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## THE ROLE OF MEDICINAL PLANTS IN RHEUMATOID ARTHRITIS-AN UPDATED REVIEW

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### Abstract

Rheumatoid arthritis (RA) is a debilitating, persistent autoimmune condition that affects by a variety of endogenous and external causes. It is distinguished by cartilage and bone deterioration. The present traditional allopathic treatment is costly and has negative side effects. Recently, some ethnopharmacological research on RA was published, including anti-RA properties and therapeutic targets of various dosage forms of Traditional Herbal Treatments (THMs). Given the increased herbalists' interest medicines among people suffers from rheumatoid arthritis, further research into their safety and efficacy is needed. The goal of this research was to carry out a comprehensive assessment of the evidence based on the use of herbal medications in the treatment of RA Randomised Clinical Trials (RCTs). Different chemical ingredients discovered in various herbal treatments have modest support for lowering pain, sensitive joint count, and stiffness. Herbal remedies were generally considered safe to use. More study is required to evaluate the effectiveness, safety, and potential medication interactions of the numerous herbal remedies advocated for RA.

**Keywords:** herbal drugs, rheumatoid arthritis, treatment, randomisd control trials.

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### 1. Introduction

The autoimmune illness rheumatoid arthritis (RA), causes cartilage and bone disintegration, is a chronic, inflammatory disorder. According to statistics, persons with RA account for around 0.1% of the global population. The prevalence of RA is higher in patients who are over 50 and predominately female [1]. With this crippling illness, many people seek out Complementary and Alternative Medicine (CAM) treatments. Research has shown that those with chronic pain, such as those with RA, and those who are dissatisfied with their existing care are very inclined to seek alternative treatments; it is believed that between 60 and 90 percent of patients with arthritis use CAM [2]. The pathogenesis of RA is being studied to better understand its cellular and molecular basis. Proinflammatory cytokines such tumour necrosis factor

(TNF), interleukin (IL)-1, and IL-6 have reportedly been implicated as key disease perpetuation mediators. The scientific study of numerous plants and plant-based products is being done to create new medicinal agents. Here, we have attempted to explore the possibility for treating RA with numerous ancient Indian Ayurvedic, Unani, and Tibbi medicinal plants, as well as some Chinese and Korean plants [3]. Up to 50% of patients have comorbidities and extra-articular characteristics, while less than 10% of patients have significant extra-articular sequelae such vasculitis, pericarditis, pleuritis, and/or Felty's syndrome. The primary predictor of mortality in RA patients is extraarticular illness [4]. Individual symptoms might be quite different. In many cases, RA begins by infecting a few joints, then spreads to other joints throughout the body over the period of a few weeks or months. Family history is the biggest genetic risk factor for RA that has been identified, and it is thought to account for about 30% of the genetic risk for the condition in some people. RA more frequently affects women than men [5]. Traditional Chinese Medicine (TCM) has been practised for a very long time and was once quite popular over much of East Asia. It is based on Traditional Chinese Medicine (TCM) principles for the treatment of various ailments, such as acupuncture and cupping; these techniques entail the flexible use of Chinese herbal medicines (CHMs) and

their associated extracts few joints, then spreads to additional joints throughout the body over a few weeks or months [6]. The most effective use of disease-modifying antirheumatic medications (DMARDs) and the growing accessibility of novel biological agents have improved RA care during the past ten years. Conventional medical practises are regularly paired with DMARDs and/or biologics in China. This is most likely due to a combination of factors, including concerns about the side effects of DMARD combination therapy, the high cost of biological agents in China, the ease of access to conventional treatments in the hospital system, and public awareness of the growing body of research on the evidence base for traditional treatments such as herbal formulations and acupuncture.

## II. Drugs Used In Treatment of Rheumatoid Arthritis

### a. Feverfew (*Tanacetum parthenium*)

In one study, half of 41 women with RA received 70-86 mg/day of dried, powdered *feverfew*, whereas the other half received cabbage that had undergone the same treatment. Throughout, individuals continued to take their NSAID and analgesic drugs as indicated. After 6 weeks, the difference in grip strength between the treatment and placebo groups was significant (ES=0.915, 95% CI 0.265, 1.57). Other clinical examinations indicated no discernible difference. The researchers concluded that feverfew might be beneficial for RA, potentially at greater doses or over a longer period of time [2].

### b. Flaxseed oil.

During a three-month period, either *flaxseed oil* or *safflower oil* was given to 22 patients every day for 30 g/days. Each and every patient also took NSAIDs. None of the preclinical parameters alterations in any group based on comparisons made within each group [2].

