

A Review on Herbal Approach to Treat Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disorder. The disease mainly affects more than one joint in the body. Many people are affected by this disease worldwide. RA is a long-term progressive disorder with different stages. As the disease progresses, the condition of the joints gets worse and joint function terminates at last. It also affects other organs in the body. Many factors, including environmental, age, weight, genetics, and lifestyle, are responsible for RA. Several etiological factors, such as autoantibodies, inflammatory mediators, and genes, are responsible for the generation of RA. The symptoms of the disease include swelling, pain, loss of appetite, joint inflammation, fatigue, and pericarditis. The treatment objective for RA includes reducing pain and inflammation and preventing joint dysfunction as well as joint deformity. Various drugs, such as non-steroidal anti-inflammatory drugs, steroids, and disease-modifying anti-rheumatic drugs, are used to alleviate the symptoms of RA. The uses of synthetic drugs are associated with several life-threatening side effects. These side effects of synthetic drugs are the main thirst of peoples for searching alternative medicines in RA. The main objective of this study is to highlight the use of herbal medicines for RA for patient benefits. Herbal medicines and isolated phytoconstituents from herbal drugs have the advantages of low cost, easy availability, better patient acceptance, and very few side effects. These drugs also improve the patient's condition and reduce stress. Many researchers have proven the efficacy of herbal drugs and phytoconstituents for RA patients. In this study, we are aiming to draw attention to the need to increase the use of herbal drugs for the treatment of RA.

Key words: Herbal medicines, joint inflammation, phytoconstituents, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of autoimmune arthritis. Approximately 1.3 million people in the United States have RA. The global prevalence of RA is 0.5–1% in developed countries, as stated by the Arthritis Foundation. In India, about 0.92% of adult people are affected by RA. Each year, about 20–40 new cases per Lac population are affected. As compared to males, females are more prone to develop RA. According to the Centers for Disease Control and Prevention, environmental factors, such as obesity, old age, smoking, being female, and inherited genes are the major risk factors for developing RA.^[1,2]

The Greek word rheuma (=flow or current) and suffix-oid (resembling) state the similarity of joint inflammation as in rheumatic fever. RA is a chronic autoimmune and inflammatory disease that affects specifically joints. It is associated with multiorgan disorders and characterized

by stiffness, pain, and swelling of joints. After rest, the pain and stiffness remain worse. RA also causes dysfunction in joints, specifically the knees, hands, and wrists. In general, the disease progression occurs bilateral or symmetrically, like both hands and both knees are affected. The disease can also affect other parts of the body, like the eyes, lungs, and heart. Low energy and fever are also associated with the disease. In a few weeks or months, the symptoms develop gradually. RA progresses at time course and affects articular and extra-articular parts of the body, resulting in early deaths, disability, and a low quality of life in developing countries. The majority of patients suffer from functional imbalance and joint destruction due to long-term inflammation. The

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presence or absence of variables like a history of genetics, episodes of swelling joints, serum antibodies, and levels of inflammation govern the course of disease in patients.

As RA is a chronic, progressive inflammatory disease, the different stages of RA are:

- Stage I (early stage RA): the involved joint has swelling, and pain occurs during movement. Synovial fluid has an increased count of immune cells due to an inflammatory response
- Stage II (moderate RA): cartilage destruction with joint narrowing occurs in this stage due to persistent inflammation of synovial tissue
- Stage III (severe RA): characterized by the production of pannus in the joint. The bone under the cartilage is exposed due to cartilage destruction. These changes can be confirmed by an X-ray diagnosis
- Stage IV (end stage RA): Termination of joint function occurs due to the production of fibrous tissue with or without bone fusion.^[3-5] The stages of RA are depicted in Figure 1.^[3-5]

ETIOLOGY OF RA

The exact cause of RA is not known. In the previous study, it was identified that transcription of pro-inflammatory cytokines was induced by certain environmental factors such as smoking, gingivitis, and intestinal bacterial flora. Various disease-susceptible genes have also been identified previously, namely, human leukocyte antigens, cytotoxic T-lymphocyte antigen-4, peptidyl arginine deiminase 4, signal transducer and activator of transcription 4, tumor necrosis factor (TNF) alpha-induced protein 3, and C-C motif chemokine ligand 21. It is suggested that induction of autoimmunity, breaking of immune tolerance to antigens, and epigenetic modifications occur due to citrullination of extracellular matrix molecules and reactions between environmental and genetic factors. The synovial tissues of patients with RA have autoreactive T-cells and B cells. When a person's self-tolerance breaks down, activation of T-cells takes places which in turn stimulate B cells for the production of autoantibodies. Allergic reaction takes place when deposition of immune complex in tissues and activation of complement occur due to autoantibodies and antigen reactions. In the inflamed tissue, the generation of lymphoid follicle-like and germinal central-like structures occurs due to the accumulation of memory T-cells and B cells. In these areas, the expression of pro-inflammatory cytokines and co-stimulators is high.

