves⁵⁸. Willow bark, in the form of a 20% decoction, is prescribed in Bulgaria to cure infected arthritis and rheumatic as well as to lessen joint pain and swelling, regulate body temperature, and enhance appetites and general well-being (Minaeva, 1991)⁵⁹. According to Zuzuk *et al.*, fresh white willow bark picked in the early hours of the day from three-year-old shoots is used in homoeopathic remedies for the relief of rheumatism, gout, and arthritis⁵⁸.

Some dietary supplements contain the components of willow bark. Trials using willow bark extracts containing 120–240 mg salicin, the alleged active ingredient, reported no major adverse outcomes⁶⁰. Two randomized, double-blinded, controlled clinical trials using a standardized willow bark extract equivalent

to 240 mg of salicin per day for the management of osteoarthritis, or RA, were reported by Biegert *et al.*, The amount of physical activity significantly decreased, and there was a reduction in pain in the willow bark group⁶¹.

4.14 *Perna canaliculus*

It is also referred to as the New Zealand mussel and is a member of the Mytilidae family. It is exclusively found in the waters off the west coast of New Zealand, although it is grown there and produced for the global food and nutraceutical markets. Many arthralgias, in both people and animals have historically been treated with *P. canaliculus* as a medicinal therapy. It has been consistently shown that the *Perna canaliculus* species contains anti-inflammatory substances, including proteins that can enhance thrombin inhibitory activity and omega-3 polyunsaturated fatty acids (OMEGA-3 PUFAs) that can reduce pro-inflammatory circumstances⁶².

For the very first time, clinical research conducted by Gibson *et al.*, revealed that freeze-dried mussel powder could potentially serve as a useful addition to or substitute for conventional therapy of RA and osteoarthritis. According to Gibson *et al.*'s original preliminary therapeutic trial, 86 patients received mussel powder prescriptions for a duration that varied between 6 months to 4.5 years. Numerous patients with RA and osteoarthritis were found to have benefited in some way from receiving this medication⁶³. The care of mild to severe degenerative joint problems in dogs is another area where a green-lipped mussel extract may be helpful⁶⁴.

4.15 *Borago officinalis* L.

An herbaceous perennial belonging to the Boraginaceae family with native origins in North Africa, boreal (*Borago officinalis* L.) is commonly cultivated throughout several Mediterranean nations. This plant has some of the medical beneficial effects in Algeria. Furthermore, it is used to make beverages and salads. Despite receiving more agricultural attention in recent years because of the large amount of gamma-linolenic acid in its seeds⁶⁵. Patients with RA who received 1.4 g/d of gamma-linolenic acid (in borage seed oil) for six months experienced a clinically applicable and significant statistical decrease in the activity of the

disease. Gamma-linolenic acid is typically offered in evening primrose and borage seed oil preparation at health food stores⁶⁶.

4.16 *Tripterygium wilfordii*

The Chinese herb *Tripterygium wilfordii* (Celastraceae) is also known as the “thunder god vine”. Numerous inflammatory and autoimmune illnesses are treated with it⁶⁷. Although this plant itself is poisonous, its root extracts have a high therapeutic potential and are a great choice for use in conventional treatments for RA. It is well known to reduce discomfort while reducing moistness and edema in the joint region⁶⁸.

This herb has more than 100 separate components, and the majority of them have significant medicinal properties for a range of autoimmune and inflammatory illnesses. *Tripterygium wilfordii* hook extracts have been shown in studies on laboratory animals to effectively cure a range of autoimmune disease models by suppressing immunological and inflammatory responses⁶⁹.

RA can be treated with the help of the chemical substances - celastrol and triptolide, which were extracted from the thunder god vine or *Tripterygium wilfordii* hook. They concentrate on many cytokines, proteases, and signalling pathways. According to Song *et al.*, triptolide suppresses NFκB, the Receptor activator of nuclear factor kappa B (RANK- κB) and its Receptor Activator of Nuclear Factor Ligand (RANKL), ligand/osteoprotegerin signalling pathway, cyclooxygenase 2, matrix metalloproteases, and cytokines⁷⁰.

A standardized extract of the roots of the medicinal plant *Tripterygium wilfordii* hook F, which has been extensively used in Chinese traditional medicine, has been shown in another trial to be an effective treatment for those with significant RA. Treatment with *Tripterygium wilfordii* hook extract during the 6-month trial led to an immediate reduction in RA clinical signs and symptoms, such as joint swelling, joint pain, and measures of general well-being, as well as in markers of inflammation like CRP, ESR, and the proinflammatory cytokine interleukin-6⁷¹.

