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Therapeutic potential of Indian plants for the treatment of rheumatoid arthritis

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Abstract

Immune system of the body is very important. It protects our body from many diseases but hypersensitivity of the immune system causes many diseases like allergies and several auto immune diseases. Rheumatoid arthritis is an auto-immune disease. It causes inflammation, swelling and redness of the affected joints. It also affects blood vessels and lymphatic tissues. The main aim of the treatment of RA is to eliminate the symptoms of the disease or to slowdowns the development of the disease. Presently many types of drugs are used for the treatment of this disease like disease modifying antirheumatic drugs (DMARDs), glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs). Long term usage of these drugs causes many adverse effects. Use of plants for the treatment of the disease causes no side-effects. India has blessed with enormous wealth of medicinal plants. Since ancient time, herbal drugs are used for the treatment of various disorders in India. In the present review many plants having antirheumatic property are mentioned.

Keywords: Autoimmune disease, inflammation, rheumatoid arthritis, hypersensitivity, herbal treatment

Introduction

The word rheumatism is derived from the Greek word 'rheuma', which means swelling. Rheumatism or rheumatic disorder is a nonspecific term for medical problems affecting the joints and connective tissue. Rheumatoid arthritis is a type of inflammatory arthritis. Rheumatism is characterized by redness, heat, swelling and pain, fever, intense soreness, swelling, stiffness of the affected muscles, pain in eyes, loss of sleep and improper urination⁴⁵. About 1% of the world's population is afflicted by rheumatoid arthritis. Rheumatic disorder is commonly found in middle aged and elderly people, it also involves problems in the internal organs, such as heart, skin, kidneys and lungs^[1]. The disease can affect the person at any age but chances of the occurrence of the disease increases with the age. It is a very painful disease. The disease badly affects the life of a person.

Causes

It is an autoimmune disorder. The real cause of the disease is yet not known. ^[43] The possibility of occurrence of disease is three times more in females than males.²⁶ More than 20% of total population of India is suffering from arthritis. ^[32] Arthritis involves the breakdown of cartilage. Cartilage normally protects a joint, allowing it to move smoothly². The process produces an inflammatory response of the synovial (sinusitis) secondary to hyperplasia of synovial cells, excess synovial fluid, and the development of panes in the synovial. The pathology of the disease process often leads to the destruction of articular cartilage and alkalosis of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in subcutaneous tissue. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in both its chronicity and progression, and RA is considered a systemic autoimmune disease. Many immune-mediated compounds are the main cause of inflammation in synovial joints^[42].

Symptoms

Symptoms include joint swelling, pain, morning joint stiffness, and poor sleep, and fatigue, loss of weight and feeling of having flu symptoms. Rheumatoid arthritis is diagnosed by rheumatoid factor, these are abnormal antibodies (IgG) which are present in blood. These are reacted with antigen and form antigen-antibody complex that leads to pain and inflammation of synovial membrane. The American College of Rheumatology requires at least four of the following seven criteria to confirm the diagnosis^[1, 38].

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- Morning stiffness around the joint that lasts at least 1 hour
- Arthritis of three or more joints for at least 6 weeks
- Arthritis of hand joints for at least 6 weeks
- Arthritis on both sides of the body for at least 6 weeks
- Rheumatoid nodules under the skin
- Rheumatoid factor present in blood testing
- Evidence of rheumatoid arthritis on X-rays

Diagnosis

RA can be hard to detect because it may begin with subtle symptoms, such as achy joints or a little stiffness. The stiffness seen in active RA is most often worst in the morning. Stiffness for a long time in the morning is a clue that one may have RA. Methods to detect RA include clinical assessment, imaging and laboratory tests. Clinical assessment and opinion is considered the 'gold standard' [29]. Diagnosis of RA depends on the symptoms and some blood tests can also help to confirm RA. Telltale signs include: Anemia (a low red

blood cell count); rheumatoid factor (an antibody, or blood protein, found in about 80% of patients with RA in time, but in as few as 30% at the start of arthritis), antibodies to cyclic citrullinated peptides (pieces of proteins), or anti-CCP for short (found in 60– 70% of patients with RA), Elevated erythrocyte sedimentation rate (a blood test that, in most patients with RA, confirms the amount of inflammation in the joints).

