REVIEW ARTICLE

Medicinal plants in the treatment of arthritis

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Chapter outline

Introduction

Arthritis is one of the oldest diseases. It is a systemic inflammatory disease, affecting mainly joints. It affects globally about 1-2 % of the population. Arthritis is classified into rheumatoid arthritis and osteoarthritis. Gout is also a type of inflammatory disease, caused by the pathogenic deposition of uric acid crystals in joints and tissues. Conventional modern medicine is devoid of satisfactory treatment to severe cases of these diseases. To a large extent, these diseases are treated symptomatically and the drugs used in the treatment have varying levels of toxic side effects. In traditional medicines including Ayurveda, Siddha, *etc.* several herbal drugs are used to treat these diseases. However,

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their efficacy and safety are not clear. Herbal drugs have a major role in the traditional medicine. In a study in India, 43 % of arthritic patients, had used complimentary alternative medicine therapies, which are mainly herbs. Herbal drugs are promising for the development of effective and safe drugs against arthritis in light of modern medicine. In the recent past, a few reviews have appeared on this topic (Arya *et al*., 2011; Kaur *et al*., 2012; Singh *et al*., 2011; Srikanth *et al*., 2012). However, it has been felt that a review with almost fuller information on the disease with focus to the development of satisfactory plant based drugs including combination therapy for successful treatment of all forms of arthritis is needed.

An overview on rheumatoid arthritis, osteoarthritis and gout

Rheumatoid arthritis (RA)

It is a chronic multisystem disease characterized by hyperactivity of certain immune reactions, persistent synovitis with diffuse proliferation, and, in most of the cases, deposition of autoantibodies to immunoglobulins known as rheumatoid factor (RF). In severe cases, the synovial inflammation leads to articular cartilage damage, bone erosion and subsequent changes in joint integrity. Usually peripheral joints are involved.

The prevalence of RA is about 0.8 %; women are affected more often than men. The life expectancy of patients with RA is shortened by 3-7 years. The prevalence increases with age and in most cases, genetics has a role in the disease susceptibility. The class II major histocompatibility complex (HLA) alleles are known to be the major risk factors for RA in certain populations. Genes outside the HLA complex are also involved in RA. However, factors other than genetics such as environmental factors have roles in the incidence and severity of RA (Lipsky, 2008).

The cause of RA is almost unknown. It is believed that RA might be caused by the adverse response of the body to an infectious agent in genetically susceptible host. Microvascular injury and an increase in the number of synovial lining cells are the initial changes observed in

synovitis in RA. Then, a perivascular infiltration with mono-nuclear cells occurs. In the initial stage, the infiltrate is predominantly composed of myeloid cells. As the disease process continues, T cells can also be found and the synovium becomes edematous and protrudes into the joint cavity. The changes include hyperplasia, and hypertrophy of the synovial lining cells, microvascular injury, thrombosis, and neovascularization. When the disease progresses, periarticular soft tissue edema also appears (Lipsky, 2008). The endothelial cells of the synovium have been altered to facilitate entry of cells and the cells express increased amount of various adhesion molecules. The predominant mononuclear infiltrating cell is T lymphocytes.

The synovitis is also characterized by the infiltration of B cells and antibody producing plasma cells. Polyclonal immunoglobulins as well as autoantibody to immunoglobulins (RF) are produced in the synovial tissue. It has been suggested that antibody generated within the synovium may contribute to RA synovitis. Further, production of immune complexes can lead to consequent complement activation and exacerbation of the inflammatory process. Treatment with monoclonal antibody to B cell marker, CD20 causes a decline in B-lymphocytes, inflammation and serum rheumatoid factor (RF). Thus, B cells have a role in the inflammatory process.

Mast cells present in the synovium may also contribute to inflammation. The synovial fibroblasts are activated to produce collagenase, cathepsins, *etc.* that degrade components of the articular matrix. Osteoclasts are also prominent at sites of bone erosion.

A number of cytokines and chemokines are secreted in the synovium by activated T cells, macrophages and fibroblasts. These products may account for many of the pathological and clinical manifestations of RA. Many of the features of rheumatoid synovitis include T cell activation and proliferation, B cell differentiation and migration of cells into the inflammatory site. Thus, it appears that the propagation of RA is an immune system mediated event. However, the original activating stimulus has not been identified. Experimental evidence suggests that the inflammatory process is driven by the CD4 + T cells infiltrating the synovium. Macrophages are activated to produce proinflammatory cytokines IL-1 and Tumor Necrosis Factor - α (TNF-α). A large amount of reactive oxygen species (ROS) is produced locally in the synovium. The exudative synovial fluid contains more Poly Morpho-Nuclear Leucocytes (PMNLs) than monocytes. PMNLs can take up immune complexes including auto-immune complexes with the resultant production of ROS and other inflammatory mediators.

Local factors such as Transforming Growth Factor- β (TGF-β) which inhibit many of the features of rheumatoid synovitis are also produced.

The cartilage destruction occurs to a large extent in juxtaposition to the inflamed synovium or pannus that cover the articular cartilage. The cytokines TNF-α and IL-1 mainly produced by macrophages stimulate the cells of the pannus (fibroblasts, chondrocytes and small blood vessels) to produce collagenase and other proteases that locally degrade cartilage and inhibit synthesis of new matrix proteins. IL-18 also has a proinflammatory role in rheumatoid arthritis (Gracie *et al*., 1999). These cytokines may contribute to the activation of osteoclasts that accumulate at the site of bone resorption (Lipsky, 2008).

Systemic manifestations of RA can be accounted by the release of inflammatory cytokines (IL-1, TNF-α, IL-6, *etc*.) from the rheumatoid synovium. Interestingly, findings suggest the involvement of cytokines IL-17 and IL-18 in the pathogenisis of chronic arthritis (Lubberts *et al*., 2001; Gracie *et al*., 1999). Systemic manifestations include malaise, fatigue and elevated levels of serum acute phase reactance. Further, rheumatoid nodules may develop in 20-30 % of patients; pleuropulmonary manifestations include pleural disease, interstitial fibrosis, pleuropulmonary nodules, pneumonitis and arteritis. Osteoporosis secondary to rheumatoid involvement is common among the patients. Further, immune complexes entering into the circulation from the synovium may contribute for systemic vasculitis. The symptoms can be ameliorated with monoclonal antibody to TNF-α. The activated memory T cells in the synovial tissue can produce TNF-α, *etc.* which amplify and perpetuate the inflammation. The cytokines/chemokines from the T cells, autoantibodies produced by B cells, complement activation, *etc*. lead to tissue injury and chronic inflammation.

Laboratory findings such as presence of RF and autoantibodies are useful to confirm a diagnosis with a suggestive clinical presentation. The ESR is also generally increased in patients with active RA. Disease activity may be correlated with elevated levels of ceruloplasmin, C-reactive proteins, *etc.* Synovial fluid in inflammatory arthritis is usually turbid with reduced viscosity and increased protein content with the predominance of PMNLs. Radiographic evaluation of the affected joints is useful to determine the extent of cartilage destruction and bone erosion.

Progression of the disease, systemic involvement and symptoms vary widely among patients. Early diagnosis is difficult because initial symptoms of RA are non specific. The typical features of RA are bilateral symmetric inflammatory polyarthritis involving small and large joints in both upper and lower extremities with sparing of axial skeleton except the cervical spine. Other symptoms which substantiate or conform the typical picture are morning stiffness, subcutaneous nodules, presence of RF, inflammatory synovial fluid with increased numbers of PMNLs, juxtaarticular bone demineralization and erosion (radiographic findings).

Medicines used to control RA in conventional medicine

The available therapies are not curative and are aimed at reducing the symptoms pain, inflammation, damage to articular structure, functional impairment and systemic involvement. Some of the therapies employed are directed at non-specific suppression of the inflammatory or immunological process (Lipsky, 2008). The therapies can be classified into 5 groups.

(i) **Non steroidal anti-inflammatory drugs (NSAIDs) and simple analgesics:** NSAIDs include ibuprofen, nabumetone, naproxen, salsalate, piroxican, ketorolak, ketoprofen, *etc.* Although these drugs reduce inflammation and pain, they exert minimal effects on the progression of the disease. Further, the major side effect of NSADs is gastro-duodenal ulceration which may range from mild dyspepsia to ulceration. Most of the NSAIDs inhibit both COX-1 and COX-2. COX-2 is upregulated at inflammation sites. New, selective inhibitors of COX-2 (known as Coxbs) are available for treatment. COX-2 inhibitors exhibit less gastro-duodenal ulcers compared to NSAIDs. However, COX-2 inhibition is associated with the risk of cardio-vascular events.

(ii) **Oral glucocorticoids:** Low dose of oral glucocorticoids are used as additional second line of therapy to suppress signs and symptoms of inflammation. Low dose may also retard the progression of bone erosions. Intra-articular injection of glucocorticoids can often provide symptomatic relief when systemic therapy has failed to resolve inflammation.

(iii) **Disease modifying antirheumatic drugs (DMARDs):** These drugs show clinical improvement in a majority of cases and decrease elevated levels of acute-phase reactants in treated patients. Therefore, these are thought to modify the inflammatory component of RA. These drugs include methotrexate, sulfasalazine, hydroxychloroquine, gold salts, D-penicillamine, *etc.* Most of them exert minimal direct anti-inflammatory and analgesic effects and therefore, NSAID may be continued with them. Methotrexate has emerged as the DMARD of choice especially in individuals with risk factor for the development of bone erosions or persistent synovitis. Toxicity of DMARDs includes gastrointestinal upset, oral ulceration, liver function abnormalities and drug induced pneumonitis.

(iv) **Biologics:** These include TNF-α neutralizing agents such as infliximab, etanercept and adalimumab, IL-1 neutralizing agents (anakinra), those that deplete B cells (rituximab) and those that interfere with T cell activation. These agents improve signs and symptoms of RA and decrease disability. TNF-α neutralizing agents are better in efficacy compared to the 3 other types of biologic mentioned above. The major side effects of these agents include potential for an increase in the risk of serious infections such as tuberculosis; increase in the risk of lymphoma and other malignancies. IL-1 receptor antagonist (anakinra) injection may lead to injection site reactions. Mixture of these biologicals (*e.g.*, TNF-α neutralizing agents + IL-1 neutralizing agent) do not increase efficacy, but increases the chances of infection. However, methotrexate can be given with the neutralizing agent to improve beneficial effects.

(v) **Immune suppressive and cytotoxic drugs:** These include leflunomide, cyclosporine, azathioprine and cyclophosphamide. These may ameliorate the disease process in some patients and exerts the therapeutic effects somewhat similar to those of DMARDs. But they cause a variety of toxic side effects. For example, leflunomide alters liver function enzymes (Lipsky, 2008).

Osteoarthritis (AO)

Definition: OA is a joint failure often initiated by joint injury. The pathological changes are hyaline articular cartilage loss, increased thickness and hardening of the subchondrial bony plate, outgrowth of osteophytes at the joint margin, stretching of the articular capsule and mild synovitis in many affected joints and weakness of muscles bridging (Felson, 2008).

OA is the most common type of arthritis with high rate of disability and high prevalence in the elderly. It is the most common cause of chronic knee pain in persons above 40 years of age. The symptoms are pain and disability; bursitis occurs commonly around knee and hip. Likely sources of pain include effusions, marrow edema and synovial inflammation. The loss of function is a consequence of weakness across the joint and of laxity and instability. As disease progresses the pain becomes continuous. Stiffness for a short time (less than 30 min in the morning) of the affected joint may be prominent. Obesity is a risk factor for AO. The occurrence of AO is on the rise (Lipsky, 2008).

In osteoarthritis (OA) synovitis is mild and not accompanied by conspicuous proliferation of cells. The hyper activity of certain immune reactions occurring in RA are absent in AO and RF is not present.

AO is a failure of joint protective mechanism or failure to repair joint injury in the elderly. The disease is heritable in a majority of cases; but its heritability varies by joint. OA commonly affects the cervical and lumbosacral joint, hip, knee and first metatarsal phalangeal joint; in the hands the distal and proximal inter phalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow and ankle. Symptomatic OA of the knee is the most prevalent which occurs about 12 % of Americans above 60 years of age; this

is followed by hip AO and hand OA. OA is uncommon in adults under 60 years of age and more common in women than in man. Age is the most potent risk factor for AO and the joint vulnerability increases with age due to weakening of joint protective mechanisms against loading and minor injuries. Joint vulnerability and loading are the two major factors contributing to the development of AO.

Treatment: In conventional medicine non-pharmacological approaches are the major AO therapies; pharmacotherapy serves an important adjunctive role in OA treatment. The simplest effective treatment for many patients is to avoid activities that precipitate pain. In the case of obese people considerable weight loss may lessen symptoms of knee and hip AO. Exercises are likely to be effective if they train muscles for the activities a person performs daily. Mild and appropriate exercise may improve the functioning of muscles surrounding the joint (Lipsky, 2008).

Correcting mal alignment either surgically or with bracing can relieve pain in patients whose knees are mal-aligned. In patients with knee OA, acupuncture produces modest pain relief compared to placebo needle.

Pharmacotherapy: Paracetamol is the initial analgesic of choice for patients with AO in knees, hip or hands. However, NSAIDs are the most popular drugs to treat AO pain. The most common side effects of NSAIDs are gastrointestinal toxicity (dyspepsia, nausea, bloating, gastrointestinal bleeding and ulcer diseases). These drugs may also cause impairment of kidney function. Blood pressure may increase modestly in some patients. COX-2 inhibitors are also used. Intra-articular glucocorticoid injections may be effective in ameliorating pain and synovial inflammation. When medical therapies have failed, in severe cases of knee and hip OA, joint arthoplasty is indicated.