### c. Ashwagandha

It is also known as *Withania somnifera*, is a popular Ayurvedic herb for its pain-relieving and anti-inflammatory properties. *W. somnifera* extract has been demonstrated to limit the production of TNF- $\alpha$ , IL-1, and IL-12 by inhibiting the activation of the NF- $\kappa$ B and Activator Protein 1 (AP-1) signalling pathways. *W. somnifera* extract lowered the rate of collagen breakdown in bovine Achilles tendon type I by decreasing collagenase activity. *W. somnifera* therapy decreased edoema, redness, deformity, and ankylosis in a collagen-induced arthritic rat model. *W. somnifera*'s ability to reduce reactive oxygen species (ROS), TNF- $\alpha$ , IL-1B, IL-6, MMP-8, and NF- $\kappa$ B activation while increasing IL-10 secretion may be responsible for its anti-arthritic properties. Sumantran et al. discovered that an aqueous extract of *W. somnifera* had a significant chondroprotective influence on OA cartilage in humans by lowering the collagenases' gelatinase activity. A recent study shown its analgesic advantages in people with RA. Therapy with 125 or 250 mg of *W. somnifera* extract was associated with significantly decreased mean Knee Swelling Index values when

compared to baseline and placebo in this 12-week clinical trial. The VAS scores for pain, stiffness, and impairment all decreased significantly. In comparison to the low and placebo doses, the greater dose indicated efficacy sooner (at 4 weeks), had higher physician global evaluations (excellent vs. good vs. fair), and needed less rescue paracetamol [7,13,14,16,17,18,19].

### d. *Eremostachys laciniata*

It is an Iranian plant, is typically used as a decoction to treat inflammatory disorders, including arthritis. The mechanical action of the plant is unknown. However, one research discovered that either crude methanol extract or *E. laciniata* fractions reduced the inflammatory response generated by carrageenan in rat paws. A reduction in H2O2- or HOCl-luminal chemiluminescence, as well as considerable DPPH radical-scavenging activity, are both indicators of possible antioxidant activity in *E. laciniata* aqueous extract. In one study, the benefits of topical *E. laciniata* administration on arthritic pain and symptoms were investigated. According to this single-blinded, randomised clinical experiment, using 0.5% *E. laciniata* ointment to afflicted joints over the course of two weeks significantly decreased VAS pain levels for individuals with RA and arthritis compared to using a control ointment. Pain ratings in arthritic and RA patients were lower after a week of using *E. laciniata* compared to a 0.5% piroxicam ointment, indicating a better initial therapeutic response. However, the pain ratings for the *E. laciniata* and piroxicam groups were equal after two weeks. *E. laciniata* therapy was associated with a greater reduction in joint inflammation during the course of the experiment when compared to piroxicam medication. The researchers also discovered that the most prevalent isolates from their *E. laciniata* extracts were iridoid glycosides, and they hypothesised that these compounds were responsible for the anti-inflammatory activity they saw in their arthritis patients [7,9,10,11].

### e. *Matricaria chamomilla*

Joint discomfort has long been treated using *Matricaria chamomilla*, popularly known as *chamomile*. The plant's dried floral component has long been used to relieve rheumatic pain and inflammation. *Chamomile* is currently listed as one of the plants that is "generally regarded as safe" by the FDA. The two most common varieties of *chamomile* are *German chamomile* and *Roman chamomile*, both of which are members of the *Asteraceae; Compositae* family. The most common *chamomile* preparation is herbal tea. *Chamomile* contains a variety of phenolic compounds, including apigenin, quercetin, patuletin, luteolin, and glucosides. These chemicals reduce cytokines and PGE2, which are implicated in the pathogenesis of arthritis. A randomised controlled clinical study comparing topical *chamomile* oil to diclofenac and placebo was conducted on patients with OA. *Chamomile* considerably reduced the requirement for acetaminophen (the rescue medicine) in contrast to diclofenac and placebo without any negative side effects, although it had

no effect on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire domain responses. A different study discovered that daily *chamomile* tea consumption of 6 grammes was linked to a decrease in RA patients' erythrocyte sedimentation rate and painful joints compared to placebo [7,12,15].