4.17 *Harpagophytum procumbens*

Harpagophytum procumbens (Pedaliaceae), often known as Devil's claw. The species grows wild in red sand in the former Transvaal locale, which now includes

the northwest, Limpopo, Gauteng, and Mpumalanga provinces of South Africa, as well as in Botswana and Namibia⁷². It is believed to possess anti-inflammatory effects in both people and animal models. Acetylated phenolic glycosides and terpenoids are the active components of iridoid glycoside. Devil's claw treatment has allegedly produced "miraculous" outcomes in patients with adult and juvenile RA, according to several claims that have recently appeared in regional newspapers in the north of England and Scotland. The medication was a pill made from the root's fluid extract⁷³.

According to another study, preparations produced via the secondary tubers of Devil's Claw was effective in treatments for people with rheumatic disorders⁷⁴. Its usage in treating inflammatory conditions of the muscles and tendons and low back pain has grown significantly in popularity in recent years⁷⁵. Grant *et al.*, also noted that *Harpagophytum procumbens* is now gaining popularity among herbalists as a supportive or additive therapy for tendonitis, other pains like headache, backache, and menstrual pain, as well as degenerative joint diseases like RA or osteoarthritis⁷⁶.

4.18 *Uncaria tomentosa*

The Amazon basin is the natural habitat of *Uncaria tomentosa*, which is part of the Rubiaceae botanical family. Bolivia, Brazil, Colombia, Costa Rica, Guyana, Nicaragua, Panama, Peru, Ecuador, Guatemala, French Guiana, and Venezuela are among the countries where it is widely cultivated. It has immunomodulatory characteristics and has been employed for the treatment of inflammatory bowel disease and arthritis because it includes the spiroindole alkaloids isopteropodine and rynchophylline⁷⁷.

The Shaninka Indians of Peru have a long history of using specific *Uncaria Tomentosa* plants as a treatment for rheumatic ailments. In conjunction with sulfasalazine or hydroxychloroquine, Mur *et al.*, show that a free extract taken from the pentacyclic chemotype of *Uncaria tomentosa* has some beneficial clinical effects on RA illness. *Uncaria tomentosa's* anti-inflammatory properties were discovered by Mur *et al.*, in phase II tests for chronic inflammatory illnesses such as RA and arthrosis. This discovery sparked research into the effectiveness of this plant extract in treating Aromatase inhibitor-induced arthralgia (AI-induced arthralgia)⁷⁸.

In another investigation, Sandoval *et al.*, discovered that freeze-dried cat's claw can decrease TNF- α generation in RAW cells stimulated with Lipopolysaccharide (LPS) was used to measure the anti-inflammatory effect of the substance. These findings showed that *Uncaria guianensis* as well as *Uncaria tomentosa* have been effective at reducing macrophage TNF- α production⁷⁹.

4.19 *Eucalyptus*

One of the most significant and commonly planted genera in the entire globe is *eucalyptus*, a native to Australia that is a member of the Myrtaceae family and has about 900 varieties and subspecies. It is primarily grown for its pulp, timber and essential oils, which have health advantages and therapeutic purposes⁸⁰.

One of the herbal remedies utilized by people with RA is *Eucalyptus*. There are numerous plant species found throughout the globe. Anti-inflammatory, anti-nociceptive, and anti-microbial effects are all present in *Eucalyptus*. We can use *Eucalyptus* externally or inhale it to relieve pain. It increases the release of endorphins and neurotransmitters in the brain. Knee discomfort can be effectively relieved by inhaling *Eucalyptus*. According to one study using *Eucalyptus* oil made from a species of Myrtassa and extracted from the plant's leaves, patients who acquire *Eucalyptus* oil inhalation experienced much less discomfort⁸¹. There was a study in which a researcher created transdermal gel containing brucine by adjusting the pH of the gel's components. *Eucalyptus* oil, Ethyl alcohol, carboxymethyl cellulose, and propylene glycol made up the gel. The produced gel shown anti-inflammatory action in *in vivo* experiments and inhibited synoviocyte proliferation⁸².

4.20 *Actaea racemosa*

Black cohosh, also referred to as *Actaea racemosa* is a plant from the buttercup family that is marketed as a nutritional product. It is derived between the roots and beneath the ground stems of the buttercup and is offered as a tablet, capsule, or liquid with dosages ranging from 120 to 540 mg. *Actaea racemosa* L. is a perennial plant with an extensive record of traditional usage, is a native of deciduous woodlands in eastern North America and is often prescribed for RA and female reproductive problems⁸³. native of Indoamerican have historically utilized *Cimicifuga racemosa* to treat a variety of

gynaecological issues, including monthly cramps, RA, aching muscles and joints, neuralgias, and more⁸⁴.