Gout

Gout is a metabolic disease typically characterized by episodic acute or chronic arthritis or periarthritis which is caused by deposition of monosodium urate (MSU) crystals in joints and connective tissue tophi. It is the result of an increased pool of urate with hyperuricemia. Most often, it affects middle aged to elderly men and postmenopausal women. Acute arthritis is the most frequent early clinical manifestation of gout. Usually only one joint is affected initially, but poly articular acute gout can occur subsequently. The metatarso phalangeal joint of the toe is often involved, but tarsal joints, ankles and knees are also commonly affected. The first episode of acute gout arthritis frequently begins at night with dramatic joint pain and swelling. After several attacks a proposion of gouty patients may present with a chronic non-symmetric synovitis. Gout is seen mostly in individuals with a strong family history of gout. Mild renal insufficiency may also contribute to gout.

The diagnosis is to be confirmed by needle aspiration of acutely or chronically involved joints or tophaceous deposits. Bacterial infection can coexist with urate crystals in synovial fluid. Characteristic radio-graphic features of advanced chronic tophaceous gouts are cystic changes, well defined erosions with sclerotic margins and soft tissue masses (Ralph Schumacher and Chen, 2008).

Treatment: Acute attack is generally treated with anti-inflammatory drugs such as NSAIDs (ibuprofen, indomethacin, diclofenac, *etc.*), colchicines or glucocorticoids. Both NSAIDs and colchicines may show adverse side effects; they may be dangerous in the elderly and in the presence of renal insufficiency and gastrointestinal disorders. Intra articular glucocorticoid injections may be preferable and effective in some cases. Adreno-carticotrophic hormone may be effective in patients with acute poly articular refractory gout. Oral administration of colchicine is a traditional and effective treatment, if used early in the attack. High doses of colchicine are extremely toxic and lethal.

Hypouricemic therapy should be considered, as in most patients, when hyperuricemia cannot be corrected by control of body weight, low purine diet, increase in liquid intake, limitation of ethanol use, *etc*. Urate lowering agents such as probenecid can be used to patients with good renal function, but under excrete uric acid. Probenecid is not generally effective in patients with high serum creatine levels (above 177 μmol/L). In these cases allopurinol (xanthine oxidase inhibitor) can be used. This is by far the most commonly used hypouricemic agent. Toxicity of allopurinol has been recognized in patients with renal insufficiency. The most serious side effects include skin rash with progression to life threatening toxic epidermal necrolysis, systemic vasculitis, bone marrow suppression granulomatous hepatitis and renal failure. Colchicine prophylaxis is usually continued along with hypouricemic therapy. Recent reports have identified that losartan, fenobibrate and amlodipine have some mild uricosuric effects (Ralph Schumacher and Chen, 2008). There is a need to develop safe and effective drugs.

Calcium phyrophosphate dehydrate, calcium apatite and calcium oxalate can also cause arthritis with some similarity to gout.

Plant based ayurvedic treatment for arthritis

Medicinal knowledge gained over trial and error over the thousands of years in India and neighbouring regions of central Asia/ South East Asia has been systematised some four thousand years ago in a system of medicine called Ayurveda. Ayurveda emphasizes preventative and healing therapies along with various methods of purification and rejuvenation.

In many cases contemporary science confirms, to a large extent, the efficacy of the herbal drugs used in Ayurveda. Fairly elaborate classification of diseases is done in Ayurveda. Many plants are used in the Ayurvedic medicines used to treat arthritis and related disease conditions. In an excellent review, most of the important plant based therapies used in Ayurveda and the known scientific basis of their actions are given (Mishra, 2003).

Arthritis and its various manifestations are described in Ayurveda in light of ayurvedic thought and philosophy. Ayurvedic treatment for any disease including arthritis differs from the treatment in modern medicine.

Treatment of Vaatharoga (Arthritis): According to Ayurveda mostly pains are caused by the aggravation of vatadosha. Arthritis is a condition which is caused by accumulation of ama and aggravation of vata. Ama is a toxic by-product of improper digestion. This ama circulates in the whole body and deposits or gets collected at the sites which are weaker. When it deposits in the joints and at the same time there is aggravation of vata, it results in a disease called amavata (Vaatharoga). Thus, as per Ayurveda, the cause of arthritis is different from that described in conventional modern medicine.

According to Ayurveda, over eating of foods that are too salty, sour, alkaline, fatty, improperly cooked, meat of the animals or birds of marshy and desert regions which have been soaked in water, excessive drinking of sugarcane juice, exposure to cold winds, sleeping in the daytime and not in the night, travelling long distances at a stretch, *etc.* cause gout in susceptible persons (Ashtangahrudayam).

Table 1: Medicines used in Shamana therapy to treat arthritis

Arishtam (fermented hot water decoction)	Balarishtam, Devadarvarishtam, Dhanwanthararishtam
Asavam (fermented cold water extract)	Punarnavasavam, Usheerasavam
Choornam (powder)	Kottamchukkadi, Jatamayadi, Kolakulathaadi
Gulika (pills)	Dhanwantharam, Yogarajagulgulu
Kashayam (water decoction)	Amruthotharam Kashayam, Ashtavargam Kashayam, Balaguluchyaadi Kashayam, Bhadraadaarvadi Kashayam, Dasamoolam Kashayam, Dhanadanayanaadi Kashayam, Dhanwantharam Kashayam, Gandharwahasthaadi Kashayam, Gulguluthikthakam Kashayam, Indukaandam Kashayam, Kokilaaksham Kashayam, Mahaaraasnaadi Kashayam, Mahaamanjishtaadi Kashayam, Manjishtaadi Kashayam, Naadee Kashayam, Panchathikthakam Kashayam, Prasaaranyaadi Kashayam, Raasnapanchakam Kashayam, Raasnasapthakam Kashayam, Raasnerandaadi Kashayam, Sahacharaadi Kashayam, Sathaavaryaadi Kashayam
Thailam (oil extract)	Kottamchukkadi, Karpooradi, Dhanwantharam, Karpasasthyaadi, Narayana, Mahamasha, Vathasinee, Pinda
Lehyam (jam like preparation)	Dashamoolahareethaki, Gomoothrahareethaki

Table 2: Some of the important kashayas used in Ayurveda therapy for arthritis and related diseases

No.	Name of Kasayams	Plant ingredients	Indications
1.	Balaguluchyaadi	*Cedrus deodara, Sida rhombifolia, Tinospora cordifolia*	Rheumatic complaints especially arthritis
2.	Kokilaaksham	*Hygrophila auriculata*	Various types of arthritis
3.	Mohaamanjishtaadi	*Acacia catechu , Acorus calamus, Adhatoda beddomei, Ailanthus triphysa, Andrographis paniculata, Asparagus racemosus, Azadriachta indica, Bacopa monnieri, Cassia fistula, Chonemorpha macrophylla, Citrullus colocynthis, Clerodendrum serratum, Coleus vetiveroides, Coscinium fenestratum, Crataeva nirvala, Curcuma longa, Cyclea*	Rheumatoid arthritis chronic skin diseases anaemia. Paralytic conditions, filariasis, ophthalmic diseases and obesity

		peltata, Cyperus rotundus, Eclipta alba, Emblica officinalis, Embelia ribes, Erythrina variegata, Hemidesmus indicus, Holarrhena pubescens, Oldenlandia corymbosa, Operculina turpethum, Picorhiza kurroa , Piper longum, Plumbago rosea, Pongamia pinnata, Psoralea corylifolia, Pterocarpus marsupium, Pterocearpus santalinus, Rubia cordifolia, Sassurea lappa , Solanum indicum, Solanum xanthocarpum, Terminalia bellerica, Terminalia chebula, Tinospora cordifolia, Tragia involucrata, Trichosanthes cucumerina, Zingiber officinale	
4.	Manjishtaadi	*Acorus calamus, Azadriachta indica, Cedrus deodara, Curcuma longa, Emblica officinalis, Rubia cordifolia, Solanum indicum, Terminalia bellerica, Terminalia chebula, Tinospora cordifolia*	Rheumatoid arthritis and skin diseases
5.	Panchathikthakam	*Adhatoda beddomei, Azadriachta indica, Solanum indicum, Tinospora cordifolia, Trichosanthes cucumerina*	Rheumatoid arthritis and skin diseases
6.	Raasnasapthakam	*Cedrus deodara, Pluchea lanceolata, Ricinus communis, Tinospora cordifolia, Zingiber officinale*	Rheumatic complaints with pain and swelling on the joints
7.	Raasnasapthakam	*Alpinia calcarata, Boerhaavia diffusa, Cassia fistula, Cedrus deodara, Ricinus communis, Tinospora cordifolia, Tribulus terrestris*	Rheumatoid arthritis especially in painful conditions
8.	Raasnerandaadi	*Aconitum heterophyllum, Adhatoda beddomei, Alpinia calcarata, Asparagus racemosus, Cedrus deodara, Cyperus rotundus, Hygrophila auriculata, Kaempferia galanga, Ricinus communis, Sida rhombifolia, Strobilanthes heynianus, Tinospora cordifolia, Tragia involucrate, Zingiber officinale*	Rheumatoid arthritis and other rheumatic disorders with pain and swelling

Table 3: List of plants used in Ayurvedic medicines/polyherbal formulations to treat arthritis

S. No.	Name of plants	Family	Plant parts used
1.	*Abrus precatorius* L.	Fabaceae	Root
2.	*Acacia catechu* (L.f.) Willd.	Mimosaceae	Fruits
3.	*Acacia senegal* Britton (Gum from acasia plant)	Mimosaceae	Gum
4.	*Aconitum heterophyllum* Wall.	Ranunculaceae	Root
5.	*Acorus calamus* L.	Arecaceae	Rhizome
6.	*Adhatoda beddomei* Clarke	Acanthaceae	Green leaf
7.	*Aegle marmelos* (L.) Correa	Rutaceae	Root, leaf and fruit
8.	*Ailanthus triphysa* (Dennst.) Alston	Simaroubaceae	Stem bark
9.	*Allium sativum* L.	Liliaceae	Bulb
10.	*Alpinia calcarata* Rosc.	Zingiberaceae	Root
11.	*Andrographis paniculata* (Burm. f.) Wall. *ex* Nees	Acanthaceae	Whole plant
12.	*Anethum graveolens* L.	Apiaceae	Seed
13.	*Asparagus racemosus* Willd.	Liliaceae	Tuber
14.	*Atylosia goensis* (Dalz.) Dalz.	Fabaceae	Whole plant

15.	*Azadirachta indica* A. Juss.	Meliaceae	Root, whole plant
16.	*Bacopa monnieri* (L.) Pennell	Scrophularaceae	Whole plant
17.	*Boerhavia diffusa* L.	Nyctaginaceae	Root
18.	*Caesalpinia bonduc* (L.) Roxb.	Caesalpiniaceae	Seed, root
19.	*Calophyllum apetalum* Willd.	Clusiaceae	Seed
10.	*Carum carvi* L.	Apiaceae	Seed
21.	*Cassia fistula* L.	Caesalpiniaceae	Stem bark, root
22.	*Cedrus deodara* (Roxb.) G. Don	Pinaceae	Wood
23.	*Chonemorpha macrophylla* (Roxb.) G.Don	Apocynaceae	Root
24.	*Cinnamomum tamala* Th. Nees & Eberm.	Lauraceae	Leaves
25.	*Cinnamomum zeylanicum* Blume	Lauraceae	Flower, stem bark
26.	*Citrullus colocynthis* (L.) Schrad.	Cucurbitacae	Whole plant
27.	*Clerodendrum serratum* (L.) Moon.	Verbenaceae	Root
28.	*Coleus vetiveroides* Jacob.	Lamiaceae	Stem, root
29.	*Commiphora mukul* (Stocks) Hook.	Burseraceae	Exudate
30.	*Coriandrum sativum* L.	Apiaceae	Seed
31.	*Coscinium fenestratum* (Gaertn.) Colebr.	Minispermaceae	Stem bark
32.	*Crataeva nurvala* Buch.- Ham.	Capparidaceae	Root
33.	*Cuminum cyminum* L.	Apiaceae	Seed
34.	*Curculigo orchioides* Gaertn.	Liliaceae	Tuber
35.	*Curcuma longa* L.	Zingiberaceae	Rhizome
36.	*Cyclea peltata* Miers	Minispermaceae	Tuber
37.	*Cyperus rotundus* L.	Cyperaceae	Rhizome
38.	*Desmodium gangeticum* (L.) DC.	Fabaceae	Root
39.	*Dolichos biflorus* L.	Fabaceae	Seed
40.	*Eclipta alba* L.	Asteraceae	Whole plant
41.	*Elettaria cardamomum* (L.) Maton	Zingiberaceae	Seed
42.	*Embelia ribes* Burm.f.	Myrsinaceae	Seed
43.	*Emblica officinalis* Gaertn.	Euphorbiaceae	Fruit pulp
44.	*Erythrina variegata* L.	Fabaceae	Leaf, stem bark
45.	*Foeniculum vulgare* Mill.	Apiaceae	Seed
46.	*Fritillaria roylei* Hook.	Liliaceae	Tuber
47.	*Glycyrrhiza glabra* L.	Fabaceae	Root
48.	*Gmelina arborea* Roxb.	Verbenaceae	Root
49.	*Hemidesmus indicus* (L.) Br.	Perilocaceae	Root
50.	*Holarrhena pubescens* (Buch.-Ham.) Wall. *ex* G. Don	Apocynaceae	Seed, stem bark

