

## Herbal Therapy for the Treatment of Arthritis: A Review

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### ABSTRACT:

The idea that herbal treatments have been used for therapeutic purposes for as long as humankind is not an exaggeration. They have been used for a very long time to cure various diseases. The therapeutic expertise of numerous generations of doctors who have been using an ancient medical system for more than a thousand years is combined to make herbal medicines. Researchers are now particularly interested in the therapeutic chemicals derived from plants because the currently available drugs either have unfavourable side effects or are very expensive. Nature has given us a tremendous wealth of herbal plants that are widely dispersed around the world as a source of therapeutic compounds for the prevention and treatment of various ailments.

**Keywords:** Herbal therapy, Rheumatoid Arthritis, Immune system, Inflammatory, Non-steroidal Anti-Inflammatory Drugs

### I. INTRODUCTION:

Immune system of our body plays a crucial role, as an overactive immune system may lead to certain fatal disease because of various hypersensitive or allergic reactions which may cause numerous derangements; loss of normal capacity to differentiate self from non-self-resulting in immune reactions against our own's cells and tissues called autoimmune diseases. Certain common autoimmune diseases like myasthenia gravis, serum sickness, pernicious anemia, reactive arthritis etc., are the severe issues for medical and pharmaceutical community because of unknown etiology [1-2].

According to WHO, 0.3-1% of the world population is affected from rheumatoid arthritis (RA) and among them females are three times more prone to the disease as compared to males [3]. RA is a chronic, inflammatory, and systemic autoimmune disease [4]. The primary symptoms of RA include pain, swelling, and destruction of cartilage and bone as a result of which permanent disability occur. Although the exact etiology is unknown but several hypotheses said that it is

triggered by the combination of genetic predisposition and exposure to environmental factors like viruses [5]. The exact pathophysiology is still unknown but release of certain free radicals such as nitrous oxide and superoxide radicals generated as by-products of cellular metabolism. The release of such free radicals may induce the production of interleukins (IL) and tumor necrosis factor (TNF- $\alpha$ ) from T-cells which ultimately influence the production of growth factors, cytokines and adhesive molecules on immune cells as such factors may cause tissue destruction and inflammation [6]. Pathological changes in RA are hyperplasia of synovial membrane, infiltration of inflammatory cells and neovascularization, which results into cartilage erosion and articular destruction [7].

The goal of treatment for rheumatoid arthritis patients is to eliminate symptoms, slow disease progression, and optimize quality-of-life [8]. Therefore, before starting the treatment of RA certain goals must be kept in mind such as relief of analgesia, reduction of inflammation, protection of articular structure, maintenance of function, and control of systemic involvement [9].

Presently for the treatment of RA, strategies have changed from traditionally used non-steroidal anti-inflammatory drugs (NSAIDs) or disease modifying antirheumatic drugs (DMARDs) to novel biological agents, like TNF monoclonal antibody. Clinically, the treatment of RA includes five strategies. The foremost approach is the use of NSAIDs followed by mild doses of glucocorticoids to minimize the signs of inflammation as well as progression of disease [10]. In chronic patients, the use of DMARDs such as methotrexate, sulfasalazine, gold salts or D-penicillamine can be included in the treatment. In certain cases, TNF- $\alpha$  neutralizing agents like infliximab, etanercept etc; IL-1 neutralizing agents like anakinra; and the drugs which interfere with T-cell activation such as abatacept can also be included in treatment of chronic cases. Finally, immunosuppressive and cytotoxic drugs such as cyclosporine, azathioprine,

and cyclophosphamide are used for the treatment of chronic patients [11-13].

The above-mentioned therapeutic agents reduce the inflammation and joint destruction, but their long-term risks are still unknown. However, long-term risks of drugs includes gastrointestinal ulcers, cardiovascular complications, hematologic toxicity, nephrotoxicity, pulmonary toxicity, myelosuppression, hepatic fibrosis, stomatitis, cirrhosis, diarrhea, immune reactions, and local injection-site reactions. Moreover, higher costs and side effects which include high risks of infections and malignancies requires continuous monitoring [14].

### **Etiology and Pathophysiology of Arthritis**

The exact etiology of disease is still unknown and the natural course varies considerably from person to person although immunological mechanism have been implicated in rheumatoid arthritis and systemic lupus erythematosus, their etiology and pathogenesis are still not well understood. The focus of rheumatoid arthritis is the synovial lining virtually all patient produce rheumatoid arthritis factor which are autoantibodies directed against IgG molecules [15].