**f. Harshingar (Nyctanthes arbour tristis)**

Since ancient times, the Indian ayurvedic medical system has employed *harshingar* (*Nyctanthes arbour tristis* Linn., NAT) as a decoction to cure sciatica and arthritis. Although it is found across the country's subtropical areas, the plant originated in the Bengal region of India. The major constituents of NAT that are active are arbortriosides, nyctanthic acid, and crocetin. Experimental arthritis has been shown to have much lower levels of inflammation in cytokines (IL-1 and TNF-) when treated with a water-soluble ethanolic extract of NAT leaves [3, 20].

**g. Strobilanthus callosus**

The Maharashtra state's native tribal people have employed karvi (*Strobilanthus callosus*, *Acanthaceae*), another medicinal plant from India, to treat inflammatory illnesses. In carrageenan-induced oedema, Lupeol and 19-H lupeol isolated from the roots of *Strobilanthus callosus* exhibit anti-inflammatory and anti-rheumatic properties [3, 21].

**h. Madimadi**

A type of fermented alcohol made from water extracts of herbal remedies, is a traditional Korean medication. The Koreans who are local to the country have long utilised it to treat RA. *Madimadi* exhibited anti-inflammatory effects and dose-dependently reduced TNF- $\alpha$ , IL-1 $\beta$ , and IL-8 production in RA patients. Additionally, TNF- $\alpha$  and IL-1 $\beta$  are downregulated by *madimadi* [3, 22].

**i. Rubia cordifolia Linn**

It belongs to *Rubiaceae*: Bovine type II collagen and Complete Freund's Adjuvant (CFA) are injected into albino rats to cause arthritis. The efficiency of the plant extract can be compared to that of the widely used nonsteroidal anti-inflammatory drug Aspirin. The change in paw volume as well as other blood markers are utilised to assess the treatment's efficacy. The anti-arthritic effectiveness of *Rubia cordifolia* ethanolic extract was statistically equivalent to aspirin [5, 23].

**j. Alangium salvifolium**

It belongs to *Alangiaceae*: Using Complete Freund's adjuvant arthritis model, *Alangium salvifolium* stem barks were found to be acutely poisonous to rats and to have anti-arthritic properties. All of the extracts (petroleum ether, ethyl acetate, chloroform, and methanol) shown significant anti-arthritic activity [5].

**k. Barringtonia racemosa**

It is possible to find *Barringtonia racemosa* Linn. in coastal swamp woodlands and Indian Ocean estuaries' peripheries, Sri Lanka, India Thailand, Laos, southern China, northern Australia, Malaysia various islands in Polynesia, including the Ryukyu Islands and Polynesian islands. Chemical constituent present in this plant are: 3,

3'-dimethoxyellagic acid, stigmaterol, gallic acid, bartogenic acid, and dihydromyricetin. It anti-inflammatory, anti-oxidant, and anti-microbial properties activity. It treats rheumatoid arthritis and the symptoms of active Bartogenic acid is the component in charge of this action (BA). BA protects rats against acquiring both primary and secondary arthritic lesions, as well as Complete Freund's adjuvant (CFA)-related haematological abnormalities [8, 24, 25].

**l. Cedrus deodara**

It is a Himalayan plant endemic to western Nepal, southwestern most Tibet, eastern Afghanistan, northern Pakistan, and north-central India (Himachal Pradesh). *Cedrus deodara* wood has been used in Ayurvedic medicine to alleviate inflammation and rheumatoid arthritis since the beginning of time. The bulk of the constituents include alkaloids, flavonoids, glycosides, phenolic compounds, saponins, and proteins. *Cedrus deodara* is a plant that has been used to treat rheumatoid arthritis and inflammation. *Cedrus deodara* significantly decreased the polyarthritis phase, as evidenced by paw swellings on the injected limbs in completely adjuvant-induced arthritis in rats [8].

**m. Tinospora cordifolia Linn**

It is found in tropical China and India. The primary ingredients include tinosporidine, columbin, tinosporide, tinosporaside, cordifolide, cordifol, clerodane furano diterpene, diterpenoid furanolactone tinosporidine, and b-sitosterol. The herb is used to boost the immune system and increase the body's defences against sickness. The bitter component contained has antiperiodic, antispasmodic, anti-inflammatory, and antipyretic properties. It is used in the treatment of rheumatoid arthritis. At a dose of 100 mg/kg, paw volume is decreased in rats with collagen arthritis [8].