X-rays can help in detecting RA, but may not show anything abnormal in early arthritis. Even so, these first X-rays may be useful later to show if the disease is progressing. Often, MRI and ultrasound scanning are done to help judge the severity of RA. There is no single test that confirms an RA diagnosis for most patients with this disease.

Therapy

For the treatment of the RA many synthetic drugs are prescribed by the physician (Table 1).

Table 1: Medications available for treatment of rheumatoid arthritis [24]

Treatment	Drugs
Over the counter	Acetaminophen(Tylenol), aspirin, ibuprofen or naproxen
Disease modifying anti rheumatic drugs(DMARDs)	Methotrexate, gold salt, penicillamine, and hydroxyl chloroquine, Common combinations of DMARDs include methotrexate-hydroxychloroquine, methotrexate-sulfasalazine, sulfasalazine-hydroxychloroquine, and methotrexate-hydroxychloroquine-sulfasalazine.
Nonsteroidal anti-inflammatory drugs (NASIDs)	Paracetamol, ibuprofen, meloxicam, etodolac, nabumeton, sulindac, tolemin, choline magnesiumsalicylate, diclofenac, diflusal, ketoprofen, oxaprozin, and piroxicam.
Biological agents	Tumor necrosis factor alpha(TNF- α) blockers etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumabpegol (Cimzia), golimumab (Simponi) Monoclonal antibody against B cells-rituximab (Rituxan)

In some cases, surgery may be done if other treatments have not worked. This may include:

- Arthroplasty to rebuild the joint
- Joint replacement, such as a total knee joint replacement

Need of herbal medicines for the treatment of Arthritis

Prolonged use of the present allopathic drugs produces many side effects in patient (Table 2). Hence there is a need of an

alternative therapeutic approach. Herbal therapy is very effective against the disease. It provides safe and effective approach towards the treatment of the disease. Nowadays many herbal medicines are used for the treatment of the disease. Many plants are under scientific observation to develop a natural herbal drug. [11]

Table 2: Toxicity of allopathic anti rheumatic drugs [7]

Sl. No.	Drug	Toxicities
1.	Methotrexate(DMARDs)	Stomatitis, rash, hepatotoxicity, rare but potentially life-threatening pulmonary toxicity
2.	Oral gold salts	Diarrhea
3.	Injectable gold salts	Stomatitis, myelosuppression, rash, thrombocytopenia
4.	Cyclosporine	Renal impairment, hypertension, gingival overgrowth
5.	D-penicillamine	Rash, Stomatitis, dysgeusia, proteinuria, myelosuppression
6.	Non-steroidal Anti-inflammatory Drugs(NSAIDs)	Gastro intestinal symptoms (indigestion, ulceration, hemorrhage, stomatitis); renal abnormalities, pulmonary neurological abnormalities, displacement of protein bound drugs, dermatologic abnormalities, hematologic abnormalities, possible systemic complications.

India is a rich source of medicinal plants (Table 3). A large number of medicinal plants are found in India. More than 2000 plants are described in ancient Indian medicinal systems

such as Ayurveda, Sidha, Unani, homeopathy and naturopathy [10].

