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A REVIEW OF HERBAL PLANTS USED IN THE TREATMENT OF *RHEUMATOID ARTHRITIS*

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ABSTRACT: An inflammatory disorder with an uncertain cause, rheumatoid arthritis (RA), is primarily distinguished by progressive cartilage loss resulting in persistent polyarthritis and joint deformity. Studies indicate that pannus development, which harms the cartilage and the bone, is caused by synoviocyte cellular growth, albeit the exact pathophysiology of the condition has not yet been determined. Recent research further supports free radicals' significance in the disease's etiology. In addition to the traditional therapy approaches, including glucocorticoids, disease-modifying antirheumatic medicines, and non-steroidal anti-inflammatory drugs, newer and safer drugs are constantly being sought after because prolonged use of these medications has led to adverse side effects. Through this review, we all have tried to explore different ancient Indian ancient Ayurvedic, Unani and Tibbi, as also some Oriental and Korean herbals for their very own potential for the treatment of RA.

INTRODUCTION: Joint pain rheumatoid arthritis is a musculoskeletal system dysfunction following mechanical and biological events that destabilize normal joining between degradation and synthesis within coordinate cartilage¹. In other words; it is a persistent, inflamed, symmetrical disease. That can even be called an autoimmune disorder. Initially, it generally influences small joints, moving on to larger articulations. The reason for decreasing is the weakness in the tendon and ligament and also the cause of the breakdown of the cartilage joint and bones breakdown. These kinds of may lead to bone erosion which is often painful for patients and also influences other people's organs like the cardiovascular system, kidney, lungs, sight, etc.

You will find about 100 types of arthritis which the most commonly occurring include osteoarthritis, arthritis rheumatoid, ankylosing spondylitis, systemic lupus erythematosus, and teen arthritis². Approximately the highest incidents of arthritis are found in Indians adopted by Americans. The particular prevalence of the main two types of arthritis that is osteoarthritis and joint disease rheumatoid in the Indian native population is 22-39% and 5%, correspondingly³. RA is characterized by immunological dysregulation and inflammation that involves several joints. Smoking, heredity, and female gender are risk factors for RA development.

The presence or absence of antibodies aids in distinguishing RA as a seropositive or a seronegative disease. Seronegative patients initially exhibit greater inflammation, while seropositive patients have increased inflammation and illness, experiencing the worst joint injury⁴. Extra-articular symptoms may be seen in cases where the disease is severe or seropositive.

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Anti-citrullinated Protein (ACPA) causes pain and bone erosions while sustaining inflammations ⁵. This disease's propensity for inflammation eventually results in permanent deformities. In general, RA patients face a significant impairment

rate, with 60% unable to work for at least 10 years following the onset of the disease ⁶. Symptoms of RA include tender, warm and swollen joints and stiffness in the morning ⁷.



FIG. 1: DIFFERENT HERBAL PLANTS USED IN RHEUMATOID ARTHRITIS



FIG. 2: CINNAMON



LEAVES



FLOWER



ROOT



POWDER

FIG. 3: GLYCYRRHIZA



FIG. 4: SAPOSHNIKOVIA

Epidemiology: Among studies reporting the prevalence of RA across the study population, the prevalence ranged from 0.28%-0.7%. In 1996, Chopra *et al.*, a study was conducted in Bhigwan village (Pune, Maharashtra) using a census developed by the World Health Organization-International League of Associations for Rheumatology (WHO-ILAR) Community Oriented Program for Control of Rheumatic Diseases (COPCORD). The report of a prevalence of RA diagnosed by ACR criteria was 0.51% (95% confidence interval, CI: 0.3, 0.7), and the prevalence of clinically diagnosed RA was 0.6% (95% CI) in nearly 6000 individuals, males and females of 16 years or older (2998 males and 3000 females)⁸. With COPCORD surveys in Jammu's urban and rural areas, a prevalence of 0.7% was found⁹.

A third COPCORD study of over 8000 adults (4010 males and 4135 females) aged 16 years and older living in the metropolitan area of Pune, Maharashtra, was held¹⁰. They found a raw prevalence of RA diagnosed using ACR criteria of 0.28% (95% CI: 0.18, 0.42) and a raw prevalence of clinically diagnosed RA of 0.45% (95% CI: 0.32, 0.63) recorded. The fourth study of five villages in Ballabgarh Township (Haryana) reported a prevalence of 0.75% in approximately 40000 men and women over 15 years of age¹¹.