51.	*Holoptelea integrifolia* (Roxb.) Planch.	Ulmaceae	Stem bark
52.	*Hordeum vulgare* L.	Poaceae	Seed
53.	*Hygrophila auriculata* (K. Schum.) Heine	Acanthaceae	Whole plant, seed
54.	*Ipomoea paniculata* R. Br.	Convolvulaceae	Tuber
55.	*Kaempferia galanga* L.	Zingiberaceae	Rhizome
56.	*Lepidium sativum* L.	Brassicaceae	Seed
57.	*Lilium polyphyllum* D.Don *ex* Royle	Liliaceae	Tuber
58.	*Malaxis acuminata* non D. Don	Orchidaceae	Rhizome
59.	*Malaxis muscifera* (Lindl.) Kuntze	Orchidaceae	Rhizome
60.	*Moringa oleifera* Bedd	Moringaceae	Leaf, seed, root, stem bark
61.	*Oldenlandia corymbosa* L.	Rubiaceae	Whole plant
62.	*Operculina turpethum* (L.) Manso	Convolvulaceae	Root
63.	*Oroxylum indicum* (L.) Benth. *ex* Kurz	Bignoniaceae	Root
64.	*Paederia foetida* L.	Rubiaceae	Whole plant
65.	*Phaseolus mungo* L.	Fabaceae	Seed
66.	*Phaseolus roxburghii* W. & A.	Fabaceae	Seed
67.	*Phaseolus trilobus* Baker	Fabaceae	Whole plant
68.	*Picorhiza kurroa* Royle *ex* Benth.	Plantaginaceae	Root
69.	*Piper chaba* Hunter	Piperaceae	Root
70.	*Piper longum* L.	Piperaceae	Fruit, root
71.	*Piper nigrum* L.	Piperaceae	Seed, leaf
72.	*Plantago ovata* Forssk.	Plantaginaceae	Seed
73.	*Pluchea lanceolata* (DC.) C. B. Clarke	Asteraceae	Tuber
74.	*Plumbago rosea* L.	Plumbaginaceae	Root
75.	*Polygonatum multiflorum* (L.) All.	Liliacae	Medha
76.	*Polygonatum vertcillatum* (L.) All.	Liliacae	Root
77.	*Pongamia pinnata* (L.) Pierre	Fabaceae	Stem bark, Leaf
78.	*Premna serratifolia* L.	Verbenaceae	Root
79.	*Pseudarthria viscida* (L.) Wight & Arn.	Fabaceae	Root
80.	*Psoralea corylifolia* L.	Fabaceae	Seeds
81.	*Pterocarpus marsupium* Roxb.	Fabaceae	Heart wood
82.	*Pterocarpus santalinus* L.f.	Fabaceae	Heart wood
83.	*Ptychotis ajowan* DC.	Apiaceae	Seeds
84.	*Ricinus communis* L.	Euphorbiaceae	Root, oil, leaf
85.	*Rubia cordifolia* L.	Rubiaceae	Root
86.	*Santalum album* L.	Santalaceae	Heartwood

87.	*Saussurea lappa* Clarke	Asteraceae	Root
88.	*Scindapsus officinalis* (Roxb.) Schott	Araceae	Dried mature inflorescence
89.	*Semecarpus anacardium* L.f.	Anacardiaceae	Seed
90.	*Sida rhombifolia* L.	Malvaceae	Root
91.	*Solanum indicum* L.	Solanaceae	Root
92.	*Solanum melongena* L.	Solanaceae	Root
93.	*Solanum melongena* L. - Wild	Solanaceae	Root
94.	*Solanum xanthocarpum* Schrad. & Wendl.	Solanaceae	Root
95.	*Stereospermum suaveolens* (G. Don) DC.	Bignoniaceaae	Root
96	*Strobilanthes heyneanus* Nees	Acantaceae	Leaf, root
97.	*Strychnis potatorum* L. f.	Loganiaceae	Seed
98.	*Terminalia bellirica* (Gaertn.) Roxb.	Combretaceae	Seed pulp
99.	*Terminalia chebula* Retz.	Combretaceae	Fruit, fruit pulp
100.	*Tinospora cordifolia* (Willd.) Hook.f. & Thoms.	Minispermaceae	Stem
101.	*Tragia involucrata* L.	Euphorbiaceae	Root
102.	*Tribulus terrestris* L.	Zygophyllaceae	Fruit
103.	*Trichosanthes cucumerina* L.	Cucurbitaceae	Root, whole plant
104.	*Trigonella foenum graecum* L.	Fabaceae	Seed
105.	*Valeriana wallichii* DC.	Valerianaceae	Root
106.	*Abutilon indicum* (L.) Sweet	Malvaceae	Root
107.	*Vetiveria zizanioides* (L.)	Poaceae	Root
108.	*Vitex negundo* L.	Verbenaceae	Root, leaf
109.	*Withania somnifera* (L.) Dunal	Solanaceae	Root
110.	*Zingiber officinale* Rosc.	Zingiberaceae	Rhizome
111.	*Zizyphus mauritiana* Lam.	Rhemnaceae	Seed

As described above ama and vatadosha are the main causes of arthritis. So efforts are made to digest ama and to reduce the vata. For digestion of toxic materials various herbal combinations such as Hinguvachadichoornam, Vaishwanarachoornam and Amrithotharam Kashayam are used. Then, external as well as internal applications of herbs in oil are followed. Medicated oils like Dhanwantharam, Mahanarayanam, Sahacharadi and Pindathailam are used for external oleation. Internal medications with ghee and oil medium are also used. This is followed by cleansing the body from accumulated toxic materials (Pancha karma). The five cleaning methods described in Ayurveda are therapeutic vomiting or emesis (*Acorus calamus etc.*), purgation (Avipathichoornam *etc.*), enema (Dvipanchamooladi *etc.*),

elimination of toxins through the nose (Maharajaprasaranithailam *etc*) and detoxification of the blood (using leach, bloodletting by cutting vain *etc*). Out of these, relevant methods of panchakarma are used for cleansing arthritis patients as decided by an experienced Ayurveda doctor.

After cleansing of the body Shamana therapy (rectification of imbalance in the body) is carried out. This is done with one or more of the medicines given in Table 1. After Shamana therapy, Rasayana therapy (Rejuvenation therapy) is done using various preparations (Narasimharasayanam, Amalakirasayanam, Chyavanaprasam *etc*).

Numerous kashayams are used to treat rheumatic diseases and osteoarthritis. However, these Kashayas are used in the

treatment of many other diseases also. Kashayams containing plant ingredients and used mainly for arthritis are given in Table 2. Important plants used in the various treatment of arthritis as per ayurvedic strategy are given in Table 3.

Clinical trials

As mentioned above, in Ayurvedic therapy, after initial treatment including food restriction, herbs or herbal formula are given to improve digestion, clean the body and reduce inflammation and pain (Mishra *et al.*, 2000). Based on body constitution, physiological state and other diseases, if any, suitable herbal formulas are recommended to each patient (Mishra *et al.*, 2000). Based on these basic strategies of Ayurvedic treatment using a variety of herbal formulas, limited clinical trials were carried out. The herbals or herbal combinations given in Table 4, were subjected to clinical trials. The clinical trials showed varying levels of efficacy; only varying percentage of patients showed moderate to slight improvement.

Table 4: List of some of the clinical trials on Ayurvedic herbal medicines for arthritis

S. No.	Ayurvedic herbal formulas	Results of the study	References
1.	Dasmularista, Pippatyasava and Vettumarangutika	The results suggested that the combination of the 3 formulas was effective in the acute stage of RA	Namboodiri *et al.*, 1984
2.	*Zingiber officinale*	Majority of patients experienced some level of relief from pain and swelling (28 with RA, 18 with OA and 10 with muscular discomfort)	Srivastava and Mustafa, 1992
3.	*Zingiber officinale -Tinospora cordifolia* (decoction)	Reduced pain and swelling (RA patients)	Mishra, 2003 (review)
4.	RasonadiKvatha (a decoction of *Zingiber officinale, Allium sativam* and *Vitex negundo*)	RA patients showed significant improvement in pain, swelling, tenderness and restriction of affected joints	Prem and Banerjee, 1988
5.	*Tinospora cordifolia* and *Balsamodendrom mukul*	Improvement in signs and symptoms of RA	Mishra, 2003
6.	*Tinospora cordifolia* and *Alpinia officinarum*	Improvement in signs and symptoms of RA	Mishra, 2003
7.	Vatagajanankusa Rasa and Maharasnadi Kwatha	Reduced pain and swelling of RA patients	Mishra, 2003
8.	Vatari Guggul (Bhasajya Ratnavali) and Maharasnadi Kavatha	A significant improvement in pain and a decrease in ESR level of RA patients	Swamy and Bhattathiri, 1998
9.	*Withania somnifera, Boswellia serrata, Curcuma longa* and a zinc complex	The herbo-mineral formulation produced a drop in the severity of disability score of OA patients.	Kulkarni *et al.*, 1991
10.	*Withania somnifera*	Improvement in signs and symptoms of RA in 76 % patients	Kikshapathi and Kumari, 1999

Plants with antiarthritis or/and anti-inflammatory properties

Numerous plants are used to treat arthritic conditions in traditional medicine which include local health traditions and traditional systems of medicine such as Ayurveda and Sidha. Based on the traditional information many of the plant extracts or/and active fractions were tested in experimental animal models of arthritis and inflammation. The plants which showed anti-arthritic activity and/or anti-inflammatory activity are given along with the experimental animal models used in Table 5. Most of the studies were carried out using adjuvant-induced arthritis in rats. Some of the studies were perfumed using carrageenan-induced rat paw edema in rodents, formalin-induced edema in rats, *etc.* (Tables 5 and 6).

The plants showed varying levels of activities against inflammation in the animal models. As such meaningful

comparison is not possible because the experimental model used and experimental conditions employed are different in almost all cases. Only *in vitro* assay methods such as inhibition protein denaturation, human blood cell membrane stabilization and inhibition of phospholipase A$_2$ were used in some studies. Further most of the studies were not focused on likely development of drugs to treat arthritis. A comparative study is required to select the best plants for antirheumatoid arthritis activity, antiosteoarthritis activity and only anti-inflammatory activities. Plants with high antioxidant property such as *Anrdographis paniculata* are likely to give some relief from arthritis because oxidative stress is associated with severe arthritic conditions. However, those plants are not listed in this review.

Clinical studies

In a clinical trial involving 60 arthritis patients who had not responded to NSAIDs, *Tripterygium wilfodii* (60 mg/day) extract for 3 months showed improvement in tenderness score, swelling, morning stiffness and grip strength (Tao *et al*., 1989). *Tripterygium wilfodii* Hook F. has been used in China for treating joint pain. The oleogum of *Boswellia serrata* (Salai guggal) was shown to be effective in controlled clinical trials in arthritic patients (Pachnanda *et al*., 1981). The clinical studies on *Withania somnifera* and *Zingiber officinale* are given under Ayurvedic treatments (Table 4). Some of the very promising plants are given below.

Boswellia serrata Roxb. ex Coleb.

This is a promising antiarthritis plant with anti-inflammatory and other beneficial pharmacological properties. Alcohol extract of salai guggul (*B. serrata*) displayed marked anti-inflammatory activity in carrageenan-induced paw edema in rats and mice. It was equally effective in adrenalectamized rats (Singh and Atal, 1986). Alcohol extract of salai guggul strongly inhibited antibody production and the infiltration of polymorphonuclear leukocyte; it decreased the volume of pleural exudates (Sharma *et al*., 1988). Special extract of gum resin of this plant reduced symptoms of rheumatoid arthritis in 50 to 60 % of patients. There was a significant reduction in swelling and pain compared to the placebo (Etzel, 1996). The plant extract has antihyperlipidemic activity also (Atal *et al*., 1980a; Atal *et al*., 1980b). Boswellic acids isolated from gum resin of this plant were found to posses significant anti-inflammatory and complement-inhibitory activities in rats (Kapil, 1994). The compound also protected mice against galactosamine/endotoxin-induced hepatitis in mice (Safahyi *et al*., 1991). The protection was interpreted in terms of its ability to inhibit the formation of leukotrienes. Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-α induction in monocytes by direct interaction with IκB kinases (Syrovets *et al*., 2005). Besides, acetyl-keto-β-boswellic acid inhibits cellular proliferation through a p21-dependent pathway in colon cancer cells (Liu *et al*., 2006).

Commiphora mukul (Hook ex Stocks) Engl

The plant is also known as *Balsamodendron mukul* Hook *ex* Stocks and *Commiphora wightii* (Arn.) Bhandari. Several investigators have reported the anti-inflammatory property of guggul (Gujaral *et al*., 1960; Shanthakumari *et al*., 1964; Arora *et al*., 1971). The oleoresin fraction of guggul possesses significant anti-arthritic and anti-inflammatory activities; the minimum effective dose being 125 mg/kg g body weight (Shanthakumari *et al*., 1964). The crude water extract of the oleo gum resin was found to suppress acute rat paw edema induced by carrageenan. It also had an inhibitory action against the granuloma formation in granuloma pouch test. In adjuvant arthritis, the extract suppressed the secondary lesions very effectively without having any significant action on the primary phase. Methanol extract of dried exudate of *C. mukul* prevents bone resorption in ovariectomized rats (Khan *et al*., 2012). One of the mechanisms of its effect could be suppression of hyper immune reactions. Crude extract and pure compound isolated from *C. mukul* inhibits MAP kinases that lead to down regulation of TNF-alpha, IL-1 beta and IL-2 (Manjula *et al*., 2006). A crystalline steroidal compound with anti-inflammatory activity was isolated from *C. mukul* (Arora *et al*., 1971). Purified gum guggul showed hypolipidemic effect in experimental animals (Satyavati *et al*., 1969) and in human clinical trials (Rout *et al*., 2012). The effectiveness of *C. mukul* has been reported in patients with osteoarthritis of the knee (Singh *et al*., 2003). New triterpenes myrrhanol A and myrrhanone A from guggul-gum resins showed potent anti-inflammatory effect on adjuvant induced air pouch granuloma of mice (Kimura *et al*., 2001). The study indicated that the anti-inflammatory effect of myrrhanol A was greater than that produced by hydrocortisone and 50 % extract of the crude resin.