Inflammatory cytokines like interleukin-1 (IL-1), IL-6, and TNF- α are produced in large amount in inflamed tissues by synovial cells and lymphocytes, in turn they are responsible for the inflammation of joints.

Furthermore, cartilage is degraded by the enzyme matrix metalloproteinases produced by cytokine-stimulated synovial cells. In addition, receptor activator of nuclear factor kappa B

ligand is also expressed by synoviocytes and lymphocytes to bring the maturation and activation of osteoclasts. The bones are destroyed and absorbed by multinucleated osteoclasts, which causes joint destruction at the contact point.^[3,7,8]

SIGN AND SYMPTOMS

In a few patients, the disease starts silently and shows symptoms such as fatigue, loss of appetite, malaise, and later synovitis. The early symptoms of RA continue from weeks to months. In the primary stage, RA consists of symmetric polyarthritis, which includes the small joints of the ankle, foot, and wrist. 10% of patients have polyarthritis, fever, and lymphadenopathy. Some patients often have delicate, warm, enlarged, and swollen joints. Joint stiffness also occurs in the morning and after inactivity. As the disease progressed, the symptoms spread to the elbows, hips, and shoulders. Pleuritis, pericarditis, interstitial lung disease, rheumatoid nodules, and foot ulcers are also affiliated in the patients of RA.^[9,10]

TREATMENT OF RA

The main objective of the treatment is to minimize inflammation and pain, increase joint function, and avoid destruction and deformation of joints. The treatment strategies for RA include pharmaceutical products, various exercises, lifestyle modification, and, if required, surgery. At every stage of treatment, an assessment of response will be done.

First-line management

NSAIDs and corticosteroids; the overall objective of first-line management is to reduce pain and minimize inflammation. Fast-acting medication includes NSAIDs such as aspirin, naproxen, ibuprofen, and etodolac. Some newer analgesics include etorocoxib and celecoxib. Corticosteroids are more specific anti-inflammatory drugs, but the side effects are more severe as compared to NSAIDs. For this reason, they are administered in low doses and for a short duration. Intra-articular injections are also administered in some patients.

Second-line management

Disease-modifying antirheumatic drugs (DMARDs).

The goal of second-line management is to support remission by preventing the progression of joint destruction and deformation. In this stage, the drugs are slow acting, and the response develops in weeks to months. The DMARDs also reduce the risk of lymphoma with RA.

The initial drug in second-line management is methotrexate. It is an immunosuppressant drug. Regular monitoring of