4.21 *Angelica sinensis*

A member of the Apiaceae family, *Angelica sinensis* is a tropical plant. Traditional Chinese, Japanese and Korean medicine have been using *angelica sinensis*, also referred to as Chinese angelica, for several thousand years. First mentioned in the Shen Nong Ben Cao Jing during the Eastern Han Dynasty, *Angelica Sinensis* is also known as “female ginseng” in China. For the management of inflammatory-related diseases, professionals may prescribe *Angelica sinensis* alone or in combination with other plants⁸⁵. Coumarins, phytosterols, polysaccharides, ferulate, and flavonoids are some of the key chemical categories that can be found in *Angelica sinensis*. One of *Angelica sinensis*'s most physiologically active constituents, ferulic acid is known to have anti-arthritis properties. IL-1 β , TNF- α , Matrix metalloproteinase-1, (MMP-1) and Matrix metalloproteinase-13 (MMP-13) expression were all reduced by ferulic acid in hydrogen peroxide-induced chondrocytes⁸⁶.

4.22 *Glycyrrhiza glabra*

One of the most well-known plants for medicinal purposes is *Glycyrrhiza glabra*, which is a member of the Fabaceae family (which is frequently known as Leguminosae). *Glycyrrhiza glabra* is a perennial herb or subshrub that grows from 3 to 7 feet tall in the temperate region. It has a long, cylindrical, branching, flexible, burrowing rootstock, and runners⁸⁷. The components that are utilized are the dried runners and roots that are gathered in the autumn. Glycyrrhizin, a triterpenoid saponin also referred to as glycyrrhizic acid or glycyrrhizinic acid, is licorice root's main active ingredient⁸⁸.

Considerable anti-allergic and anti-inflammatory properties are present in glycyrrhiza. A review study examined the potential use of licorice's active ingredients, Glycyrrhizin (GL) and Glycyrrhetic Acid (GA), in the treatment of RA using the COX-2/thromboxane A2 (TxA2) pathway⁸¹. Shin EM discovered that the key licorice component of glycerol inhibits the synthesis of nitric oxide, PGE2, IL-1 β and IL-6⁸⁹. Licorice extract was discovered to lower arthritis score and paw edema in a mouse collagen-induced

arthritis model by lowering the expression of Matrix metalloproteinase-3 (MMP-3) in inflamed articular cartilage and suppressing the generation of IL-1 β and TNF- α in the Collagen-Induced Arthritis (CIA) mice⁹⁰.

4.23 *Centella asiatica*

The perennial, clonal creeper *Centella asiatica* is a member of the Apiceae (Umbellifere) family. India, Pakistan, South Africa, Madagascar, the South Pacific, Sri Lanka, and Eastern Europe are among the tropical and subtropical nations where it is present⁸⁵.

A triterpene of the aglycone type from *C. asiatica* called Asiatic acid has been studied by Yun *et al.*, for its impact on the pathway of inflammation in RAW 264.7 macrophage cell cultures. Nitric oxide (NO) and prostaglandin E2 (PGE2) production that was increased by lipopolysaccharide was shown to be potently suppressed by Asiatic acid. In addition, it inhibited nuclear factor- κ B (NF- κ B) activation and decreased the generation of inflammatory mediators such as IL-6, IL-1, and Tumor Necrosis Factor (TNF)⁹¹. One of the most prevalent triterpenoid components in *Centella asiatica*, Madecassoside (MA), is thought to be the main bioactive ingredient in the therapy of RA⁹².

4.24 *Urtica dioica*

The plant *Urtica dioica* is a member of the Urticaceae family. In Europe, it has been frequently applied to the treatment of benign prostatic hyperplasia. It has also been used to treat RA, osteoarthritis, and excessive urination⁹³. It is thought that phytochemicals such as lignans, flavonoids, lectins, polysaccharides, and steroids are responsible for its biological actions⁹⁴.

Stinging nettle (*Urtica dioica*) leaf extracts are effective in anti-inflammatory treatments for RA because they strongly inhibit the transcription factor NF- κ B⁹⁵. Studies showed that *Urtica dioica* extract reduced the levels of MMP-1, -3, and -9 proteins that were induced by IL-1 β , indicating that *Urtica dioica* may be exploited as an IL-1 β inhibitor for the treatment of RA⁹⁶.