Symptoms: RA is an autoimmune disease that primarily affects the joints, and this disease shows several symptoms, which can be mild to severe. Symptoms that can be observed are swollen joints, stiffness (which is severe in the morning), fatigue, loss of appetite, and fever. In some cases, RA

patients don't get affected in joints; they affect other organs like the Skin, Kidney, Lungs, salivary gland, heart, and bone marrow. RA signs and symptoms vary from person to person, and the same with the severity of the disease, and it may come and go. Generally, it can't be cured, but sometimes the symptoms may disappear.

Pathogenesis of Rheumatoid arthritis: RA's particular pathogenesis is not understood until time. Any external result like infection or even trauma sets away from an autoimmune response, resulting in synovial hypertrophy and persistent joint inflammation employed with the prospect of extra-articular manifestation, which is often theorized to happen in genetically susceptible individuals.

The development and progression of RA can be categorized into phases as follows:

Phase 1: Describes the interaction between genetic and environmental risk factors of RA.

Phase 2: Produce of RA auto-antibodies. e.g., rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP).

Phase 3: Occurrence of arthralgia or joint stiffness.

Phase 4: Development of arthritis in one or two joints.

Phase 5: Fully established RA.

Synovial cell hyperplasia and even endothelial cell account activation are early situations in another technique of RA. Innate factors and resistant system abnormalities bring about disease distribution.

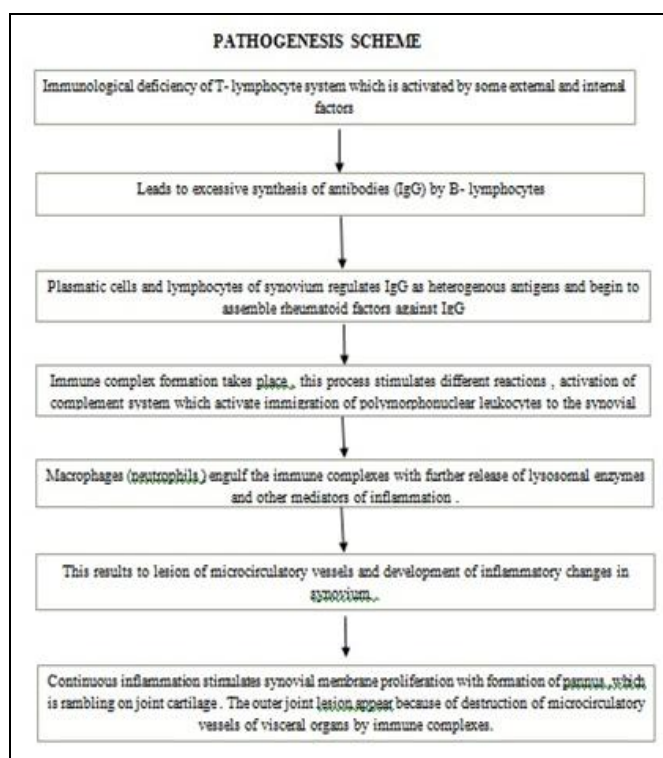


FIG. 5: PATHOGENESIS OF RHEUMATOID ARTHRITIS

Clinical Trials using a Single HERB:

Boswellia Sp: Boswellia, often known as frankincense, has been used in Ayurvedic remedies for millennia. This kind of herb has potent properties, including suppressing microsomal prostaglandin E2 (PGE2) synthase-1 together with 5-lipoxygenase, reducing the production or account activation of inflammatory mediators like matrix metalloproteinase (MMP)-9, MMP-13, cyclooxygenase (COX)-2, and nitric oxide (NO) typically, together with analgesic and anti-arthritic effects¹². Boswellia is expected to help with joint pain by reducing osteophytes, improving the knee joint gap, and lowering inflammatory mediators, including C-reactive health proteins and hyaluronic chemicals, that are linked to be able to knee OA¹³.

Many researchers have looked at the safety in addition efficacy of Boswelliaserrata. According to Majeed et al., OA patients who also received oral M. In comparison to the placebo, serrata removed for 8 several weeks improved their Aesthetic Analog Scale (VAS), Japanese Knee Osteoarthritis Measure (JKOM), in addition to Western Ontario in addition to McMaster Universities Osteoarthritis Index (WOMAC) ratings considerably. Another clinical exploration found that using Boswellia extract by mouth for more than 4 months increased physical performance within OA patients simply by

lowering pain in addition to stiffness compared to placebo,¹⁴ without producing substantial negative effects. Razavi et al. found out that topical cream administration of Boswellia carterii B. (oliban oil) was connected to a substantial reduction in OA pain and signs and symptoms compared to placebo.