Rheumatoid arthritis factor containing immune complexes found in joint activate the pathological process. The earliest lesion is vasculitis, inflammation of small blood vessels. The inflammation causes edema of the synovium and infiltration with polymorphs, lymphocytes & plasma cells. There is intense local production of IgG by the plasma cells. Synovial fluid in rheumatoid arthritis contains various PGs, mainly PGE2 and leukotrine D. PGE2 comes from inflamed synovial lining cells and is responsible for the pain in rheumatoid joints. The cartilage degranulation is now considered due to release of factors capable of stimulating chondrocytes to degrade their own extra cellular matrix [16]. This factor form the synovial lining has characteristics similar to interleukin- I (IL-I). Interleukin- I has been shown to stimulate release of lytic enzymes and PGE2 from chondrocyte monolayer and inhibit synthesis of proteoglycans by articular cartilage. Thus IL-1 could contribute of cartilage and bone destruction, to the production and release of PGE2 and to the fibrosis. The cellular infiltration that is so conspicuous in the rheumatoid arthritis joint could be the result of local synthesis of IL4. It is now believed this that monokine is a central mediator of rheumatoid process [17].

### **Diagnosis of Rheumatoid Arthritis**

Most patients suffering from rheumatoid arthritis have antibodies called rheumatoid factors in their bloodstream that are part of the inflammatory process of the disease. Doctors to help confirm a diagnosis of rheumatoid arthritis use the presence of rheumatoid factor. However, rheumatoid factor may not be a definitive test for rheumatoid arthritis. Rheumatoid factor is also found in cases of chronic infection and in some other types of autoimmune disease. High levels of rheumatoid factor are often seen in severe cases of rheumatoid arthritis[18]. Treatment of Arthritic Diseases Arthritis drugs have long been considered the "traditional" treatment option. Since individual response to drugs can vary and because potential side effects and adverse reactions are also a factor, finding the most effective combination of arthritis drugs can be a more difficult process than one would expect. Drug therapy can be divided in to two class's i.e. 1. To relieve pain, inflammation and muscle stiffness. 2. To modify the course of the disease or induced remission. Drug Therapy to Relieve Pain, Inflammation and Muscle Stiffness They act rapidly, relieve pain and control inflammation thus help to improve and maintain joint function to prevent deformities. They do not halt the underlying destructive process in joints.

Drugs used in this category are NSAIDs and COX-2 Inhibitors. NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are among the most commonly prescribed and widely used arthritis drugs. There are three types of NSAIDs, Salicylates (acetylated, such as aspirin and non-acetylated), Traditional NSAIDs and COX-2 Selective Inhibitors. NSAIDs work by blocking the activity of the enzyme cyclooxygenase, also known as COX. Research has revealed that there are two forms, known as COX-I and COX-2. NSAIDs affect both forms. COX-1 is involved in maintaining healthy tissue, while COX-2' is involved in the inflammation pathway. COX-2 selective inhibitors became a new subset of NSAIDs born of this research. E.g. Diclofenac, Sulindac, Piroxicam, Indomethacin, Mefenamic acid, COX-2 inhibitor includes-Celecoxib, Rofecoxib, Valdecoxib etc 4 Drug therapy to modify the course of the disease or induced remission [19-20]. They arrest the basic destructive process in the joints and thus modify the course of disease and may even induced remission.

They act slowly and several week must pass before their beneficial effects are visible (slow acting antirheumatic drugs; SAARD), have also

been labeled as DMARDs (Disease modifying Anti rheumatic drugs) and "Second line agent". Research has shown the effectiveness of DMARDs in the treatment of Rheumatic arthritis, psoriatic arthritis, and ankylosing spondylitis and the importance of early aggressive treatment with these drugs e.g.- Chloroquine, Hydroxychloroquine, gold salts, Sulfasalazine and immunosuppressants like Minocycline, Methotrexate, belong to this group. Drugs belonging to this group modify some of basic rheumatoid processes [21-22].

- They may stabilize the lysosomes in cynovium-gold salts, chloroquine.
- They may suppress immunoglobulin production by B lymphocytes-gold salts, penicillamine.
- They may interfere with complement activation-penicillamine.
- They may suppress T lymphocytes-penicillamine, immunosuppressants.
- They may suppress antibody production by B lymphocytes-immunosuppressants.