4.25 *Cedrus deodar*

Cedrus deodara (Roxb.) Loud, a striking and ornamental evergreen tree is a part of the Pinaceae family and is extensively grown across the lower regions of the Himalayas. Deodar forests are prevalent from

regions such as Kashmir (at altitudes of 1500-3000 m), specifically in areas like Kishtwar, Krishna Ganga, and Jhelum, to Garhwal⁹⁷. The wood of *C. deodara* has a rich history of use in Ayurvedic medicine for many centuries, particularly in the treatment of inflammation and RA⁹⁸.

The most popular chronic test model for arthritis is adjuvant-induced arthritis, in which the pathology and clinical alterations are similar to those found in RA in humans. The oral anti-inflammatory properties of the volatile oil produced by steam distilling *Cedrus deodara* wood were investigated. As seen with the paw swellings on the non-injected limbs, the oil's effect on adjuvant-induced arthritis in rats demonstrated that the polyarthritis phase was substantially suppressed. Additionally, it suppressed the acute phase of the adjuvant-induced response, demonstrating its effectiveness against the acute inflammatory response⁹⁹.

4.26 *Barringtonia racemosa* Linn.

Due to its therapeutic properties, *Barringtonia racemosa* (L.), often known as putat, fish poison tree, or powder puff tree, is a type of extremely valuable species of plant. It's a member of the Lecythidaceae family. Geographically widespread throughout eastern Africa and Madagascar to the Micronesian and Polynesian Islands, this species remains closely linked to a variety of ethno-botanical applications by numerous cultures worldwide¹⁰⁰.

This plant contains 3, 3'-dimethoxy ellagic acid, dihydromyricetin, gallic acid, bartogenic acid, and stigmaterol as chemical components. It possesses anti-inflammatory, antioxidant, and anti-microbial properties. Bartogenic acid is the active ingredient which triggers the anti-arthritis effect and is used to treat RA¹⁰¹. In the ayurvedic literary work, the fruits of *Barringtonia racemosa* are recommended for the alleviation of pain, inflammation, and rheumatic disorders. The study, activity-guided isolation of bartogenic acid, and its assessment in Complete Freund's Adjuvant (CFA)-induced arthritis in rats were previously reported by Patil *et al.*, Bartogenic acid defends rats from the initial and secondary arthritic lesions, alterations in body composition, and haematological disturbances brought on by CFA. The Bartogenic acid-treated arthritic rats also showed a decrease in the blood levels of inflammatory and

arthritic indicators such as C-reactive protein and rheumatoid factor¹⁰².

4.27 *Justicia gendarussa* Burm f.

Chinese native *Justicia gendarussa* Burm f. sometimes known as willow-leaved *Justicia*, belongs to the Acanthaceae family. The majority of India and the Andaman Islands are frequent locations for species. One of the significant herbs utilized in the Ayurvedic medical system is *Justicia gendarussa* Burm f. The leaves are mostly employed for therapeutic purposes. Friedelin, lupeol, β -sitosterol, and aromatic amines are all present in the leaves¹⁰³.

Using arthritic rat models generated by Freund's adjuvant and collagen, the anti-arthritis efficacy of the alcohol-based extract of the herb *Justicia gendarussa* was assessed. After administering both the ethanolic extract of *Justicia gendarussa* and regular aspirin to the rats, the ethanolic extract significantly reduced the animal's symptoms of arthritis and was statistically comparable to aspirin's effects¹⁰⁴.

4.28 *Cleome gynandra* Linn.

The Cleomaceae family of plants has 601 plant species under the name Cleome. The renowned therapeutic herb *Cleome gynandra* Linn. has both traditional and pharmacological significance. After thorough investigation, it becomes clear that the plant has a wide variety of pharmacological applications, including anti-inflammatory, free radical scavenging, immunomodulator, anti-cancerous, and anti-diabetic compounds¹⁰⁵. The herb *Cleome gynandra* can be used medicinally and is widespread around the world. In Taiwan, *Cleome gynandra* is prescribed for the relief of RA, gonorrhoea, diarrhoea, and malaria¹⁰⁶.

4.29 *Juglans regia* Linn.

A member of the Juglandaceae family is *Juglans regia* Linn. It is often referred to as a walnut tree. According to some reports, the bark of *Juglans regia* contains anti-inflammatory, blood-purifying, anti-cancer, diuretic, depurative, and laxative properties. The bark is ground into a fine powder to be used as a mouthwash and to stop gum bleeding¹⁰⁷.