Curcuma longa L.

The plant rhizome possesses multiple pharmacological properties including antiarthritis and anti-inflammatory properties. The major active principle in this plant is curcumin. This compound is endowed with several therapeutically valuable pharmacological properties. It is a chemopreventive and chemotherapeutic agent in diseases such as inflammatory disorders including arthritis, cancer, diabetes, obesity, *etc*. These are highlighted in a recent review (Beevers and Huang, 2011). Many studies have revealed that curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Cell culture studies, animal experiments and clinical trials indicate that curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis (Jurenka, 2009). Turmeric extract containing curcuminoids prevents experimental rheumatoid arthritis (Funk *et al*., 2006).

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Withania somnifera (L) Dunal

It is an important medicinal plant with antiarthritis and several other pharmacological properties. The root extract showed anti-inflammatory activity which was comparable to that of 5 mg/kg hydrocortisone sodium succinate (Ai-Hindawi *et al.*, 1992). The extract was found to reduce total white blood cell count and reduce leucopenia induced by sub lethal dose of gamma radiation in mice (Kuttan, 1996). It has been shown to have anti-RA activity in animal models (Anbalagan and Saddique, 1981; Al- Hindawi, *et al.*, 1992; Sadique *et al.*, 1980). In a clinical trial, it showed some level of improvement in signs and symptoms of RA (Bikshapathi and Kumari, 1999). Withaferin A, a steroidal lactone from the plant root was effective in inhibiting growth of Ehrlich ascetic tumour in mice (Sharada *et al.*, 1996). The root water extract has antioxidant property also. It prevented stress induced rise in lipid peroxidation in rabbits and mice (Dhuley, 1998). It should be noted that oxidative stress is more in arthritis patients. It has several other pharmacological properties such as hepatoprotection to rats from CCl_4 toxicity and enhancement of mental arithmetic and motor function in human clinical trial (Sarah and Balick, 2001).

Tinospora cordifolia (willd.) Hook. F. and Thoms.

It is an immune modulatory plant with several other pharmacological properties. The important pharmacological activities reported for this plant are immunomodulatory, antiarthritis, antioxidant, antidiabetes, antistress, hepatoprotective, antileprotic, antineoplastic, antispasmodic and antiallergic activities (Sankhala *et al.*, 2012; Singh *et al.*, 2003; Bishayi *et al.*, 2002). The aqueous extract of *T. cordifolia* showed anti-inflammatory effect on cotton pellet granuloma and formalin induced arthritic models. The dried stem of *T. cordifolia* exhibited anti-inflammatory effect in both acute and subacute models of inflammation. *T. cordifolia* was found to be more effective than acetylsalicylic acid in acute inflammation (Singh *et al.*, 2003). Its antineoplastic activity has been reported in cultured HeLa cells (Jagetia *et al.*, 1998). *T. cordifolia* affects the proliferation, differentiation and mineralization of bone like matrix on osteoblast model systems *in vitro*. Thus, it appears to be an anti-osteoporotic agent. Alcohol extract of *T. cordifolia* has been shown to stimulate the growth of osteoblasts, to increase the differentiation of cells into osteoblastic lineage and to increase the mineralization of bone like matrix *in vitro* (Abiramasundari *et al.*, 2012). Ecdysteroids isolated from this plant have antiosteoporotic effects on mammals. Beta-ecdysone from this plant induces a significant increase in the thickness of joint cartilage, induces osteogenic differentiation in mouse mesenchymal stem cells and attenuates osteoporosis in osteoporotic animal models (Gao *et al.*, 2008). Further, the β-ecdysone has shown beneficial effects on the joint epiphyseal cartilage tissue and trabecular bone in ovariectomized rats

(Kapur *et al.*, 2010). Thus, *T. cordifolia* has effects on cartilage and bone function and is a potential plant in the treatment of osteoporosis and osteoarthritis. Although it is an immune-stimulatory plant, it appears to have direct positive influence on the function of bone and cartilage.

Zingiber officinale Rosc.

The rhizome of this important traditional medicinal plant has multifarious beneficial pharmacological properties. Single or formulations with *Zingiber officinale* have been used in the treatment of RA in traditional medicine. In a human clinical study, ginger has been reported to be beneficial to arthritic patients. More than 70 % of the patients (out of 28 RA, 18 OA and 10 muscular discomfort patients) experienced varying degrees of relief from pain and swelling. None of the patience reported adverse effects during the treatment period from 3 months to 2.5 years. Ginger is an inhibitor of both prostaglandin and leukcotrine biosynthesis and the authors suggest that its beneficial effects could be, to a large extent, due to these inhibitory effects (Srivastava and Mustafa, 1992; Srivastava and Srimal, 1985; Mishra, 2001). It is a potent anti-inflammatory agent and the active principles include sesquiterpene lactones (Kohli *et al.*, 2005; Kaur *et al.*, 2012).

Ncytanthes arbortristis Linn

In traditional medicine, this plant leaves are used as laxative, diuretic, antiarthritic, antiparasitic, *etc*. The leaf extract inhibited the acute inflammation induced by carrageenan, formalin, histamine, 5-hydroxytryptamine and hyaluronidase in rat paw (Saxena *et al.*, 1984; Kaur *et al.*, 2012). It also inhibited inflammation in Freund's adjuvant-induced poly-arthritic rats (Bhalerao *et al.*, 2011; Sandhar and Kaur, 2011). It showed antiarthritis activity against gouty arthritis also (Bhalerao *et al.*, 2011). The leaf extract administration resulted in depletion of TNF-α and a decrease in the levels of interferon-γ in mouse serum (Paul and Saxena, 1997). Leaves and fruits extract showed antiarthritic activity with a concomitant reduction in TNF α, IL-1 and IL-6 (Rathore *et al.*, 2007). The plant leaf extract possesses antioxidant property also (Rathee and Hassarajani, 2007). Other reported pharmacological properties include hepatoprotection, antiviral, antileishmaniasis, anthelmintic, antispasmodic and antidiabetic (Sandhar *et al.*, 2011).

Aloe barbadensis Mill.

This plant is also known as *Aloe vera* L. In India, in local health traditions, *Aloe barbadensis* is used in the treatment of various skin ailments, eczema, inflammation, *etc*. Tropical application of *A. vera* extracts results in reduction of inflammation in adjuvant induced arthritis in rats. The anti-inflammatory property is due to anthroquinones found in this plant (Davis *et al.*, 1986; Joseph and Raj, 2010). *A. vera* contains sterols (mainly β-sitosterol) and lupeol. β-sitosterol is an anti-inflammatory and anticholesterol agent. Lupeol is a

powerful pain killer and has antimicrobial activity. The plant contains anthraquinone and anthranilic acid both of which are quite efficacious against arthritis and articular rheumatism. These two constituents can restrict the biosynthetic function of bradykinin, a substance causing pain and inflammation (David *et al*., 1986; Davis *et al*., 1994).

Camellia sinensis (L.) O. Ktze

This plant is endowed with many health benefits. Beneficial effects of drinking tea include antimicrobial effects, reducing risk of cancer and cardiovascular diseases. Theophylline, a compound present in tea, is a medicine for the treatment of respiratory diseases such as asthma (Sharangi, 2009). One of the polyphenols, epigallocatechins, present in tea is a potent antioxidant (Kaur *et al*., 2012). In collagen-induced arthritic rats, green tea markedly reduced inflammation, inflammatory cytokines TNF-α & γ-interferon and COX-2. The levels of total IgG antibodies and collagen specific antibodies were reduced by green tea (Kaur *et al*., 2012; Ahmed, 2010). Recent findings suggest that black tea extract has antiarthritic activity in both experimental and clinical study. Black tea water extract showed antiarthritic activity in Freund's complete adjuvant induced arthritic rats with an associated decrease in the serum levels of PGE2, TNFα, IL-1β and IL-6 (Datta *et al*., 2012).

Table 5: Recent studies on antiarthritis and/or anti-inflammatory plants

S. No.	Botanical name of plants	Plant parts/ extracts/ active principles used	Effects observed/ major findings	References
1.	*Aglaia roxburghiana* (W.&A.) Miq. Meliaceae	Alcohol extract of aerial portions and fruits	Anti-inflammatory activity in animal models	Janaki *et al*., 1999
2.	*Aloe vera* (L.) Burm. f. Liliaceae	Extract and anthraquinones	Antiadjuvant induced arthritis in rats	Joshph and Raj, 2010; Devis *et al*., 1986
3.	*Ammannia baccifera* L. Lythraceae	Alcohol and water extracts	Antiadjuvant induced arthritis in rats	Tripathy *et al*., 2010
4.	*Anisomeles malabarica* (L.) R. Br. *ex* Sims. Lamiaceae	Methanol extract of leaves	Human blood cell membrane stabilization	Lavanya *et al*., 2011
5.	*Aristolochia bracteata* Aristolochiaceae	Methanol extract of root	Antiadjuvant induced arthritis in rats	Havagiray *et al*., 2009
6.	*Asystasia dalzelliana* Sant. Acanthaceae	Methanol extract of leaves	Inhibition of protein denaturation	Kumar *et al*., 2011
7.	*Bacopa monnieri* (L.) Pennel Scrophulariaceae	Methanol extract of fresh whole plant	Inhibition of protein denaturation, *etc*	Volluri *et al*., 2011
8.	*Barringtonia racemosa* (L.) Spreng. Lecythidaceae	Methanol extract of fruit and bartogenic acid	Antiadjuvant induced arthritis	Patil *et al*., 2011
9.	*Borassus flabellifer* L. Arecaceae	Ethanol extract of flower	Anti-inflammatory and antiarthritis (cotton-pellet granuloma) activity in rats	Mahesh *et al*., 2009
10.	*Boswellia serrata* Roxb. *ex* Coleb. Burseraceae	Hexane extract of gum resin	Antiadjuvant induced arthritis in rats	Mishra *et al*., 2011
11.	*Calotropis gigantea* (L.) R. Br. Asclepiadaceae	Latex extract Root extract	Antiadjuvant induced arthritis in rats; Anti-inflammatory activity	Kumar and Roy, 2007; Babu and Karti, 2011
12.	*Camellia sinensis* (L.) O. Ktze. Theaceae	Polyphenols	Antiarthritic activity	Ahmed, 2010

13.	*Cassia uniflora* Mill. Cesalpinaceae	Extracts of leaves	Antiadjuvant induced arthritis in rats	Chaudhari *et al*., 2012
14.	*Cardiospermum halicacabum* L. Sapindaceae	Alcohol extract of leaves	Anti-inflammatory activity in rats	Gopala *et al*., 1976
15.	*Centella asiatica* (L.) Urban Apiaceae	Methanol extract of fresh whole plant	Inhibition of protein denaturation, *etc*	Chippadal *et al*., 2011
16.	*Cisssampelos pareira* L. Menispermaceae	Aqueous ethanolic extract of root	Analgesic activity in mice and antiadjuvant induced arthritis in rat	Amresh *et al*., 2007
17.	*Clerodendrum inerme* (L.) Gaertn.Verbenaceae	Petroleum ether extract of leaves	Inhibition of protein denaturation	Sangeetha *et al*., 2011
18.	*Cleome gynandra* L. Capparidaceae	Ethanol extract	Antiadjuvant induced arthritis in rats	Narendhirakumar *et al*.,2007
19.	*Cleome rutidosperma* DC. Capparidaceae	Whole plant alcohol extract	Antiadjuvant induced arthritis and anticotton-granuloma in rats	Chakraborty and Roy, 2010
20.	*Coldenia procumbens* L. Boraginaceae	Methanol extract of leaves	Inhibition of protein denaturation	Lavanya *et al*., 2010
21.	*Commiphora incisa* Chiov. Burseraceae	Resin (Mansumbinoic acid)	Antiadjuvant induced arthritis in rats	Duwiejua *et al*., 1993
22.	*Commiphora mukul* (Stocks) Engl. Burseraceae	Gum-guggul	Anti-adjuvant induced arthritis in rats	Sharma and Sharma, 1977; Mishra, 2003
23.	*Curcuma longa* L. Zingiberaceae	Curcumin and turmeric extract (curcuminoids)	Anti-inflammatory activity; antiarthritic joint pain and prevention of experimental osteoarthritis	Srivastava and Srimal, 1985; Funk *et al*., 2006
24.	*Cyperus rotundus* L. Cyperaceae	Essential oil	Antiformaldehyde induced arthritis in rats	Biradar *et al*., 2010
25.	*Cyperus esculentus* L. Cyperaceae	Essential oil	Antiformaldehyde induced arthritis in rats	Biradar *et al*., 2010
26.	*Dalbergia volubilis* Roxb. Fabaceae	Chemical isolate	Anti-inflammatory and antiarthritic activity	Hye and Gafur, 1975
27.	*Daucus carota* L. Apiaceae	Ethanol extract	Antiformaldehyde induced arthritis in rats	Vasudevan *et al*., 2006
28.	*Erythrina variegata* L. Legumenosae	Flavonoids from bark	Anti-inflammatory activity (inhibition of phospholipase A_2 activity)	Shan Biren *et al*., 2006
29.	*Euphorbia tirucalli* L. Euphorbiaceae	Methanol extract of stem, bark and leaves	Antiadjuvant induced arthritis in rats	Priya and Roa, 2011
30.	*Ficus benghalensis* L. Moraceae	Stem bark extract	Antirheumatic activity	Monocha *et al*., 2011