Curcuma Sp: Turmeric is an essence created from the origins of the Curcuma herb. Curcumin is the polyphenol extract associated with turmeric, which has an extended history of use in traditional China and Ayurvedic treatments for its potent and antioxidant attributes¹⁵. Curcuma's anti-inflammatory attributes are linked to a variety of associated processes¹⁶. Curcuma therapy has been proven to reduce the particular production of inflamed mediators substantially, for example, interleukin (IL)-1, tumor necrosis factor-alpha (TNF-), IL-8, NO, and also a range of MMPs simply by inhibiting the service of the NF- κ B, protein kinase M (Akt), and MAPK signaling pathways^{17, 18}. Curcuma is proven to inhibit COX-2, ensuing in a reduction in prostaglandin production¹⁹. Recently the anti-osteoarthritic effects of turmeric extract and curcumin have been extensively studied. Kuptniratsaikul et al. demonstrated that patients randomized to Curcuma domestic experienced significant improvement in WOMAC scores compared to baseline within 4

weeks with less abdominal pain and discomfort compared to ibuprofen²⁰. Another study found that curcumin was as effective as diclofenac but with greater safety and fewer side effects. Curcumin is also associated with weight loss, anti-ulcer benefits, and histamine H₂-receptor antagonists (H₂ blockers) free²¹.

***Eremostachys laciniata*:** Decoctions of *Eremostachys laciniata*'s roots and flowers are commonly utilized to treat inflamed disorders like joint disease²². It's uncertain exactly how this plant functions. However, a new study found that dealing with rat paws along with crude methanol draw-out or fractions associated with *E. laciniata* decreased the inflammatory reaction produced by carrageenan²³. The aqueous draw out of *E. laciniata* has also already been demonstrated to get encourage antioxidant activity, as evidenced by higher DPP radical-scavenging exercise and a decrease in H₂O₂- or HOCl-luminal chemiluminescence²⁴.

***Eucommia ulmoides*:** *Eucommia ulmoides* is the plant that offers recently shown guarantee in remedying OA and RA. *E. ulmoides* offers been demonstrated to counteract LPS-induced manufacturing of IL-1, IL-6, TNF-, inducible nitric oxide synthase (iNOS), and COX-2 within murine macrophages through regulating the service of toll-like radio (TLR) 4^{25, 26}. Within OA and RA rat models, *E. ulmoides* reduced the particular production of IL-17, IL-1, IL-6, MMP-3, and TNF-through inhibiting the service from the phosphoinositol 3-kinase (PI3K)/Akt signaling path^{27, 28}. Inside a rat OA model, an aqueous extract of *E. ulmoides* was reported to reduce serum MMP-1, MMP-3, plus MMP-13 while protecting the annular cartilage²⁹. Finally, this has been found out that aucubin, the bioactive element associated with *E. ulmoides*, decreases reactive oxygen varieties³⁰. Most recently, the combination of eucommia and meloxicam is highly effective in reducing pain, and patient satisfaction compared with the meloxicam monotherapy group³¹. Presently, a 12-week, the multicenter, randomized, double-blind, placebo-controlled clinical trial is ongoing to evaluate the safety and efficacy of an *E. ulmoides* extract in patients with mild OA³².

***Matricaria chamomilla*:** *Matricaria chamomilla*, or chamomile, has been applied to relieve shared

discomfort for years³³. Historically, the dried-out floral element of the plant has been utilized to alleviate rheumatic pain and inflammation. Chamomile provides now been integrated into the FDA's listing of "generally deemed as safe" plant life. Chamomile will come in 2 varieties: German chamomile and Roman chamomile, both of which can be members of the particular Asteraceae; Compositae loved ones. Herbal teas the most typical chamomile preparation. Apigenin, quercetin, patuletin, luteolin and glucosides are usually among the phenolic chemical compounds in chamomile. These types of chemicals have potent properties via reducing cytokines and PGE₂, which can be involved in arthritis aetiology^{34, 35}.

***Paeonia lactiflora*:** Radix *Paeonia*, the dried-out root of *G. lactiflora* Pallas, offers been utilized in Chinese language medicine for hundreds of years. Radix *Paeoniae* decoctions happen to be used to treat RA plus other inflammatory/autoimmune ailments³⁶. Radix *Paeoniae* Clarear water/ethanol extracts consist of total glucosides associated with peony (TGP), mainly paeoniflorin³⁷. TGP plus paeoniflorin have already been demonstrated to reduce the generation associated with PGE₂, leukotriene B₄, NO, ROS, plus other-inflammatory mediators in the previous study. *Paeonia* has furthermore been demonstrated to have anti-inflammatory qualities by lowering microvascular permeability and inflamed cell infiltration. Via suppression of NF-κB, the paeoniflorin component of TGP might also inhibit osteoclast development and TNF-α-induced apoptosis^{38, 39}.