In addition, chloroquine has anti-inflammatory affect. Immunosuppressants, particularly cyclophosphamide, may be lifesaving when vasculitis complicates the clinical picture and

threatens life These drugs have potent adverse effects like in gold salts adverse effect occurs in about one third of patients. They include pruritus, dermatitis, glossitis and stomatitis most commonly and also leucopenia and thrombocytopenia (which may threaten life), hepatic and renal damage. In case of hydroxychloroquine, it may accumulate in many organs, including the eye where it can cause retinal damage that may be irreversible. The toxicity profile of methotrexate, used in long term regimen for rheumatoid disease include chronic liver diseases, pneumonitis and opportunistic infections. In case of penicillamine patient may experience gastrointestinal upset and dose related impairment of taste is common. So all these agent proves to be harmful in longterm therapy of disease as required in chronic stages[23]

Herbal Treatment of Arthritis Herbal remedies are used or the treatment of Arthritis from long back across the globe. The plant kingdom is abundant in species that act as anti-inflammatory and anti-arthritic to animal tissue. Various plants are studied for for anti-arthritic effects like Guggal, sunth, arand, giloy, haritaki, punernava etc. Some indigenous plant investigated for anti-arthritic and anti-inflammation effects is given in table 1.

**Table 1: Some indigenous plant along with their active constituents for anti-arthritic and anti-inflammation effects**

S. No.	Plant Name	Botanical Name	Family	Part use	Active constituents
1.	Calamus Sweet Flag	Acorus calamus	Araceae	Rhizome	volatile oils containing a number of Sesquiterpenes and Asarone 7
2.	Garlic	Allium sativum	Liliaceae	Bulbs	Starch, mucilage, selenium, allicin, allin [8]
3.	Aloe	Aloes gum	Liliaceae	Gum	Glycosides and Rasins, aloin, barbaloin [9]
4.	khulinjan	Alpinia officinarum	Zingiberaceae	Rhizome	Volatile oils methul cinnamate, cineole n [10]
5.	ShalariAjamoda	Apium graveolens	Umbelliferae	Seed	Volatile ois limonene, phthalides, choline [11]
6.	Neem	Azadirachta indica	Meliaceae	Whole Plant	Seed oil and leafs contains Limonoids, sterols [11]
7.	Guggul salai	Boswellia serrata	Burseraceae	Gum	Essential oils, mucilage, tannies, [10]
8.	Sultan campa	Calophyllum inophyllum	Guttiferae	Seed	Volatile oils, fixed oils, glycosides [12]
9.	Lal miirch	Capsicum annum	Solanaceae	Fruit	Pungent phenolic compounds, capsaicinoids [10]
10.	Myrrh	Commiphora myrrha	Burseraceae	Gum resin	volatile oils, Rasin, GuggulsteronesGuggulsterol

					s [13]
11.	Curcuma	Curcuma longa and curcumin	Zingiberaceae	Rhizome	Curcumins, volatile oils [11]
12.	Nagarmotha	Cyperus rotundus	Cyperaceae	Tubers	Essential oils, cyperene, cyperols, cineol [14]
13.	Sheesham	Dalbergia sissoo	Leguminosae	Root	Dalbergenone, dalbergin, methyl dalbergin, [11]
14.	Bhangra	Eclipta alba	Compositae	Herb	Alkaloid, Ecliptine, thiopheneacetyne [11]
15.	Babera Baybiyanga	Embeliaribes	Myristicaceae	Fruit	Embalic Acid, Tannins, embeline
16.	Red gum tree	Eucalyptus teriticornis	Myrtaceae	Fresh flower	volatiles and essential oils
17.	Red caustic weed	Euphorbia prostrata	Eupharbiaceae	Whole plant	Flavonids, luteolin glycosides [15]
18.	Pipal	Fiscus religiosa	Moraceae	Bark	Tannis, arabinose, mannose, glycoside [16]
19.	Liquorice Muthali	Glycyrrhiza glabra and glycyrrhizin	Leguminosae	Root and stolon	Saponin glycoside, glycyrrhizine, asparagin [15]
20.	Aaraar	Juniperus communis	Cupressaceae	Berries	essential oils [16]
21.	Mehanti	Lawsonia alba/inermis	Lythraceae	Leaves	carbohydrates, phenolic, flavonoids, saponins,
22.	Asafotida Nutmeg	Myristica fragrans	Myristicaceae	Seed	Volatile oils Myristicin, elemicine
23.	Tulsi	Ocimum sanctum	Labiatae	Leaves	Volatile oils eugenol, Methyl euginol, caryophyllin
24.	Skunkvine	Paedariafoetida	Rubiaceae	Whole plant	Iridoid glycoside, sitosterol, alkaloids, carbohydrates, [14]
25.	Phaar	Pluchea lanceolata	Compositae	Whole plant	choline, cpluchinetaraxsterol,
26.	Aerand castor	Ricinus communis	Euphorbiaceae	Root	Triglycerides of ricinoleic, Isoricinolic acid
27.	Jasmine	Nyctanthesarbo rtristis	Oleaceac	Leaves	Mannitol, Flavanoid glycosides [15]
28.	Marking nut tree	Semecarpus anacardium	Anacardiaceae	Nuts	Biflavonoids, sterols and glycosides