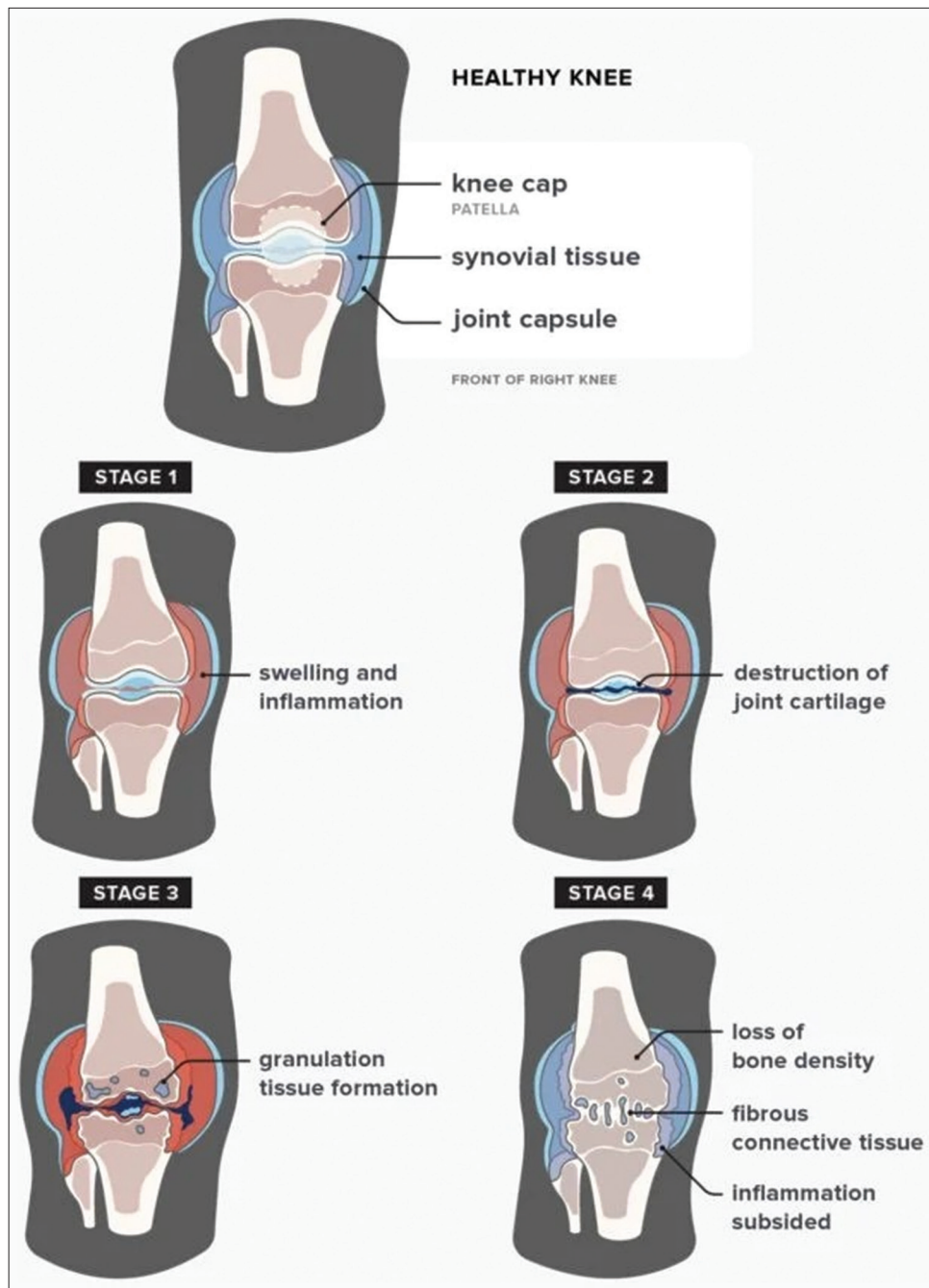


Figure 1: Stages of rheumatoid arthritis^[6]

blood parameters can be done due to the higher side effects of methotrexate.

The antimalarial drug hydroxychloroquine can be used long-term in RA. Sulfasalazine can also be used in combination with anti-inflammatory drugs. Targeted Synthetic DMARDs: Baricitinib and Tofacitinib. Biological DMARDs: TNF-alpha inhibitors (Adalimumab, Certolizumab pegol, Etanercept, Golimumab); anti-B-cell (Rituximab); anti-T-cell costimulation (Abatecept); anti IL-6 inhibitors (Sarilumab, Tocilizumab). IL-1 inhibitors (anakinra, canakinumab, and rilonacept). Granulocyte macrophage colony-stimulating factor inhibitor

(mavrilimumab, otilimab). Listed above are the current pharmacological approaches to treat rheumatoid arthritis.

Surgery

Surgery is mainly used in the end stage of RA. When all the non-surgical approaches have failed, surgery is the last option to reduce the pain in deformed joints. The main objective of surgery is to alleviate pain and restore the functionality of joints. Surgical procedures are mainly customized according to the needs of the patient. Some important surgical

procedures are tenosynovectomy, arthroscopy, osteotomy, arthroplasty, and joint replacement.^[5,11]

SIDE EFFECTS OF TREATMENT OF RA

The drugs used in the management of RA have various side-effects, and this consideration limits the use of drugs at different stages of the disease. Some of the side effects are depicted in Table 1.