***Withania somnifera*:** Ayurveda medicine *Withania somnifera* (Ashwagandha) is recognized because of its anti-inflammatory plus analgesic properties. *Watts. somnifera* extract has been proven to reduce the service of the NF-κB and activator proteins 1 (AP-1) signaling pathways, suppressing the generation associated with TNF-, IL-1, and IL-12⁴⁰. Collagenase exercise was inhibited simply by *W. somnifera* draw out, which reduced the particular degradation of the kind I collagen within bovine Achilles tendons⁴¹. In a collagen-induced arthritic rat design, *W. somnifera* therapy reduced edema, inflammation, deformity, and ankylosis⁴². *W. somnifera*'s anti-arthritic properties are because of its capacity to prevent ROS, TNF-, IL-1B, IL-6,

MMP-8, NF- κ B activation, and increase IL-10 secretion⁴³.

Zingiber officinale: Turmeric, or *Zingiber officinale*, has a lengthy good being utilized to treat inflamed symptoms. Ginger's anti-inflammatory qualities have been analyzed extensively in individuals and *in-vitro* and *in-vivo*. PGE2, NO, IL-1, IL-12, TNF-, monocyte chemoattractant protein-1 (MCP-1), and regulated upon activation, normal to cell expressed plus secreted (RANTES) had been all reduced right after ginger treatment. Turmeric has also already been proven to reduce the expression associated with MHC class 2 molecules, interferon-gamma (IFN-), and interleukin-2 (IL-2), reducing macrophage antigen-presenting activity plus T cell functionality. Ginger suppressed to cell proliferation plus activation by reducing T-bet expression plus raising GATA-3 activity, according to Aryaeian *et al.* Turmeric also altered the particular activation of NF- κ B, COX-1, COX-2, plus peroxisome proliferators, in accordance to research^{44, 45, 46}.

Clinical Trials Using Herbal Combinations: Any time different herbs usually are combined, there is usually proof of synergistic effects, for example, increased therapeutic outcomes in addition to safety. For sufferers with intermediate leg OA, oral supplements with *B. suspensio*, N-acetyl-D-glucosamine, and turmeric for six months had been reported to substantially improve pain-free going for walks distance and WOMAC signs/symptoms when compared with common OA care, together with no safety or even tolerability concerns⁴⁷. The combination of boswellic acid and methylsulfonylmethane has been shown to improve leg OA pain supervision and functional healing while reducing anti-inflammatory drug employment⁴⁸. Curamin significantly increased physical performance checks, and WOMAC shared pain indices inside a 3-month randomized, placebo-controlled trial contrasting the efficacy of curcumin and boswellic acid (Curamin) with curcumin (CuraMed) in addition to placebo. Furthermore, the particular result size regarding the curcuminboswellic intricate was bigger compared to curcumin alone⁴⁹. One more study looked at the combined results of *C. longa* and *B. suspensio* (CB). CB (500 mg twice daily) was proved to be a lot more effective than celecoxib (100 mg two

times daily) in phrases of pain alleviation, going for walks distance, and shared line tenderness, together with results just like celecoxib in terms of crepitus relief in addition to joint range regarding motion. Tolerance had been high in the two curcumin-boswellia combination studies, without significant aspect effects recorded⁵⁰.

A new complex of *Curcuma longa*, *Harpagophytum procumbens* (Devil's claw), and bromelain reduced VAS ratings from baseline regarding acute and long-term OA patients in addition to providing clinically appropriate joint pain enhancement, with greater tolerability without serious negative events in a new multicenter, open-label examine⁵¹.

Ginger's anti-arthritis rewards have also already been tested in blend with other plant life. After 4 days, some great benefits of a turmeric and *Acmella oleracea* complex on discomfort and inflammation were examined in new pilot research together with a quasi-experimental style. Significant improvements inside WOMAC, Tegner Lysholm Knee Scoring, exercise, and fat-free bulk were found in your data. In the two knees, there is a new considerable reduction in pain severity⁵².

CONCLUSION: The prevailing assessment gives an index of the herbs utilized to treat rheumatoid arthritis symptoms. The application of herbal medicine has been extensively spread among patients. Herbal drugs may just be used to treat arthritis, while older synthetic drugs might result in uncomfortable side effects.

Pharmacological properties and clinical studies have justified using herbal medicines to treat arthritis. Research and development of herbal treatment may pave the way for even more effective treatment of arthritis and its associated symptoms.

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