The Herbal drugs are use a single drug or combination of two or more drug as poly herbal formulation for topical and oral therapy both like Triphala- A combination of equal part of Emblicaofficinals, Terminalia bellerica and Terminalia chebula, Wintergreen oil- Essential oil from bark of Betuallenta& leaves of Gaultheria procumbens, Oils of Moringa oleifera seeds (moringaceae) and oil of Celastruspanniculatus, seeds (celastraceae) in combination of oil of

Turpentina and other marketed formulation of herbal and Ayurvedaic as proprietary products [24].

#### Herbal Therapy for the Treatment of Arthritis

Herbal medicines are used for the treatment of various ailments from ancient times and it is not an exaggeration to say that the use of the herbal drugs is as old as mankind. Herbal medicines are synthesized from the therapeutic experience of generation of practicing physicians of ancient system of medicine for more than hundreds

of years [25]. Nowadays, researcher shows a great interest in those medicinal agents that are derived from plants because the currently available drugs are either have certain side effects or are highly expensive [11]. Nature has blessed us with enormous wealth of herbal plants which are widely distributed all over the world as a source of therapeutic agents for the prevention and cure of various diseases [26]. According to WHO, world's 80% population uses herbal medicines for their primary health care needs. Herbal medicines will act as parcels of human society to combat disease from the dawn of civilization. The medicinally important parts of these herbal plants are chemical constituents that produce a desired physiological action on the body [27].

Since ancient time India uses herbal medicines in the officially alternative systems of health such as Ayurveda, Unani, Sidha, Homeopathy, and Naturopathy [15]. In India, there are more than 2500 plants species which are currently used as herbal medicaments. For than 3000 years, the herbal medicines are used either directly as folk medication or indirectly in the preparation of recent pharmaceuticals. Thus, from the knowledge of traditional plants, one might be able to discover new effective and cheaper drugs. In this review article, we have tried to cover all the ayurvedic strategies that are followed for the treatment of RA without any possible side effects. The future treatment of RA should provide more effective relief [28].

### Polyherbal Formulations for Arthritis

Analgesics and NSAIDs are helpful in reducing pain and inflammation in either acute or chronic RA patients. Although the treatment of RA is available but due to potential adverse effects or irreversible organ damage the new approaches are developed for maintaining the balance between these potential risks and acknowledged benefits [29]. Currently for the treatment of RA safer and more potent medicaments are developed from oriental sources. Large number of herbal extracts and products such as polyherbal formulations are prepared to reduce such side effects and increase the benefits.

Rheum off Gold is a polyherbal formulation that is commonly recommended by Ayurvedic medical practitioners for the treatment of arthritis. The anti-arthritis activity was confirmed on complete Freund's adjuvant (CFA) induced arthritis model in wistar rats and it was observed that significant reduction in arthritis

index, paw thickness and inflammatory markers such as C-reactive protein, serum rheumatoid factor and erythrocyte sedimentation rate (ESR) when compared with dexamethasone. Thus, the formulation possesses a potential anti-arthritis activity [30].

A Unani polyherbal formulation was evaluated for its anti-arthritis activity in rats. The anti-arthritis efficacy of Manjoon Suranjan was evaluated using formaldehyde and CFA induced arthritis models. The data obtained suggested the anti-arthritis activity of the formulation [31].

Evaluation of Sudard as a potent anti-arthritis polyherbal formulation was studied using formaldehyde and adjuvant induced arthritis models in wistar rats. The formulation at the doses of 150 mg/kg and 300 mg/kg p.o. proves to have an anti-inflammatory and anti-arthritis activity [32].