Traditional medicine has utilized extracts of *J. regia*'s leaves and pericarp. In north-eastern Italy, a poultice made from *Juglans regia* stem bark is used to cure

inflammation, while in Turkey, rheumatic discomfort in adults is treated with *Juglans regia* leaves¹⁰⁸. According to Hosseinzadeh *et al.*, *J. regia* extracts are potent analgesics and anti-inflammatory treatments for conditions like RA¹⁰⁹.

4.30 *Mangifera indica* Linn.

Mango (*Mangifera indica* Linn.), often known as Amba. This plant naturally grows in India, although it is also known to exist in Southeast Asia and the Indo-Malayan region. Indian tribes and all Indians made use of the fruit, root, bark, and leaves to treat a variety of sicknesses and problems¹¹⁰. Vimang represents an aqueous extract of *Mangifera indica* L. that has long been used in Cuba as an anti-inflammatory, analgesic, and antioxidant. Methotrexate (MTX) and *Mangifera indica* extract (Vimang tablets, 300 mg) have been shown to reduce RA disease activity. The painful and swollen joint counts, erythrocyte sedimentation rate, Disease Activity Score 28 (DAS 28), Visual Analogue Scale (VAS), and Health Assessment Questionnaire (HAQ) were used to assess RA activity. The only patients who showed statistically significant progress were those in the MTX-Vimang group¹¹¹.

Vimang has been experimentally shown to decrease TNF- α production in macrophage cell line RAW264, which has been treated with proinflammatory stimuli. A proinflammatory cytokine called TNF- α , whose plasma levels are directly linked to phagocytes' capacity to produce superoxide and increase inducible nitric oxide synthase (iNOS) activity, which in turn increases NO levels. Anti-TNF- α antibody therapy decreased Nitric Oxide Synthase (NOS) activity and disease severity in RA patients¹¹².

4.31 *Pandanus fascicularis* Lam.

Pandanus tectorius, also known locally as Pandan laut and by its botanical names of *P. odoratissimus*, *P. fascicularis*, and *P. amaryllifolius*, is one of the 700 species or so mangrove coastal plants in the Pandanaceae family that are found around the world in subtropical and tropical regions, including Malaysia and Indonesia¹¹³. The chemical composition of a crude drug's ingredients governs its pharmacological activity. As a result, a variety of chemicals, including alkaloids, flavonoids, terpenoids, glycosides, and phenolics, have been linked to definite physiological effects in plants¹¹⁴.

Due to its analgesic, anti-inflammatory, and antipyretic properties, plants are frequently employed in many ancient medical practices like Ayurveda, Siddha, and Unani. The plant has been used to treat rheumatic fever, rheumatism, and RA in traditional medicine¹¹⁵.

4.32 *Nigella sativa*

The fatty acid and terpenoid content of *Nigella sativa* (black cumin) seed oil makes it a further potential therapy for RA sufferers. This plant is a member of the Ranunculaceae family¹¹⁶. A clinical investigation was carried out in response to its long-standing use, its ability to reduce inflammation and preliminary animal research that suggested it might be beneficial for RA.

The herb is also additionally referred to as Kalajira (Bengali), Black Cumin (English), Shonaiz (Persian), and Black Caraway Seeds (USA). 40 Egyptian women with RA participated in one study and received 500 mg of cold-pressed black cumin oil daily for one month after taking a placebo for one month. Throughout the experiment, methotrexate, folic acid, hydroxychloroquine, and diclofenac were all given to each individual concurrently. When compared to the placebo phase, the disease activity score was significantly lower following the black cumin oil phase¹¹⁷. 43 Iranian women with RA were randomly assigned to take either a placebo or 500 mg of black cumin oil twice daily for two months in a more thorough double-blind trial. Both the highly sensitive C-reactive protein level and disease activity were considerably decreased in the black cumin oil group when compared to the placebo group¹¹⁸.

5. Conclusion

RA is a medical condition characterized by inflammatory immune responses. It occurs as the body's immune system directs its attack towards tissues neighbouring the joints. This process is triggered by the release of specific chemicals and enzymes, which proceed to erode cartilage and bones. Arthritis is one of the most prevalent ailments globally, affecting a substantial number of individuals. While there exist established medical treatments and therapies for addressing this condition, they can bring about various side effects. This prompts the exploration of herbal alternatives in the management of rheumatoid arthritis.

Plant-derived products hold significant potential, but they necessitate extensive research in both preclinical and clinical settings to ascertain their effectiveness. Researchers turn to herbal remedies for managing various disorders due to their effectiveness, safety, and lower incidence of adverse effects compared to conventional medications. This avenue holds promise for achieving better symptom relief and overall improvement in the condition.

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