APPROACH OF HERBAL TREATMENT IN ARTHRITIS

India is known for the presence of a vast variety of herbal medicines. Ayurveda, Unani, and Siddha system in India are well-known systems that were used conventionally. In Ayurveda, a healthy body means a metabolic balance in a body. As long as people's metabolism is balanced, they will live a healthy life. At present, 60% of the world's population uses alternative systems of medicine. Both developing and developed countries are using these alternative medicines despite the availability of allopathic medicines. Alternative medicines are composed of herbals, minerals, and organic matter in the traditional system of medicines. The source of herbal drugs is naturally occurring medicinal plants. The Indian subcontinent has a plethora of medicinal plant varieties that are used conventionally. More than 20 thousand medicinal plants are recorded in India; however, more than 25 thousand herbal formulations are used as traditional and folk medicines.^[13-15]

The history of the Ayurvedic system of medicine in India is about 5000 years old. It includes herbal medicines and diets for the prevention and treatment of disease. In developed countries, plants and their secondary metabolites, as well as

phytoconstituents, have a long history in traditional systems of medicine. In the middle of the twentieth century, the use of herbal medicines increased very rapidly. The full details, in terms of pharmacology and indication, of selected medicinal plants as herbal drugs are available in various monographs in developed countries.^[16]

At present, worldwide, people are using herbal medicines for primary health care. Herbal medicines and their active constituents are proficiently used to treat chronic disorders. The affordability of herbal drugs compared to typical pharmaceuticals is the key advantage.^[17]

The use of synthetic drugs in the treatment of RA has the major drawback of producing various side effects. Each class of pharmaceuticals used in the treatment of RA has possible side effects. The use of herbal medicines in RA has the advantages of cost effectiveness, easy availability, and fewer side effects. The effectiveness of herbal medicines can be high in certain diseases and condition, as showed by various researchers. Another advantage of herbal drugs is that they can be used by individuals who are allergic to other drugs as they are comparatively safe, and they also give support to detoxification of the body.^[18] Due to the above-cited advantage, of herbal medicines, now a day the herbal medicines gain attention for their use and they have also proved efficacious in many disorders. The beneficial effect of herbal medicines may be felt not only on the symptoms but also on the course of the disease.^[19]

NEED OF ALTERNATIVE AND COMPLIMENTARY MEDICINES IN THE TREATMENT OF RA

At present, the drugs used in the treatment of RA are not effectively capable of restoring the structure and function of damaged cartilage. Except for analgesics, the use of synthetic pharmaceuticals in the management of RA warranted the need for new, safe, and effective therapy for arthritis patients. This problem can be solved with the potential of herbal medicines. The popularity of herbal medicines and nutraceuticals now may be due to several factors, like the fact that present allopathic therapy may not be capable and people don't like it due to various side effects; the patient needs more relief from symptoms and disability; they wish to minimize the stress generated due to chronic illness; and patients also believe that herbal medicines are safe and effective as the history of use of herbal medicines is very old. These reasons augment the patient-driven exploration of alternative medicines in the treatment of RA.^[20]

HERBAL MEDICINES AND PHYTOCONSTITUTENTS IN THE TREATMENT OF RA

A large variety of medicinal plants and their phytoconstituents have been proven their efficacious in the treatment of RA

Table 1: Side effects of drugs used in RA^[11,12]

Drug class used in RA	Side effects
NSAIDS	Tinnitus, hearing loss, gastric tolerance, nausea, abdominal pain, ulcers, gastro intestinal bleeding, heart burn.
Corticosteroids	Bone thinning, diabetes, immuno suppression, weight gain.
Targeted synthetic DMARDS	Upper respiratory tract infection, digestive infections
Biological DMARDS	Abdominal pain, liver problem, cirrhosis, bone marrow suppression, eye problem, gastro intestinal upset, kidney damage
Anti-T Cell	Muscle and joint pain, nausea, breathing problem, diarrhea
Anti B cell	Itching, rashes, nausea, hives, headache

by previous researchers. Some of the medicinal plants and phytoconstituents having anti-arthritic activity are given below in Tables 2 and 3, respectively.

CLASS OF PHYTOCONTITUENTS USED IN THE TREATMENT OF RA

Many years ago herbal the approach to treat various disorders including RA has been explored by various researchers. The therapeutic response of the present available treatment of RA is not optimal; this condition poses challenges and hurdles in the treatment of RA. Thus, there is a need for the development of drugs that are safe and effective and have a better therapeutic effect as well. According to the report of the American College of Rheumatology, the present treatment of RA has restricted efficacy and increased toxicity. The

Table 2: Medicinal plants having anti-arthritic activity

Medicinal plant	Family	References
<i>Aloe barbadensis</i>	<i>Liliaceae</i>	[21]
<i>Boswellia serrata</i> Linn	<i>Burseraceae</i>	[22]
<i>Piper nigrum</i> Linn	<i>Piperaceae</i>	[23]
<i>Zingiber officinale</i>	<i>Zingiberaceae</i>	[24]
<i>Curcuma longa</i> Linn	<i>Zingiberaceae</i>	[25]
<i>Calotropis procera</i> Linn	<i>Asclepiadaceae</i>	[26]
<i>Terminalia chebula</i> Retz.	<i>Combretaceae</i>	[27]
<i>Saraca asoca</i> Roxb	<i>Caesalpinaceae</i>	[27]
<i>Arnica montana</i>	<i>Asteraceae</i>	[19]
<i>Panax notoginseng</i>	<i>Araliaceae</i>	[19,28]
<i>Symphytum officinalis</i>	<i>Boraginaceae</i>	[29]