Anti-arthritis potential of Tongbiling (TBL-II) which was prepared by some modification in Chinese herbal formulation TBL. The anti-arthritis efficacy of formulation was studied using the collagen induced arthritis model in wistar rats and it was revealed that at the doses of 100 and 300 mg/kg p.o. the levels of IL-1 $\beta$  and TNF- $\alpha$  was significantly reduced. Thus it was concluded that the formulation have an anti-arthritis potential [33].

Chinese herbal formula HLXL was used in the treatment from last hundred years for the treatment of inflammation and arthritis. Moreover, after certain modifications in HLXL herbal formulation it was evaluated for its anti-arthritis property using CFA model in rats. It was concluded that the polyherbal formulation shows an anti-arthritis activity through significant inhibition of paw edema and levels of TNF- $\alpha$  and IL- $\beta$  [34].

The therapeutic effect of Ganghwaljetongyeum on RA in rabbit knee synovial membrane was evaluated. It was observed that there would be significant inhibition of proliferation of HG-82 cells which shows that the polyherbal formulation have an anti-arthritis activity. Moreover, there was significant reduction in TNF- $\alpha$ , IL-10 and NO species [35].

PHF at 250 and 500 mg/kg showed significant antiarthritis activity, and the activity was comparable with that of indomethacin. PHF significantly increased the body weight of animals compared with the arthritic controls and the antiarthritis activity of PHF is comparable with that of the standard drug indomethacin.

The PHF was formulated using the ethanolic extracts of the stem bark of G.



pentaphylla, whole plant of *T. procumbens*, and leaves of *M. Indica*, which are mixed properly in 2:2:1 ratio. The antiarthritic activity of the individual plants of PHF has been proven. The stem bark of *G. pentaphylla* showed significant antiarthritic and antidiabetic activities against FCA induced arthritis and streptozotocin-induced diabetes, respectively, in rats at the dose levels of 400 and 800 mg/kg.[30] The aqueous extract of the leaves of *M. indica* showed a significant anti-inflammatory in in vivo and in vitro studies.[21,32] Ethanolic extract of the whole plant of *T. procumbens* showed significant antiarthritic activity against FCA induced arthritis in rats at 250 and 500 mg/kg b.wt. In some studies, the leaves of *T. procumbens* showed significant antidiabetic potential in rodents.[36]

Freund's complete adjuvant induced arthritis model are extensively used to study the pathogenesis of rheumatoid arthritis for testing therapeutics and this model is characterized by a very rapid erosive disease. The bacterial peptidoglycan and muramyl dipeptide present in the FCA are responsible for the induction of adjuvant arthritis [36].

In the a study, the arthritic rats exhibited a reduced RBCs count, reduced Hb level and increased ESR level. All these symptoms indicate an anemic condition, which is a common diagnostic feature in patients with chronic arthritis. The ESR is related to the number and size of the RBCs and to the relative concentration of plasma proteins, especially fibrinogen and  $\beta$  globulins. An increase in the ESR is an indication of active but obscure disease processes. The acute phase proteins in ESR produce inflammation similar to that produced by an injection, injury, and surgery or tissue necrosis. The treatment with extracts improved the RBCs count, Hb level and ESR to a near-normal level, indicating significant recovery from the anemic condition and arthritic progress, thus establishing that the extract has a significant role in arthritic conditions.[37]

## II. CONCLUSION

It is not an exaggeration to suggest that the usage of herbal remedies dates back as far as humankind. They have long been used to treat a variety of illnesses. Herbal medications are created by combining the therapeutic knowledge of generations of doctors who have been practising an old system of medicine for more than a thousand years. Because the currently available medications either have undesirable side effects or are very expensive, researchers are now very interested in

the therapeutic compounds originating from plants. As a source of therapeutic substances for the prevention and treatment of many diseases, nature has endowed us with an enormous richness of herbal plants that are widely scattered across the world.

White blood cells are a major component of the body's immune system. Indications for a WBCs count include infections and inflammatory disease. In arthritic conditions there is a mild to moderate rise in the WBC count. Apart from prostaglandin, other cyclooxygenase products and various cells involved in inflammatory changes and free radical activities have all been implicated in the development of rat adjuvant arthritis. The radiographic analysis of the knee joint in the arthritic and drug-treated animals further supported and confirmed the potent dose-dependent antiarthritic effect.

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