Table 3: Plants used for the treatment of Rheumatoid Arthritis [39, 41, 34, 13, 33, 52, 36, 14, 44, 21, 23, 4, 17]

S. No	Botanical name	Family	Plant part used
1.	Aloe vera(L).Burm	Liliaceae	Leaves
2.	Asparagus recemsus wild.	Asparagaceae	Whole plant, root
3.	Achyranthes aspera L.	Amaranthaceae	Root, stem and leaves
4.	Ajuga bracteosa Wallich ex Benth.	Lamiaceae	Whole plant
5.	Argemone mexicana L.	Papaveraceae	Seed
6.	Boerhavia diffusa L.	Nyctaginaceae	Root
7.	Boswellia serrata Roxb.	Burseraceae	Olegum, resin

8.	<i>Crocus sativus</i> L.	<i>Iridaceae</i>	Stigma
9.	<i>Curcuma longa</i> L.	<i>Zinziberaceae</i>	rhizome
10.	<i>Cassia fistula</i> L.	<i>Caesalpiniaceae</i>	Leaves
11.	<i>Celastrus paniculatus</i> Willd.	<i>Celastraceae</i>	Seed
12.	<i>Cissampelos pareira</i> L.	<i>Menispermaceae</i>	Leaves
13.	<i>Costus speciosus</i> (Koenig ex Retz.) J.E.Smith.	<i>Zinziberaceae</i>	Root
14.	<i>Crateva adansonii</i> Jacob	<i>Capparaceae</i>	Leaves
15.	<i>Cryptolepis buchanani</i> Roemer & Schultes	<i>Asclepiadaceae</i>	bark, leaves
16.	<i>Cynodon dactylon</i> (L.) Persoon	<i>Poaceae</i>	whole plant
17.	<i>Capparis spinosa</i>	<i>Capparidaceae</i>	Bark
18.	<i>Calotropis procera</i> (Ait.) Dry.	<i>Asclepiadaceae</i>	Latex, Root
19.	<i>Cannabis sativa</i> L.	<i>Cannabinaceae</i>	Fruit, flower
20.	<i>Coriander sativum</i> L.	<i>Umbelliferae</i>	Fruits
21.	<i>Datura alba</i> L.	<i>Solanaceae</i>	Seed
22.	<i>Eucalyptus citriodora</i> (Labill)	<i>Myrtaceae</i>	Leaves
23.	<i>Gloriosa superba</i> L.	<i>Liliaceae</i>	Root
24.	<i>Gynandropsis pentaphylla</i> DC.	<i>Capparidaceae</i>	
25.	<i>Holoptelea integrifolia</i> (Roxb.) Planchon	<i>Ulmaceae</i>	Seed
26.	<i>Ipomoea carnea</i> Jacquin	(<i>Convolvulaceae</i>)	leaf
27.	<i>Jatropha curcas</i> L.	<i>Euphorbiaceae</i>	seeds
28.	<i>Lantana camara</i> L.	<i>Verbenaceae</i>	Leaves
29.	<i>Melia azedarach</i> L.	<i>Meliaceae</i>	seeds
30.	<i>Momordica charantia</i> L.	<i>Cucurbitaceae</i>	fruit
31.	<i>Nicotiana tabacum</i> L.	<i>Solanaceae</i>	Leaves
32.	<i>Nyctanthes arbor tristis</i>	<i>Oleaceae</i>	Leaves
33.	<i>Piper longum</i> L.	<i>Piperaceae</i>	Seeds
34.	<i>Punica granatum</i> L.	<i>Lythraceae</i>	Seeds and juice
35.	<i>Prunus persica</i> (L.) Batsch	<i>Rosaceae</i>	The oil of seeds
36.	<i>Ricinus communis</i> L.	<i>Euphorbiaceae</i>	Root, seed
37.	<i>Semecarpus anacardium</i>	<i>Anacardiaceae</i>	Fruits
38.	<i>Sida cordifolia</i> L.	<i>Malvaceae</i>	Whole plant
39.	<i>Semecarpus anacardium</i> L. f.	<i>Anacardiaceae</i>	Fruit
40.	<i>Swertia chirayita</i> L.	<i>Gentianaceae</i>	Whole plant
41.	<i>Strobilanthes callosus</i> L.	<i>Acanthaceae</i>	Leaves
42.	<i>Tinospora cordifolia</i> L.	<i>Menispermaceae</i>	Leaves, stem
43.	<i>Trewia polycarpa</i> Benth.	<i>Euphorbiaceae</i>	Roots
44.	<i>Trewia nudiflora</i> L.	<i>Euphorbiaceae</i>	Roots
45.	<i>Trigonella foenumgraecum</i> L.	<i>Papilionaceae</i>	Seeds
46.	<i>Vitex negundo</i> L.	<i>Verbenaceae</i>	Root
47.	<i>Vitex negundo</i> L.	<i>Verbenaceae</i>	Leaves
48.	<i>Woodfordia fruticosa</i> (L.) Kurz.	<i>Lythraceae</i>	Root
49.	<i>Xanthium strumarium</i> L.	<i>Compositae</i>	Whole plant
50.	<i>Zinziber officinalis</i> Rosc.	<i>Zinziberaceae</i>	Rhizome