31.	*Glycyrrhiza glabra* L. Fabaceae	Methanol extract of rhizomes	Antiadjuvant induced arthritis in rats	Mishra *et al.*, 2011
32.	*Hemidesmus indicus* (L.) R.Br.Asclepiadaceae	Ethanol extract of root	Antiadjuvant induced arthritis in rats; Inhibition of inflammation induced by viper venom	Metha *et al.*, 2012; Alam and Gomes, 1998
33.	*Hetrotheca inuloides* Cass. Asteraceae	Chemical isolates	Anti-inflammatory activity	Delgado *et al.*, 2001
34.	*Hybanthus enneaspermus* (L.) F. v. Muell.Violaceae	Alcohol and water extracts	Antiadjuvant induced arthritis in rats	Tripathy *et al.*, 2009
35.	*Inula viscosa* (L.) Aiton Asteraceae	Glycosyl analogue of diacyl glycerol, *etc*	Anti-inflammatory activity	Manez *et al.*, 1999
36.	*Justicia gendarussa* Burn f. Acanthaceae	Ethanol extract of leaves	Antiadjuvant induced and collagen-induced arthritis in rats	Paval *et al.*, 2009
37.	*Lawsonia inermis* L. Lythraceae	Hydroalcoholic extract of leaves	Antiadjuvant as well as antiformalin induced arthritis in rats	Kore *et al.*, 2011
38.	*Leucas aspera* (Willd) Spreng. Lamiaceae	Alcohol extract of aerial parts	Antiadjuvant induced arthritis in rats	Kripa *et al.*, 2010
39.	*Merremia tridentata* (L.) Hall. Convolvulaceae	Erhanol extract of root and aerial parts	Antiadjuvant induced arthritis in rats	Kamalutheen *et al.*, 2009
40.	*Nyctanthes arbortristis* L. Oleaceae	Alcohol extract of leaves	Antiadjuvant induced and formalin-induced arthritis in rat	Bhalerao *et al.*, 2011; Sandhar *et al.*, 2011
41.	*Paederia foetida* L. Rubiaceae	Butanol fraction of leaves Water extract	Inhibition of granuloma tissue formation in rats Antiadjuvant and formalin induced arthritis in rats	De *et al.*, 1994; Singh *et al.*, 1994
42.	*Perilla frutescens* (L.) Britton Lamiaceae	Benzoxepin derivatives	Inhibition of cyclooxygenase	Liu *et al.*, 2000
43.	*Piper nigrum* L. Piperaceae	Ethanol extract	Inhibition of carrageenan induced paw edema in rats	Bang *et al.*, 2009
44.	*Premna corymbosa* (Burm. f.) Rottl & Willd. Verbenaceae	Ethanol extract of leaves	Antiadjuvant induced arthritis in rat	Karthikeyan and Deepa, 2010
45.	*Premna serratifolia* L. Verbenaceae	Ethanol extract of wood	Antiadjuvant induced arthritis in rat	Rajendran *et al.*, 2010
46.	*Sacrophyte piriei* Hutch. Balanophoraceae	Biflavanoid	Anti-inflammatory activity (carrageenan induced paw edema)	Ogundaini *et al.*, 1996
47.	*Saraca asoka* (Roxb.) wilde Leguminosae	Extract	Antiadjuvant induced arthritis in rats	Saravanan *et al.*, 2011

48.	*Saussurea lappa* Clarke Asteraceae	Root extract	Antiarthritic activity in rats	Uma *et al.*, 2011
49.	*Semecarpus anacardium* L. f. Anacardiaceae	Chloroform extract of nut	Antiadjuvant induced arthritis in rat	Sarf *et al.*, 1989
50.	*Sesbania grandiflora* (L.) Poir. Fabaceae	Dried bark extracts	Inhibition of carageenan induced inflammation in rats	Patil *et al.*, 2010
51.	*Sesbania sesban* (Jacq.) W. Wight. Fabaceae	Dried bark extracts	Inhibition of carragee-nan-induced inflamm-ation in rats	Patil *et al.*, 2010
52.	*Sida rhombifolia* L. Malvaceae	Ethanol and water extracts	Antiadjuvant induced arthritis in rat	Gupta *et al.*, 2009
53.	*Strychnos potatorum* L..f. Loganiaceae	Water extract of seed	Antiadjuvant induced arthritis in rat	Sanmugapriya *et al.*, 2010
54.	*Syzygium cumini* (L.) SkeelsMyrtaceae	Methanol extract	Antiadjuvant induced arthritis in rat	Kumar *et al.*, 2008
55.	*Terminalia chebula* Retz. Combretaceae	Hydro-alcoholic extract	Antiadjuvant as well as antiformalin induced arthritis activity in rat	Nair *et al.*, 2010
56.	*Tinospora cordifolia* (Willd.) Hook. f. & Thoms. Menispermaceae	Water extract of bark	Antiarthritis activity; inhibits COX-2	Paval *et al.*, 2011
57.	*Tripterygium wilfordii* Hook f. Celastraceae	Root extract	Anticollagen induced arthritis in rats	Gu *et al.*, 1992
58.	*Urginea indica* (Roxb.) Kunth Liliaceae	Ethanol and water extracts of whole plant	Inhibition of protein denaturation	Rehaman *et al.*, 2011
59.	*Vanda tessellata* (Roxburg) W.J.Hook. ex G. Don. Orchidaceae	Alcohol extract	Anti-inflammatory activity in albino rats	Prasad and Achari, 1966
60.	*Vernonia anthelmintica* (L.) Willd. Asteraceae	Ethanol extract of seed	Anti-adjuvant induced arthritis in rat	Otari *et al.*, 2010
61.	*Vitex negundo* L. Verbenaceae	Ethanol extract of leaves	Antiadjuvant induced arthritis in rat	Ramesh Petchi *et al.*, 2011
62.	*Withania somnifera* (L.) Dunal Solanaceae	Root extract	Antigranuloma activity in rats; Antiinflamma-tory activity in rats	Al-Hindawi *et al.*, 1992; Anbalagan and Sadique, 1981
63.	*Zingiber officinale* Rosc. Zingeberaceae	Extracts of rhizome	Anti-inflammatory activity; Inhibition of prostaglandin and leucotrine bio-sunthesis; Anti-knee osteoarthritis activity in patients	Vtpalendu *et al.*, 1999; Subramoniam, 2004;Zaken *et al.*, 2011

Figure 1: *Boswellia serrata*

Figure 2: *Commiphora mukul*

Figure 3: *Withania somnifera*

Figure 4: *Curcuma longa*

Figure 5: *Tinospora cordifolia*

Figure 6: *Zingiber officinale*

Figure 7: *Ncytanthes arbortristis*

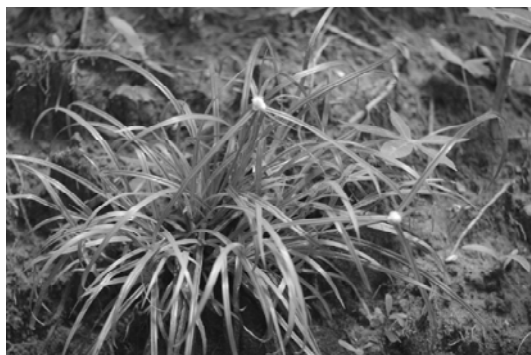**Figure 8:** *Aloe vera*

Figure 9: *Camellia sinensis*

Figure 10: *Cyperus rotundus*

Cyperus rotundus **L.**

In Ayurveda, *C. rotundus* rhizomes are considered as astringent, diaphoretic, diuretic, analgesic, antispasmodic, aromatic, carminative, antitussive, emmenagogue, litholytic, sedative, stimulant, stomachic, vermifuge, tonic and antibacterial (Sivapalan, 2013). It has a wide range of pharmacological properties such as antiarthritis, anti-inflammatory, antipyretic, analgesic, antidiabetic, antidiarrheal, cytoprotective, antimutagenic, antimicrobial, antioxidant and apoptotic (Singh *et al*., 2012). The plant leaves showed anti-inflammatory effect on acute and subacute inflammation in experimental rat models (Sundaram *et al*., 2008). Further, it has been reported that essential oil of this plant possesses anti-inflammatory, antiarthritic, analgesic and anticonvulsant activities in rats (Biradar *et al*., 2010). A double blind trial of crude powder of *C. rotundus*, *Withania somnifera* and their combination (1:1) was carried out in 200 patients suffering from rheumatoid arthritis. *C. rotundus* was more effective than *W. somnifera*, and when both drugs were combined, the response was better than the response of single drug (Singh *et al*., 1976). However, detailed studies are required to confirm the therapeutic value of this plant as an anti-arthritic agent.

Phytochemicals with antiarthritis and/or anti-inflammatory properties

Anti-inflammatory and/or anti-arthritis activities were reported from the extracts and crude preparations from more than 60 plants. The active principles were isolated and identified in many cases. More than 50 active principles showing marginal to moderate activities, particularly anti-inflammatory activities in carrageenan-induced paw edema, were identified from the plants. The chemical isolates which showed varying levels of anti-inflammatory and/ or anti-arthritic activities are given in Table 6.

A few human clinical studies were carried out on the therapeutic value of γ-linolenic acid. These studies have suggested marginal to moderate beneficial effects of γ-linolenic acid to RA patients. γ-linolenic acid is present in borage (*Borago officinalis*) seed oil, evening primrose (*Olenotheca blennis*) oil, black-current (*Ribes nigram*) seed oil, *etc* (see review, Soeken *et al*., 2002). Curcumin, a constituent of turmeric (*Curcuma longa* Linn.) is known to have several pharmacological activities including anti-inflammatory activity. In a clinical trial, curcumin treatment (1200 mg/day) to RA patients showed improvement in morning stiffness, walking time and joint swelling (Deodar *et al*., 1980).

Although more than 50 phytochemicals have been shown to have varying levels of anti-inflammatory activity, these studies are, to a large extent, preliminary in nature. Sufficient follow up studies were not done to determine their therapeutic use, if any, in arthritic conditions. Compounds like boswellic acid, degradation products of chlorophyll-a, curcumin, ecdysone and β-sistosterol are examples of promising compounds which require further studies.

Table 6: Phytochemicals with anti-inflammatory and/ or antiarthritic activities

S. No.	Phytochemicals	Plant source	Biological activities	References
1.	Boswellic acid	*Boswellia serrata* Roxb. *ex* Coleb.Burseraceae	Showed anti-inflammatory and complement inhibitory activities in rats; down requlation of TNF-α and IL-1	Kapil, 1994; Manjula *et al.*, 2006
2.	Bavachinin (Flavonoid)	*Psoralea corylifolia* L. Fabaceae	Reduced inflammation in carrageenan induced edema in rats(showed analgesic and anti-pyretic activities also)	Shah Biren *et al.*, 2006 (review)
3.	Berberine (Alkaloid)	*Berberis aristata* DC.Berberidaceae	Reduced inflammation in carrageenan induced edema, in cotton pellet-granuloma and in formaldehyde-induced arthritis	Chatterjee and Pal, 1984 (review)
4.	Bergenin (phenolic)	*Peltophorum pterocarpum* (DC.) Baeker *ex* K. Heyne Caesalpiniaceae	Inhibition of carrageenan-induced edema in rats	Shah Biren *et al.* 2006
5.	Callophllin B (Xanthone)	*Callophyllum inophyllum* L. Clusiaceae	Reduced inflammation in carrageenan induced edema and in cotton pellet-granuloma	Shah Biren *et al.*, 2006(review)
6.	Calophyllolide (Coumarin)	*Callophyllum inophyllum* L. Clusiaceae	Reduced inflammation in carrageenan induced edema, cotton pellet-granuloma and formaldehyde-induced arthritis	Shah Biren *et al.*, 2006 (review)
7.	Caryolane-1, 9-β-diol (Flavanoid)	*Heterotheca inuloides* Cass. Asteraceae	Anti-inflammatory activity	Degado Guillermo *et al.* 2001
8.	Centaureidin (Flavonoid)	*Tanacetum microphyllum* DC.Asteraceae	Anti-inflammatory activity	Abad *et al.* 1993
9.	Chlorophyll-a and Mg free chlorophyll-a (pheophytin-a)	All green plants	Anti-inflammatory activity against carrageenan and formalin induced inflammation; inhibition of TNF-α gene expression	Subramoniam *et al.*, 2012
10.	Chrysoeriol glucopyranosyl D-apiofuranoside	*Dalbergia volubilis* Roxb. Fabaceae	Anti-inflammatory and anti-arthritic activity	Hye and Gafur, 1975
11.	Coumarins (herniarin, aesculetin, scopolin and scopoletin)	*Santolina oblongifolia* Boiss Asteraceae	Anti-inflammatory activity [Inhibited eicosanoid release from ionophore stimulated mouse peritoneal macrophages]	Shah Biren *et al.*, 2006(review)
12.	Curcumin (diferuloyl methane)	*Curcuma longa* L. Zingiberaceae	Anti-rheumatoid activity in human clinical trials;Reduced inflammation in carrageenan induced edema, cotton pellet -granuloma and adjuvant-induced arthritis	Deoder *et al.*, 1980; Shah Biren *et al.* 2006