Table 3: Isolated phytoconstituent having anti-arthritic activity

Medicinal plant	Isolated active phytoconstituent	References
<i>Andrographis paniculata</i>	Andrographolide	[30]
<i>Coptidis rhizome</i>	Berberine	[31]
<i>Centella asiatica</i>	Madecassoside	[32]
<i>Cannabis sativa</i>	Cannabidiol	[33]
<i>Paeonia lactiflora</i>	Gallic acid	[34]
<i>Nigella sativa</i>	Thymoquinone	[35]
<i>Boswellia carteri</i>	Boswellic acids	[36]
<i>Veratrum nigrum</i>	Resveratrol	[37]
<i>Curculigo orchioides</i>	Curculigo glycoside	[38]
<i>Matricaria chamomilla</i>	Apigenin	[39]
<i>Epimedium grandiflorum</i>	Icariin	[40]
<i>Emblica officinalis</i>	Quercetin	[41]

patient compliance and unlikely is more with the available medications of RA. More than 75% of patients are dependent on alternative systems of medicines procured from natural resources. Herbal medicines are traditional, having incredible potential and ample structural multiplicity, which are absent in synthetic drugs.^[42]

Some of the varied classes of phytoconstituents having anti-arthritic activity as reported by previous researchers in different animal models and in arthritic patients are given with examples as follows: Alkaloids (Berberine, Piperlongumine), Aldehydes (Cinnamaldehyde), Coumarins (Herniarin, Scopolin), Flavonoids (Luteolin, Hesperitin, Naringenin), Phenols (Bergenin, Epicatechin, Punicalagin, Ellagic Acid, Gingerol), Terpenoids (Nimbin, Celasterol, Betuloic Acid, Glycyrrhizin, Boswellic Acid), Steroids (Guggulsterone, Stigmasterol), Saponins (Diosgenin), Tannins (Chebulic Acid), and Xanthones (Mangiferrin, Mangostin). The isolation, phytochemical, and pharmacological studies of given phytoconstituents with different drug delivery systems made them essential drugs of choice in the treatment of RA. In the near future, the use of bioactive compounds in the management of RA may be an important approach.^[43,44]

CONCLUDING REMARK

India is well-known for its traditions, and the Indians are fortunate to have a wide variety of traditional medicines. In the current scenario, herbal drugs and medicinal plants have boosted use in acute and chronic disorders. Stress and disturbed metabolism in the body are two of the factors responsible for the generation of autoimmune disorders like RA. It is characterized by inflammation of joints in a long-term manner. At present, arthritic disorders are increasing day by day due to improper lifestyles. In the body, inflammation occurs due to noxious stimuli or defective metabolism. Unbalanced diet, anger, unplanned food timings, and stress are the major factor for defective metabolism in the body. When metabolism is disturbed, it produces reactive oxygen species (ROS), which in turn is a key factor in the generation of inflammatory disorders. An increase in ROS causes the progression of oxidative stress, a pathological factor in various diseases.

RA refers to a chronic disease autoimmune in nature, and symptoms include synovitis, bone destruction, cartilage breakdown, and deformation of joints as well. The disease also destructs other organs in the body. The medicines used in the treatment of arthritis have severe side effects, some may be life-threatening. The new drug entities from medicinal plants have the advantage of varied effects as well as fewer side effects. Herbal drug discovery in today's time, are the prime areas for many researchers worldwide, for the development of new drugs. Outstanding attainment has been done in the field of herbal drug discovery for RA in recent years. Various phytoconstituents are isolated from medicinal

plants to treat RA, which involves specific mechanisms like reduction of inflammation and oxidation, regulation of the immune system, inhibition of the growth of new blood vessels, suppression of osteoclastogenesis, and inhibition of the synovial fibroblast. These are the key targets for treating arthritic disorders.^[45,46]

We conclude the study with the point that herbal medicines and isolated phytoconstituents play a key role in the management of RA, as they are proving efficacy through different mechanisms of action. This herbal approach becomes more advantageous for the patient in many ways as compared to conventional pharmaceuticals.

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