Many plants or plant extracts have been used as anti-rheumatic agents. Use of plants or plant extracts as anti-rheumatic agents/drugs is based on the presence of anti-rheumatic phytochemical compounds in them. Many active chemicals are found in anti-rheumatic plants. These phytochemicals include alkaloids, tannins, steroids etc. These chemicals play an important role in reducing the symptoms of the disease. Bromelain extracted from the pineapple stem has anti-inflammatory property. Many active compounds found in Bromelain (*Sulphydryl proteolytic enzyme*) are peroxidase, acid phosphates and several protease inhibitors. [12]

Vitex negundo originates in southern India and Burma, [47] this plant has its traditional use in rheumatism, headache, syphilis, diarrhea and cholera. Leaves of this plant along with garlic, rice and gul is a remedy for rheumatism [46, 36]. In Ayurvedic, Chinese and Unani medicine system the leaves extract of this plant is used for the treatment of rheumatism [48, 35]. The chemical compounds present in the plant are, nishindine, flavones, luteolin-7-glucoside, casticin, iridoid glycosides, vitamin C, β -sitosterol, and phthalic acid [16, 28, 15].

Xanthium is commonly found in the tropical parts of India. In Chinese and Ayurvedic medicine system the plant infusion is used for the treatment of rheumatism [49, 25]. The main

chemical constituents present in the plant are alkaloids; sesquiterpenes, lactones such as xanthinin, xanthumin, xanthatin; sulphated glycoside such as xanthostrumarin, atractyloside, carboxyatractyloside; phytosterols, xanthanol, isoxanthanol, xanthosin, 4-oxobedfordia acid, hydroquinone, xanthanolides, and deacetyl-xanthumin [14, 18, 31, 22]. *Trigonella* is commonly used as food and food additive. Fenugreek seeds have high content of mucilage, choline and trigonelline. Extract of this plant possess anti-inflammatory and anti-rheumatic activity [44, 17, 51]

Sida rhombifolia is commonly found in India and Ceylon [21]. The major chemical compounds present in plant are β -phenethylamine, N-methyl- β -phenethylamine, S (β)N- β -methyltryptophan methyl ester, vasicinol, vasicinone, vasicine, choline, hypaphorine methyl ester, hypaphorine, and betaine. In Indonesia and Johore whole plant juice is used for the treatment of rheumatism [3, 40]

Piper longum is commonly used for the treatment of the cold, cough, asthma and snake bite since ancient times. In rheumatism, roasted aments are bitten up with honey and taken in a prescribed dose. [9, 27] In Java and Indonesia, the whole plant was applied topically, as it relieves muscular pains and inflammation. Major constituents are piperine,

piperlongumine, piperlonguminine, and methyl 3, 4, 5-trimethoxycinnamate. Others include resin, volatile oil, starch, fatty oil, and inorganic matter [23].