13.	Dehydrocyclogua nadine (Xanthone)	*Callophyllum inophyllum* L. Clusiaceae	Reduced inflammation in carrageenan induced edema and cotton pellet-granulom a in rats	Shah Biren *et al*., 2006 (review)
14.	Dicadalenol (Flavonoid)	*Heterotheca inuloides* Cass. Asteraceae	Anti-inflammatory activity	Degado Guillermo *et al*. 2001
15.	5, 3-dihydroxy 4-methoxy-7-carbomethoxy flavonyl	*Tanacetum microphyllum* DC. Asteraceae	Anti-inflammatory activity	Abad *et al*. 1993
16.	Diinsininol and diinsinin (Biflavanoid)	*Sacrophyte piriei* Hutch. (Balanophoraceae)	Ati-inflammatory activity	Shah Biren *et al*., 2006 (review)
17.	Dysobinin	*Disoxylum binectariferum* Hook.f.Meliaceae	Reduced inflammation in carrageenan induced paw edema	Chatterjee and Pal, 1984
18.	β-ecdysone	*Tinospora cordifolia* (Willd.) Hook.f. & Thoms. Minispermaceae	Stimulats cartilage and osteobalst function and protects from bone erosion	Abiramasundari *et al*., 2012; Kapur *et al*., 2010.
19.	Ergolide (sesquiterpene lactone)	*Inula britannica* L. Asteraceae	Anti-inflammatory activity mediated by inhibition of COX-2 and iNOS	Whan-Han *et al*., 2001
20.	Euxanthone	*Mesua ferrea* L.Clusiaceae	Reduced carrageenan induced edema and cotton pellet-granuloma in rats	Chatterjee and Pal, 1984
21.	Epicatechin (Phenolic compound)	*Anacardium occidentale* L. Anacardiaceae	Reduced inflammation in carrageenan induced edema, in cotton pellet-granuloma and in formald ehyde-induced arthritis	Chatterjee and Pal, 1984 (review)
22.	Flavonoids (7-0-methylaro madendrin, rhamnocitrin and 3-0-acetylpa dmatin)	*Inula viscosa* (L.) Aiton Asteraceae	Anti-inflammatory activity	Shah Biren *et al*., 2006 (review)
23.	Gangetin	*Desmodium gangeticum* (L.) DC. Fabaceae	Reduced carrageenan induced edema and cotton pellet-granuloma (showed analgesic and anti-pyretic activities also)	Shah Biren *et al*., 2006 (review)
24.	Glycyrrhizin	*Glycyrrhiza glabra* L. Fabaceae	Reduced inflammation in formaldehyde and adjuvant arthritis	Chatterjee and Pal, 1984 (review)
25.	Glycyrrhetinic acid	*Glycyrrhiza glabra* L. Fabaceae	Reduced inflammation in cotton pellet-granuloma in rats	Chatterjee and Pal, 1984

26.	Gossypin	*Hibiscus vitifolius* L. Malvaceae	Anti-carrageenan induced edema and anti-adjuvant induced arthritis	Chatterjee and Pal, 1984
27.	Hedragenin	*Blighia sapida* Koenig Sapindaceae	Reduced inflammation in carrageenan induced edema and in formaldehyde-induced arthritis	Chatterjee and Pal, 1984
28.	4-hydroxy 3, 5-dipprenylis oflavavanone; 4-hydroxy 6,3, 5-trilisoflavavan one; 3,9-dihydroxy 2,10-diprenyl-prterocarpene	*Erythrina variegate* L. Fabaceae	Anti-inflammatory activity (phospholipase A_2 inhibition)	Shah Biren *et al*., 2006 (review)
29.	2-hydroxy 4-methoxy benzoic acid	*Hemidesmis indicus* (L.) Br. Periplocaceae	Neutralized inflammation induced by *Viper russelli* venom	Alam and Gomes, 1998
30.	Ilicic acid and inuvisolide (sesquiterpene)	*Inula viscosa* (L.) Aiton Asteraceae	Inhibition of TPA induced ear edema in mice	Shah Biren *et al*., 2006 (review)
31.	Inugalactolipid A	*Inula viscosa* (L.) Aiton Asteraceae	Inhibition of TPA induced ear edema in mice	Shah Biren *et al*., 2006 (review)
32.	Lanceolarin	*Dalbergia lanceolaria* L. f. Fabaceae	Reduced inflammation in carrageenan induced edema and in formaldehyde-induced arthritis	Chatterjee and Pal, 1984
33.	Mangiferrin (Xanthone)	*Canscora decussata* (Roxb.) Schult. Gentianaceae	Reduced inflammation in carrageenan induced edema, in cotton pellet-granuloma and in formaldehyde-induced arthritis	Shah Biren *et al*., 2006 (review)
34.	Mangostin (Xanthone)	*Garcinia mangostana* L. Clusiaceae	Reduced inflammation in formaldehyde-induced arthritis in rats	Chatterjee and Pal, 1984
35.	Mansumbinone and mansumbinoic acid (triterpenes)	*Commiphora incisa* Chiov. Burseraceae	Mild inhibition of carragee nan-paw edema; Anti-adjuvant -induced arthritis in rats	Duwiejua *et al*., 1993
36.	Mesuazanthone B	*Mesua ferrea* L. Clusiaceae	Reduced inflammation in carrageenan induced edema and in cotton pellet-granuloma in rats	Shah Biren *et al*., 2006 (review)
37.	Myrrhanol A and myrrhanone A (triterpenes)	*Commiphora mukul* (Stocks) Hook. Burseraceae	Potent anti-inflammatory effect on adjuvant-induced air-pouch granuloma in mice	Kimura *et al*., 2001
38.	Nepitrin (flavonoid)	*Nepeta hindostana* (Roth.) Haines. Lamiaceae	Reduced inflammation in formal dehyde as well as adjuvant induced arthritis in rats	Shah Biren *et al*., 2006 (review)

39.	Nimbidin	*Azadirachta indica* A. Juss. Meliaceae	Reduced inflammation in form- aldehyde as well as adjuvant induced arthritis in rats	Chatterjee and Pal, 1984
40.	Nimbin	*Malia indica* (A. Juss.) BrandisMeliaceae	Reduced inflammation in carrag -eenan induced edema and in formaldehyde-induced arthritis	Shah Biren *et al*., 2006(review)
41.	Oleanolic acid -3-β-glucoside	*Randia dumetorum* (Retz.) PoirRubiaceae	Anti-inflammatory activity in rats	Shah Biren *et al*., 2006(review)
42.	Quercetin (flavonoid)	*Heterotheca inuloides* Cass. Asteraceae	Anti-inflammatory activity	Delgado *et al*., 2001
43.	Perilloxn and dihydroperillixin (Prenyl 3-benzoxepin derivatives)	*Perilla frutescens* (L.) Britton var *acuta* Lamiaceae	Anti-inflammatory activity by inhibiting cyclooxygenase	Shah Biren *et al*., 2006 (review)
44.	Roxburghiadiol A and B (Triterpenes)	*Aglaia roxburghiana* (Wight and Arn.) Miq. Meliaceae	Reduced inflammation in carrageenan induced edema and in cotton pellet- granuloma in rats	Janaki *et al*., 1999
45.	β-Sitosterol	*Cyperus rotundus* L. Cyperaceae(reported in other plants also)	Reduced inflammation in carrageenan induced edema and in cotton pellet- granuloma	Shah Biren *et al*., 2006(review)
46.	Spartidienedione (Sesquiterpene)	*Psila spartioides* (Hook. and Arn.) Cabrera Asteraceae	Antiinflamatory activity in rabbits and guinea pigs (it also showed anti-phyretic activity)	Shah Biren *et al*., 2006(review)
47.	Spinasterol A	*Symplocos spicata* Roxb. Symplocaceae	Anti-acute inflammation induced by carrageenan in rats	Shah Biren *et al*., 2006(review)
48.	Taxifolin (Flavonoid)	*Madhuca longifolia* (Koenig) J.F. Macbr. Sapotaceae	Reduced inflammation in carrageenan induced edema and in cotton pellet- granuloma in rats	Chatterjee and Pal, 1984
49.	Triterpene saponins (2 new compounds)	*Myrsine australis* Myrsinaceae	Inhibited inflammation by inhibiting phospholipase D activity	Shah Biren *et al*., 2006(review)
50.	Tylophorine (alkaloid)	*Tylophora indica* (Burm. f.) Merr. Asclepiadaceae	Reduced inflammation in carrageenan induced edema and in adjuvant- induced arthritis in rats (also exhibited anaphylactic and immunocytoadherence)	Chatterjee and Pal, 1984; Shah Biren *et al*., 2006
51.	Vitoxin	*Ochrocarpus longifolius* (Wight) Anders. Clusiaceae	Reduced inflammation in carrageenan induced edema and in cotton pellet-granuloma in rats	Chatterjee and Pal, 1984
52.	Zanhasaponin A & B	*Zanha africana* (Radlk.) Excell. Sapindaceae	Anti-inflammatory activity (inhibition of phospholipase A_2 activity)	Shah Biren *et al*., 2006

Mechanism of action of plant based antiarthritic drugs

Some of the anti-inflammatory and/or antiarthritis plants were studied for their mechanisms of actions. However, most of the studies were not carried out systematically and fully with a therapeutic approach. Plant extracts and active fractions are likely to have more than one mechanisms of action. The mechanisms emerged from the studies include suppression of certain hyper immune reactions occurring in the case of RA, exerting anti-inflammatory action by one or more mechanisms such as inhibition of phospholipase A_2, phospholipase D, Cyclooxygenases, lipoxgenases, *etc*. Another important mechanism is immune modulation by influencing the levels of specific cytokines and lymphokines.

Release of arachidonic acid by the action of phospholipase A_2 may result in production of excess eicosanoids which in turn can result in inflammation. Some plant constituents are known to activate phospholipase A_2. Flavonoids from the bark of the Samoan anti-inflammatory plant, *Erythrina variegata* L. (Legumenosae) inhibit Phospholipase A_2. Zanhasaponin A and B (triterpene saponins) and cyclitol pinitol isolated from the root bark of *Zanha africana* (Sapindaceae) are also inhibitors of phospholipase A_2 (Shah Biren *et al*., 2006).

Two new triterpene saponins (anti-inflammatory phytochemicals) from the leaves of *Myrsine australis* inhibited PMA (phorbal-12-myristate-13-acetate) as well as fMLP (N-formyl-methionyl-leucyl-phenylalanine) stimulated phospholipase D activation (Shah Biren *et al*. 2006).

The anti-arthritic rhizome of *Z. officinale* (ginger) is an inhibitor of both prostaglandin and leucotrine bio-synthesis (Srivastava and Mustafa, 1992). Anti-inflammatory biflavonoids from the rhizome of *Sacrophyte piriei* inhibits prostaglandin synthesis and platelet activation factor induced exocytosis. Anti-inflammatory coumarins isolated and purified from *Santolina oblongifolia* (Compositae) inhibit eicosanoid release from ionophore stimulated macrophages (Shah Biren *et al*. 2006).

One of the important traditional antiarthritic medicinal plants is *Boswellia serrata*. Boswellic acids (active principles) present in the oleogum of this plant inhibit 5-lipoxygenase, a key enzyme involved in the synthesis of leukotrienes. This could be at least one of the mechanisms of its anti-arthritic activity (Shah Biren *et al*. 2006). Further, acetyl-boswellic acids inhibit lipopolysaccharide mediated TNF-α induction in monocytes by direct interaction with IκB kinases (Syrovets *et al*., 2005). The oleoresin fraction of *Commiphora mukul* possesses significant anti-arthritic activity. One of the mechanisms of its action could be suppression of hyper immune reactions. Crude extract and a pure compound isolated from *C. mukul* inhibits MAP kinases that lead to down regulation of TNF-α , IL-1-β and IL-2 (Manjula *et al*., 2006). Extracts of leves and fruits of *N. arbortristis* decreased the serum levels of TNF-α, interferon-γ, IL-1 and IL-6 in arthritic mouse (Paul and Saxena, 1992; Rathore *et al*., 2007). One of the mechanisoms of the anti-arthric and anti-inflammatory activity of the extract could be its influence on these regulators of immune function.

Recently Subramoniam and co-workers have shown that chlorophyll-a and its major degradation products pheophytin-a and pheophorbide-a can exert anti-inflammatory activity in carrageenan as well as formalin induced paw edema in mice (Subramoniam *et al*. 2012). Chlorophyll-a and its degradation products inhibited expression of the pro-inflammatory cytokine, TNF-α in cultured cells (Subramoniam *et al*. 2012). The study strongly suggests that the major mechanism of the anti-inflammatory activity of chlorophyll-a and its degradation products is inhibition of expression of TNF-α (Subramoniam *et al*. 2012).

The anti-inflammatory compound, ergolide, a sesquiterpene lactone from *Inula britannica* suppresses inducible nitric oxide synthase (iNOS) and COX-2 in lipopolysaccharide (LPS) or γ-interferon stimulated macrophages and markedly decreased the production of prostaglandin E-2 in a concentration dependent manner (Whan Han *et al*., 2001). Ergolide inhibited activation of nuclear factor kappaB (NF-κB), a transcription factor necessary for the expression of these enzymes in response to LPS/ γ-interferon. The study suggests that the inhibitory effect of ergolide may be mediated by alkylation of NF-κB or an upstream molecule of NF-κB. Ergolide also directly inhibited the DNA binding activity of active NF-κB in macrophages (Whan Han *et al*., 2001).

Ecdysteroids isolated from *T. cordifolia* has direct stimulatory effects on cartilage and bone function (Abiramasundari *et al*., 2012; Kapur *et al*., 2010).

Other mechanisms include stabilization of lysosomal membrane and reduction in reactive oxygen species (ROS) production as seen in the case of curcumin (Shah Biren *et al*. 2006). Excess ROS has a role in the pathogenesis of arthritis. Andrographolide isolated from the leaves of *Andrographis paniculata* is a hepatoprotective compound. This compound is reported to have anti-inflammatory and anti-oxidative properties also (Mishra, 2003). Andrographolide prevented phorbal-12-myristate-13-acetate (PMA) induced RAS production as well as N-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced adhesion of neutrophils (Shen *et al*. 2000). It is also shown to inhibit nitric oxide generation in endotoxin-stimulated macrophages (Chiou *et al*., 2000).