**n. Premna corymbosa Rottl.**

It is a short tree or shrub. India is home to a sizable population of the plant. The plant's components can all be used. preliminary phytochemical analysis of *Premna* leaves Alkaloids, glycosides, flavanoids, steroids, and triterpenoids were all found in *corymbosa Rottl.* The roots are purgative Digestive, carminative, stomachic, laxative, febrifuge, antibacterial, and tonic properties are all present. They are also astringent, bitter, acrid, and sweet, as well as thermogenic, anti-inflammatory, alexeteric, cardiotoxic, and alterant and expectorant. The leaves are stomachic, carminative, and galactagogue, and they can be used to treat tumours, Coughs, dyspepsia, colic flatulence, agalactia, fevers, rheumatism, and neuralgia. Long-term use of *Premna corymbosa Rottl.* considerably slowed the progression of chronic arthritis brought on by Complete Freund's Adjuvant [8].

**o. Strychnos potatorum**

In the southern and central regions of India, Sri Lanka, and Burma, one may find the medium-sized tree *Strychnos potatorum* Linn. Its main alkaloid, diaboline, and its acetate, as well as triterpenes, sterols, and

mannogalactans, are present. According to reports, the seeds are hepatoprotective, anti-diabetic, anti-hypercholesterolemic, diuretic, anti-diarrheal, anti-arthritic, and anti-ulcer. In rats given the Freund's adjuvant-induced arthritis, the extract of *Strychnos potatorum* Linn., seed at a dose of 200 mg/kg, p.o. reduced paw volume [8].

### III. Discussion

In this study, we have provided an overview of preclinical studies showing the effectiveness of herbal medications when used to treat RA. We discovered many herbs that, through reducing inflammation and oxidative stress and relieving pain, have potential for treating the symptoms of arthritis. Control of immune cell activity and modification of inflammatory signalling pathways are two of these herbs' main modes of action. RA are linked to inflammation and oxidative stress despite differing in pathophysiology and clinical symptoms. As a systemic autoimmune illness, RA depends heavily on cytokines to control macrophages, T cells, and B cells activity. Herbs offer anti-inflammatory and antioxidant qualities that have been shown when taken for arthritis. These plants boost anti-inflammatory pathways like PPAR and decrease NF- $\kappa$ B, MAPK, and Akt are pro-inflammatory signalling pathways. As a result, the synthesis of chemokines and pro-inflammatory cytokines is reduced, whilst the synthesis of anti-inflammatory cytokines is encouraged. As a result, these herbs lessen immune cell activation as well as collagenase and MMP activity and synthesis. The symptoms of RA may get better as a result of these modifications. The herbal remedies that we studied could have a favourable effect on RA therapy and might have few side effects [7].

According to reports, RA sufferers typically have a life expectancy 6 to 11 years lower than the average person, and most of them are female (Cush, 2021). Organ structural alterations and functional problems (such as immunological dysregulation, inflammation, angiogenesis, oxidative stress, etc.) that occur throughout the course of RA development cause irreparable joint damage and ultimately result in disability. It was discovered that the tested herbal products might cure RA through a variety of mechanisms, the most well-known of which is the anti-inflammatory one. By controlling the dynamic balance between anti-inflammatory and pro-inflammatory molecules *in vivo* and blocking well-known inflammatory pathways including NF- $\kappa$ B and MAPK, these herbal products may reduce the invasion of inflammatory cells in RA. By controlling immune cells, they might also restore the immune system's equilibrium (T cells, macrophages, DC cells and so on). Additionally, they might enhance the regeneration of articular cartilage by enhancing apoptosis and reducing RA-FLS proliferation. By preventing osteoclast differentiation, they might also stop bone loss. They might control RA-related miRNAs. Additionally, these herbal products restore oxidative equilibrium by

enhancing anti-oxidant enzymes like GSH, SOD, and CAT and regulating associated pathways in addition to inhibiting angiogenesis by lowering the production of VEGF. Moreover, new research have supported the multi-target treatment of herbal products. In various nations and places, these herbal drugs are employed as conventional treatments to alleviate RA. However, preclinical trials including radiographic inspection and clinical efficacy should be employed for assessment in order to better clarify the efficacy and safety of herbal products and its active constituents [3].

### IV. Conclusion

RA is a severe condition that causes inflammation in several joints. The severity of this disease ranges from slight discomfort to joint deformity. While the exact origin of the condition is unknown, the therapy includes NSAIDs and DMARDs. However, biologic response modifiers are on the market but are currently being studied for their impact in RA patients. With increased knowledge, a considerable number of RA sufferers have begun to use alternative therapy techniques. A number of known ancient Indian Ayurvedic and Unani medicinal plants must be screened and scientifically evaluated in order to provide innovative and safer therapeutic choices with minimal adverse effects.

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Not Applicable

### IX. Author Contribution

All authors are contributed equally.

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