Punica granatum is a native of India, California, Asia and Africa. In Iranian medicinal system the seeds and juice are considered as a tonic for the treatment of rheumatism [48]. Some of the major chemical constituents present in the *Punica granatum* are aegolic acid, anthocyanins, ellagitannins, flavones, flavonoids, antocyanidins, sterols, quercetin, rutin, and other fatty acids.

Lantana camara is an Indian native plant. In Ghana the plant infusion is used for the treatment of arthritis. The active constituents are flavones, isoflavones, anthocyanins, coumarins, lignins, alkaloids, tannins, saponins, triterpenoids, catechins, and iso catechins [5, 6].

Curcuma longa is commonly found in the tropical and subtropical regions of the world. The major chemical constituents are curcumin, methylcurcumin, demethoxy curcumin, sodium curcumin, and Arturmerone [20]. The essential oils of rhizome possess the anti-arthritis activity. An active compound found in turmeric is curcumin. This active compound has anti oxident property. Regular use of turmeric reduce morning stiffness and swelling around the affected joints.¹³ Coriander is a herbaceous plant distributed all over the India. Oil of this plant is very effective for the treatment of rheumatism [17].

Gingerol found in ginger rhizome inhibit the production of nitric oxide.⁵⁰ *Curcuma longa* is swidely used in the treatment of RA. In Indian medicinal system decoction of *Nyctanthes* leaves has been used from a very ancient times for the treatment of RA.¹⁷ Main active compounds found in *Nyctanthes* are nyctanthic acid, crocetin and arbortriosides. In a clinical trial it has been reported that water soluble ethanolic extract of *Nyctanthes* leaves reduces the level of inflammatory cytokines (IL-1, TNF- α) [33].

Crocetin and carotinoids are found in saffron stigma. These compounds have anti-inflammatory action [19].

Gentiana macrophylla root has anti-inflammatory action due to the presence of chemical compound Gentiana. The anti-inflammatory action of the compound is as effective as the conventional drug Prednisone, used in the treatment of rheumatoid arthritis [52]. Tetrandrins are found in the root of *Stephania tetrandra* & *Stephania moore*. This chemical reduces the level of inflammatory cytokines, histamine and tumor necrotic factor. Anti-arthritis activity of *Capparis spinosa* L. fruits are due to the presence of Stachydrins (alkaloids). Colchicine is an alkaloid, having anti-inflammatory action. This alkaloid is found in corms of crocus like plant.

In *Tinospora cordifolia* many active chemical compounds are found which plays an important role in the management of RA such as tinosporin, tinosporidin and tinosporaside. These chemicals have anti-inflammatory and antispasmodic properties. These chemicals also improve the immune system. Anti-arthritis and anti-inflammatory activity of *Aloe vera* is due to the presence of anthraquinone compounds. Boswellic acid, isolated from *Boswellia serrata*, has anti arthritic and anti inflammatory action [8].

Conclusion

From the very ancient time, the plants had been used for the treatment of rheumatoid arthritis. Different plant extract and plant product are found very effective against different diseases. Now a days, humans are moving towards the herbal therapy. At present investigation of anti-arthritis activity of

traditional medicine led to the development and studies of many herbal preparations used for the treatment of arthritis. This information is very helpful in preserving folk medicinal plants having anti-arthritis potential. Use of plants is safe. It produces no side effects like the allopathic drugs. Herbal therapy is also very cheap in comparison to different medications used for the treatment of the disease. Much of the current research is focused on the identification, isolation and characterization of active principle(s) from crude extracts of medicinal plants or herbs, often overlooking the fact that strong synergism of several constituents in the crude drug may prove more potent and effective than any single purified compound and this may help to nullify the toxic effects of individual constituents. This review reveals the importance of different plants used for the treatment and management of rheumatoid disease.

The aim of this review is to revive and explore the traditional medicinal knowledge of plants. Awareness among the people for the conservation of anti-rheumatic plants is very important and it is a demand of time because many plant species are decreasing very rapidly.

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