Methods of screening plant extracts and active fractions/compounds for antiarthritic action

Rheumatoid arthritis

The commonly used important *in vivo* methods to test anti-RA agents (drug candidates) are adjuvant-induced arthritis, collagen-induced arthritis, collagen anti-body-induced arthritis, zymogen-induced arthritis, antigen-induced arthritis, streptococcal cell wall-induced arthritis and spontaneous transgenic models of arthritis (Asquith *et al*. 2009; Bendele, 2001; Oliver and Brahn, 1996). Agents currently in clinical use or trials that are active in these models include corticosteroids, methotrexate, NSAIDs, cyclosporin A, leflunomide, interleukin-1 receptor antagonists and soluble TNF-α receptors (Mishtra 2003). Other common methods include formaldehyde induced arthritis in rats and cotton pellet induced granuloma. The other methods such as carrageenan-induced paw edema are widely used to measure anti-inflammatory activity.

Adjuvant-induced arthritis in rats

Most of the experimentally induced polyarythritic studies are undertaken with adjuvant-induced arthritis in rats. This method is widely used for preclinical testing of many anti-arthritic agents (Bendele, 2001). This model shows reliable onset and progression of the disease, easily measureable, polyarticular inflammation, bone resorption, *etc*. However, in this model cartilage destruction is mild in comparison to the inflammation and bone destruction. Male Lewis rats (165-200 grams) are generally used in studies of adjuvant arthritis. In females, the disease is much more variable in onset and severity (Henson and Brunson, 1970).

Induction of adjuvant disease can be done with either Freunds complete (FCA) supplemented with mycobacterium or by injection of the synthetic adjuvant N, N-dioctadecyl-N', N'-bis(2-hydroxyethyl) propanediamine (LA) (Chang, 1980). Adjuvant can be injected at the base of the tail or in one of the foot pads. If injection is into the footpad, it allows study of the acute inflammatory reactions in that local area as well as the immunological reaction that develops approximately 9 days later in the paw and various organs. Hind paw swelling is monitored from day 9 (onset of disease) to 15 or greater depending on duration desired (Bendele, 2001).

To assess disease progression, measurements of ankle joint width or volume using a plethysmometer are done prior to the onset of arthritis, and then every other day until the study is terminated on day 15 post injection of the adjuvant. Treatments are initiated on day 0 (prophylactic model) or day 8 (therapeutic model). At termination, the tibiotarsal joint is transected and weighed. Paws are then collected into formalin for histopathological evaluation for beneficial effects on arthritis parameters and also for evaluation of potential deleterious effects of treatment on bone marrow (review, Bendele, 2001).

Ankle joints (with digits removed) are decalcified and transected in the longitudinal plane to give approximately equal halves. Then, joints are processed for paraffin embedding, sectioned and stained with hematoxylin and eosin for general evaluation and stained with toluidine blue for specific evaluation of cartilage changes. Adjuvant arthritic ankles are given scores of 0-5 for inflammation and bone resorption as previously described (Bendele *et al*., 1999a). This model offers an opportunity to study pathological changes in a variety of tissues other than the joints (Bendele, 2001). Ideally, an agent active in adjuvant disease should restore the spleen weights and morphology to normal as is the case with methotrexate treatment (Bendele *et al*., 1999a).

Clinically used agents that are active in adjuvant arthritis include corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and low dose methotrexate (Bendele *et al*., 1999a). The newer biologic agents such as soluble TNF-α receptors and the interleukin-1 receptor antagonist (IL-1ra) also have activity in this model (McComb *et al*., 1999; Bendele, 2001). Inhibition of IL-1 in the adjuvant model markedly inhibits the bone resorption that is a prominent feature of this disease but has a little effect on the inflammation. Studies such as those with specific inhibitors have helped delineate the importance of various cytokines in disease progression in adjuvant disease. Combination therapies, a likely clinical scenario, in this model using IL-1ra and methotrexate have shown additive effects (Bendele *et al*., 1999b).

Collagen-induced arthritis in rats or mice

Collagen-induced arthritis (CIA) shares many similarities with human RA and is a useful model (Asquith *et al*., 2009). CIA was first described in rats; it is inducible in susceptible strains of mice, following inoculation with type II heterologous collagen in complete Freund's adjuvant (Trenthan *et al*., 1999). Susceptibility has been linked to strains that have MHC Class II I-Aq haplotypes; however, it is clear that many mouse strains have variable degrees of susceptibility to CIA. Similarly, restricted class II genotypes can be found in RA patients. DBA/1 mice are most widely used in CIA model. Clinical signs of disease typically develop 21–25 days after the initial inoculation and presents as a polyarthritis, which is characterized by synovial inflammatory infiltration, cartilage and bone erosion and synovial hyperplasia similar to human RA. The development of CIA is associated with both B and T lymphocyte responses with the production of anti-collagen type II antibodies. Disease severity is expected to peak at approximately day 35, after which DBA/1 mice enter remission,

marked by increased concentrations of serum IL-10 and a subsequent decrease in pro-inflammatory Th1 cytokines. A role for IL-17 in synovial inflammation and joint destruction has been shown in collagen-induced arthritis (Lubberts *et al*., 2001). In a further development of the model, inoculation with homologous type II collagen has been reported to cause chronic relapsing arthritis more akin to human RA, and has been suggested to be more useful for studying remission-inducing therapies. With the development of a working protocol for the induction of CIA in C57BL/6 mice, (most of the transgenic mice are C57BL/6 background), studying arthritis in genetically modified mice is becoming more feasible. The C57BL/6 strain develops arthritis 4-7 days later compared with DBA/1 mice. There are differences in the onset and progression of disease between the DBA/1 and C57BL/6, which may cause discrepancies when comparing studies between these two strains. Although both strains of mice are useful to study the pre-clinical development or prophylactic treatment of arthritis, the C57BL/6 model requires further characterization in different B6 substrains. It is generally recognized that variability in incidence, severity and intergroup consistency are associated with the CIA model. This may reflect the model's exquisite sensitivity to environment, maintenance conditions and general stress in the animals. Thus, careful, independent, internal controls are mandatory for valid interpretation of data (Asquith *et al*., 2009).

Collagen antibody-induced arthritis

In CIA, anti-type II collagen IgG antibodies are detectable, transfer of serum from an immunized mouse into a non-immunized recipient can result in arthritis. Anti-collagen antibody cocktails have been shown to induce the development of arthritis (review, Asquith *et al*., 2009). Similar protocols are now commonly used for the induction of collagen-antibody induced arthritis (CAIA). Identification of auto-antibody to collagen epitopes allows the development of more arthritogenic antibody cocktails that may better represent the humoral auto-immunity in RA. Although the clinical development of arthritis is similar to that in CIA, CAIA is characterized by infiltration of macrophage and polymorphonuclear inflammatory cells, but is not associated with a T and B cell response; however, the administration of type II collagen reactive T cells has been shown to enhance disease severity. Therefore, CAIA can provide insight into the separate roles of innate and adaptive immune response in the development of arthritis. Furthermore, as disease develops within 48 h of antibody administration with 100% penetrance and is inducible regardless of the MHC class II haplotype, CAIA is well suited for studying the development of arthritis in genetically modified strains of mice (review, Asquith *et al*., 2009).

Zymosan-induced arthritis

The cell wall of *Saccharomyces cerevisiae* contains zymosan, a polysaccharide with repeating glucose units connected by b-1,3-glycosidic linkages. It binds to TLR2 in macrophages leading to the induction of proinflammatory cytokines, arachidonate mobilization, protein phosphorylation and also activation of complement *via* the alternative pathway. Injection of zymosan intra-articularly into the knee joints of mice results in a proliferative inflammatory arthritis with mononuclear cell infiltration, synovial hypertrophy and pannus formation with the peak of disease at about day 3 and inflammation subsiding by day 7. Recent data, however, demonstrate that the model is biphasic, with both early and late phases. The main limitation of this model is the monoarthritic nature of the disease and the technical skill required for an intra-articular injection in mice. Furthermore, an intra-articular injection model precludes analysis of the systemic component of the disease (review, Asquith *et al*., 2009).

Antigen-induced arthritis

Mice of several strains may develop inflammatory arthritis when primed with an antigen (*e.g*., methylated BSA in complete Freund's adjuvant) and subsequently challenged with intra articular injection of the same antigen. The pathological changes include immune complex mediated inflammation followed by articular T cell mediated responses. However, the model does not recapitulate the endogenous breach of tolerance that is typical of RA pathogenesis. However, prior adoptive transfer of transgenic ovalbumin-specific T cells to mice followed by ovalbumin priming and later intra-articular challenge results in development of arthritis with auto-reactivity to collagen, and the presence of rheumatoid factors. This model has the advantage of facilitating imaging of the pathogenic T cells that in turn promote breach of self-tolerance to articular antigens (Asquith *et al*., 2009).

Spontaneous transgenic models of arthritis

TNF-α transgenic mouse model of inflammatory arthritis in mice: A transgenic mouse over-expressing human TNF-α was developed by Keffer and co-workers (Keffer *et al*., 1991; Asquith *et al*., 2009). The mouse develops chronic polyarthritis and treatment with a monoclonal antibody against human TNF- α completely prevents the disease. In contrast to CIA and adjuvant-induced arthritis, which are acute and self-limiting, the chronic progressive nature of the arthritis in this model bears close resemblance to the human disease. Since then multiple lines of TNF-α transgenic mice have highlighted the importance of TNF-α in the cytokine hierarchy of RA. Anti-TNF- α therapy in humans has shown considerable success. Thus, the TNF-α transgenic mice provide a useful tool for evaluating the efficacy of novel therapies in RA. Moreover, the model has proven particularly

useful in determining the specific roles of effecter cytokines that regulate inflammation and those that regulate cartilage and bone destruction.

The K/B_N spontaneous mouse model of arthritis: This model was first described by Kouskoff and co-workers (Kouskoff *et al*., 1996; Asquith *et al*., 2009). These mice were generated by crossing the TCR transgenic KRN line with mice expressing the MHC class II molecule Ag7. K/B_N mice develop severe and destructive inflammatory arthritis. They have high titers of autoantibodies to glucose-6-phosphate isomerase, and serum from these mice induces arthritis in a wide range of normal recipient mouse strains. The mechanism of action involves TNF-α as well as IL-1 mediated complement activation and mast cell degranulation. This model remains useful for the study of initial events involved in the induction of arthritis.

Other spondaneous transgenic models of arthritis include SKG model, human/SCID chimeric mice, human DR4-CD4 mice, mice with deficience of IL-1 receptar antagonist, *etc* (review, Asquith *et al*., 2009).

Osteoarthritis

In vitro methods

The *in vitro* systems used to assess drug effects upon chondrocytes include homogenates of cartilage (Zafarullah *et al*., 1992), chondrocyte monolayer cultures, suspensions of aggregated chondrocytes, cells cultured in or over an artificial matrix like agarose, cartilage explants and organ culture (Korver *et al*., 1989). The 2 main cartilage constituents are collagen type II fibrillar network and proteoglycans attached to hyaluronic acid filaments. Proteoglycans are the more sensitive and the first ones to change in cartilage degradation. Therefore, the *in vitro* assays are mainly performed with chondrocytes; protoglycan synthesis and/ or degradation are measured.

Under *in vitro* conditions, interleukin-1 and retinoic acid induce enhanced matrix degradation as well as reduced matrix synthesis as observed in OA. These agents are used to induce a disease-relevant condition *in vitro*. Their role in the actual disease process *in vivo* is not clear. To address respective mechanisms of drug action, more specific follow-up studies like enzyme inhibition or cytokine release or inhibition assays are required (Kolibas and Goldberg, 1989).

Modulation of cellular proteoglycan metabolism assay

In modulation of cellular proteoglycan metabolism assay, compounds including mixtures of phytochemicals, can be tested for their effect upon the normal turnover of cartilage matrix by chondrocytes and potential impairment of cartilage function. Specific matrix staining reveals the amount of newly formed matrix around the cells at the end of the experiment. Incorporation of radio-labeled sulfate into the newly formed proteoglycans can be done to quantify the synthetic activity (Bassler *et al*., 1992). Normally the assay starts 5 days after cell preparation and various concentrations of the test compound are added to the medium and added new with each change of medium over a total period of 8 days. An untreated control group as well as standard compound group is always included. A standard compound, pentosane polysulfate to check the matrix increase or retinoic acid to cause matrix decrease can be used. The limitation of these primary culture assays lies in the elaborate preparation and isolation of the chondrocytes. Appropriate cell lines can be developed to overcome this (Green *et al*., 1995).

Cellular chondrocytic chondrolysis

In this assay IL-1 is added to articular chondrocytes grown in agarose gel; IL-1 suppresses proteoglycan synthesis and increases its degradation. This process is also observed in degradative joint diseases *in vivo*. This process is called chondrocytic chondrolysis. The test is used to detect the likely interference of a drug candidate with this pathological process. Effect upon proteoglycan synthesis is studied by radiolabelling at the end of the experiment and measuring the amount of incorporated sulfate. The effect upon proteoglycan degradation can be studied by prelabelling with $Na_2^{35}SO_4$ (Aydelotte *et al*., 1986).

Cartilage explants chondrolysis

The methods are described by Lafeber *et al*. (1993). Since chondrocytes vary in their metabolic activity and cytokine response depending on their relative location within the joint, explants assays are recommended as a follow-up to cellular tests. Further, the cellular assays are a homogenous mixture of an otherwise heterogenous cell population. Chondrocytes are more reactive after isolation compared to those in tissue culture. Morover, intact cartilage matrix acts as barrier for certain drug candidates of high molecular size and fixed charges, so they may not reach their target cells.

A step towards organ culture represents the culture of full thickness cartilage with subchondral bone on moist lens tissue (Chayen *et al*., 1994).

In vivo methods

The destruction encountered in RA includes inflammatory process, synovial tissue proliferatiuon, simultaneous degradation of cartilage proteoglycans and collagens and bone eroson. In OA inflammation is only an intermittent event, not instrumental in the degenerative cartilage destruction wherein proteoglycan gegradation is an early event whereas collogen degradation occurs at a later stage. Therefore, animal models with a predominant inflammatory component are not very relevant to study OA.

Surgical methods are used to either stiffen the joint in a defined position (Meyer-Carrive and Gosh, 1992) or inflict

joint instability by partial miniscectomy or articular crucial ligament dissection. Chemical modifications like intra articular injection of iodoacetate, cytokines like IL-1 or enzymes like chymopapain are carried out in chicken or rabbits (Williams *et al*., 1992). Mechanical forces are applied on bent or opened joints like impule loading on sheep or rabbit (Farkas *et al*., 1987). Spontaneously occurring OA is described in many mammal species. However, for pharmacological studies guinea pig and mice strains are adopted (Raiss *et al*., 1992). Animal models of OA include Spontaneous OA model in STR/1N mice, Canine antirior cruciate ligament transaction and Chymopaoain-induced cartilage degeneration in the rabbit.

Spontaneous OA model in STR/1N mice

In the spondaneous model OA develops gradually starting with cartilage surface erosion and fibrillation to osteophyte formation, subchondral bone remodeling and finally eburnation in a moderate time frame. These disease progressions with only intermittent inflammatory flares are almost similar to human OA. However, there are variances in on set and severity of OA among the mice (Raiss and Caterson, 1992). The STR/IN mice can be obtained from the National Institute of Health, Bethesda MA, USA.

Canine antirior cruciate ligament (ACL) transection model

ACL transaction in the dog knee and the subsequent joint instability results in progressive cartilage erosion, fibrillation and formation of osteophytes. This dog model is described in detail by Adams and Peltetier (1988). In general, older animals show more rapid degeneration while younger ones display more repair phenomena. Rabbit is also used for joint instability models (DiPasquale *et al*., 1988).

Chymopapain-induced cartilage degeneration in the rabbit

Intraarticular injection of chymopapain into the rabbit knee joint results in cartilage degradation with rapid loss of proteoglycans. Inflammation occurs shortly after chymopapain injection which normally subsides after 1-2 days. Reversibility and severity of the cartilage damage can be modified using different protocols. The damage can be modified to emphasize repair phenomena or to assure severe cartilage loss (Williams *et al*., 1993).

Other models include meniscotomy and ligament transection in guinea pigs, meniscotomy in rabbits and dogs. The above models have only limited proven track record of predictability in human disease presentation other than symptomatic relief (Bendale *et al*., 1999).

Methods for testing immunological factors involved in arthritis

There are many methods for testing specific aspects of immune function. Some of the *in vitro* methods are Inhibition of histamine release from mast cells, Mitogen-induced lymphocyte proliferation, Inhibition of T cell proliferation, Chemiluminescence in macrophages, and PFC (plaque forming colony) test *in vitro*.

In vivo methods for testing immunological factors include Adjuvant arthritis in rats and Collagen type II induced arthritis in rats described above under *in vivo* methods for RA. There are many other immune methods such as Acute systemic anaphylaxis in rats, Antianaphylactic activity, Passive cutaneous anaphylaxis, Arthus type immediate hypersensitivity, Delayed type hypersensitivity, Reversed passive Arthus reaction, Proteoglycan-induced progressive polyarthritis in mice, Experimental autoimmune thyroiditis, Coxsackievirus B3-induced myocarditis, Experimental allergic encephalomyelitis, Acute graft versus host disease in rats, Prevention of experimentally-induced myasthenia gravis in rats, Glomerulonephritis induced by abtibasement membrane antibody in rats, Autoimmune uveitis in rats, Inhibition of allogenic transplant rejection and Spontaneous autoimmune diseases in animals.

Development of polyherbal drugs and pure chemical entity combination drugs for arthritis

More than 110 plants are used in various polyherbal preparations to treat arthritis and related diseases in Ayurveda. Many of these plant drugs are not scientifically evaluated for their possible anti-inflammatory and/or anti-arthritic activities. Further, many traditional medicinal plants used to treat arthritis in local health traditions in remote villages and tribal pockets remain to be studied.

Although there are numerous studies on anti-inflammatory and/or arthritis traditional medicinal plants and isolated pure anti-inflammatory chemical entities, these studies do not suggest the use of any of them as such (extract or active fraction or isolated pure compound) as a satisfactory medicine to treat RA or OA. Most of the studies were not focused on possible drug development. Some of the traditionally used anti-arthritis plants may be potential as anti-inflammatory agents.

However, there are anti-arthritis medicinal plants such as *Boswellia serrata*, *Commiphora mukul*, *Withania somnifera*, *Curcuma longa*, *Tinosphora cordifolia*, *Zingiber officinale* and *Ncytanthes arbortristis* with not only anti-inflammatory activity but also with other beneficial pharmacological properties (Figures 1 to 7). Other important plants include *Aloe vera, Camellia sinensis* and *Cyperus rotundus* (Figures 8 to 10). These plant active fractions or principles are to be subjected to detailed investigations including mechanism of action studies. Mecchanism action studies are required, among other things, for their use in rational poly herbal formulation development.

Although there are many animal models to study arthritis, the antiarthritis meditational plants were evaluated, to a large extent, using adjuvant-induced arthritis in rats and, to some extent, formalin-induced arthritis in rats (Table 5 and 6); that too without measuring all relevant parameters. In most of the cases, anti-inflammatory activity of phytochemicals from medicinal plants was evaluated as seen from the literature (Table 6) using carrageenan induced paw edema in rats or mice. There is a need to use relevant methods for antiarthritis study, keeping in view with determination of efficacy and elucidation of mechanism of action of herbal drug candidates including isolated compounds. We have to use appropriate models to evaluate the suitability of candidate herbal drugs and phytochemicals to develop medicine for RA, OA and gout.

Although the animal models used may not have fuller relevance to various types of human RA and OA, potential plants have to be tested in different currently used models for efficacy and mechanism of actions because they shed a lot of light on their medicinal value.

In the case of RA, the under lying mechanism of the disease progression is mainly immune mediated, although the initiation of the disease is not clear. Inflammatory process has a major role in RA; other destructive components include synovial tissue proliferation, simultaneous degradation of cartilage proteoglygan and collagen and bone eroson. Therefore, the treatment approach should include drugs to counter the specific hyperimmune reactions occurring (particularly in the affected joints), prevention of the proliferation of synovial tissue, protection from cartilage destruction, protection from bone eroson, *etc*.

The main cause for OA is the failure of joint repair mechanisms in response to over load-induced joint injuries, particularly in the elderly people. In OA, inflammation is an intermittent event and proteoglygan degradation is an early event and collagen degradation occurs at a later stage.

In the case of gout, the reason for the accumulation of uric acid crystal has to be addressed and agents which counter this accumulation have to be found out. Plants may be screened for safe urate lowering activity.

Polyherbal formulation: Now, it is increasingly recognized that low doses of several active phytochemicals acting on multiple targets involved in a complex disease may prove better and safer compared to a high dose of a pure chemical entity drug acting on a major target. For example, combination with another therapeutic agent, soluble IL-1 receptor allows the reduction in dose of more toxic agents such as methotrexate while achieving superior efficacy than could be achieved with either agent alone (Bendele *et al*., 1999b).

Further, treatment with soluble TNF-α-receptor and IL-1 receptor antagonist in rat model of RA showed combination benefits (Bendele *et al*., 2000). There are several targets in arthritis. These include COX-2 inhibitors, TNF-α gene expression inhibitors, IL-1 receptor antagonists, inhibitors of autoantibody production, inhibition of oxidative stress, inhibitors of matrix mettaloproteinase, *etc*. Low doses of these agents in combination may provide remarkable relief to the patients, rather than a higher dose of a single agent. However, possible adverse interaction of phytochemicals have to be taken care of.

It is of interest to note that all green plants containing chlorophyll-a have anti-inflammatory activities. It has been discovered recently that chlorophyll-a and its degradation products have anti-inflammatory activity (Subramoniam *et al*., 2012). The anti-inflammatory mechanism of chlorophyll-a and its degradation products appears to be mainly due to its ability to inhibit the expression of mRNA for TNF-α, a powerful pro-inflammatory cytokine (Subramoniam *et al*., 2012). Since the bioavailability of chlorophyll-a, pheophytin-a (Mg free chlorophyll-a) and pheophorbide-a (chlorophyll-a without Mg and phytidyl side chain) is poor, they may be effective for topical application on the inflamed joints. Further, these plant drugs may be effective in the case of arthritic conditions where TNF-α level is high in the inflamed joint. It should be noted that TNF-α antagonists are newer therapeutic agents for RA. This can be included as an ingredient in the polyherbal formulation for specific beneficial effect.

Although *T. cordifolia* has immunostimulatory activity, it is of interest to note that the plant has antiarthritic activity. This could be mainly due the presence of phytosteroids which directly stimulate cartilage function and osteoclast function (see above under *T. cordifolia*). These compounds are idel in poly herbal medicine development to protect cartilage and bone.

A poly herbal formulation or a combination therapy could work well in the case of arthritis rather than a single drug. The formulation should contain at least one ingredient to suppress the underlying hyper immune reactions (including high levels of certain cytokines) in the case of RA in addition to a safe and effective anti-inflammatory agent and an analgesic agent. Agents which protect chondrocyte function and prevent cartilage degradation and bone eroson may be included. Matrix metallo protease (MMP) catalyzed cartilage degradation can be counteracted by MMP inhibitors. In the case of OA an agent which induces physiological vigor regarding joint function may be needed in addition to anti-inflammatory and analgesic agents. It is beneficial to include antioxidants; oxidative stress and free radical accumulation are seen in arthritic patients. Antihyperlipidemic extract or fraction is also required in the case of hyperlipidemic arthritic patients.

Table 7: Pharmacological actions required in the antiarthritic herbal formulation or combination medicine

Rheumatoid arthritis	Osteoarthritis
● Suppression of hyper immune reactions	● Joint repair mechanism enhancing activity
● Cartilage protection activity	● Cartilage and bone protection activity
● Anti-inflammatory activity	● Anti-inflammatory activity
● Inhibition of excess oseoclast activity and stimulation of osteoblast function	● Analgesic activity
● Analgesic activity	● Antioxidant activity
● Antioxidant activity	● Antihyperlipidemic activity
● Inhibition of cell proliferation (antineoplastic activity in the joint)	
● Antihyperlipidemic activity	

Plan of action in the development of antiarthritic medicine

In the development of plant based drugs for the treatment of arthritis what is required is a focused and detailed comparative study on all promising plants. Elucidation of the mechanisom of action of promising anti-arthritic plants, among other things, will facilitate the development of poly herbal formulations with the desired activities. Therefore, the study should include determination of mechanism of action of all promising plants using appropriate experimental models. The plan of action should be as follows.

a. i. Selection of promising traditional medicinal plants including those used in traditional systems of medicine such as Ayurveda and Siddha and local health traditions

ii. Selection of plants based on reported studies

b. Selection of a few best plants for each of the above mentioned pharmacological properties (Table 7). In some cases a single compound or extract is capable of interacting with many molecular targets involved in arthritis and will exert more than one activities indicated in Table 7.

c. Try to determine optimum dose based on animal experiments for each activity.

d. Preparation of rational combinations of agents with the above activities (Table 7) by mixing optimum dose of each ingredient and lower doses for efficacy evaluation in animal experiments. Each formulation with different ratios of the ingredients should be tested for efficacy in animal experimental models. The best formulations may be selected for safety (toxicity evaluation). Therapeutically promising formulations based on safety and efficacy evaluation in animal experiments should be carried forward for clinical trials.

Conclusion

In traditional medicine, in India, numerous plants are used as single drug or poly herbal formulations to treat arthritis and other inflammatory diseases. More than 60 plants were tested for their anti-inflammatory and/or anti-arethritis activities using animal experimental models, particularly adjuvant induced arthritis in rats. More than 50 isolated phytochemicals showed varying levels of anti-inflammatory activity in experimental animal models; carrageenan induced paw edema was used in most of these studies. Although a lot of studies were carriedout, the studies were not focused in the development of therapeutic agents against RA, OA and/or gout. Most of the studies are preliminary in nature. However, plants such as *Boswellia serrata*, *Commiphora mukul*, *Withania somnifera*, *Curcuma longa*, *Tinospora cordifolia*, *Zingiber officinale* and *Ncytanthes arbortristis* are promising for further studies leading to possible development of satisfactory medicine for arthritis. In the development of drugs for RA, AO, *etc* promising plants, based on etnomedical use and/or preliminary studies, have to be screened using appropriate animal models to select the best plants. Since arthritis is a complex disease, combination drugs acting on several targets relevant to the disease may prove very effective and safe, rather than high doses of a single compound acting on a crucial target. In the case of RA, hyper activity of macrophages, T cells, B cells, *etc* in the inflamed joint with concomitant elevation of cytokines such as IL-1 and TNF-α are occurring. Further, cartilage destruction, bone erosion, proliferation of cells in the synovium, *etc* are major pathological events. The medicine (poly herbal formulation or combination of phytochemicals or extracts) should contain chemical agents to counteract each of the pathological processes. Medicinal plants contain such activities. For example, *T. cordifolia*, a known immune stimulatory plant, contains compounds which stimulate cartilage and osteoblast

function. Ginger inhibits both cyclooxygenases and lipoxygenases. *B. serrata* inhibits lipopolysaccharide mediated TNF-α induction in monocytes. In the case of AO, stimulants of bone repair mechanisms may also be included. In the treatment of gout, along with symptomatic treatments, a safe uric acid lowering agent (and /or agent for the prevention of uric acid deposition) may be needed. Thus, in light of modern science, carefully prepared rational poly herbal formulations or combination drugs using medicinal plant resources could result in the development of satisfactory medicines to treat RA, OA and gout patients.

Conflict of interest

The authors declare no conflict of interest.

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