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Natural remedies for rheumatoid arthritis

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Abstract
Arthritis is a chronic disease and a major cause of disability in the world today. The pathology of the disease involves dysregulation of proinflammatory enzymes and cytokines and, Elevated levels of nitric oxide, prostaglandins and proliferation of synovial fibroblasts. There is an urgent need for alternative and effective therapies for arthritis as synthetic agents prove inadequate due to side effects and dose dependency. Traditional medicinal plants are practiced worldwide for treatment of arthritis especially in developing countries where resources are meager. This review presents the plants profiles inhabiting throughout the world regarding their traditional usage by various tribes/ethnic groups for treatment of arthritis.

Keywords: prostaglandins, rheumatoid, arthritis

Introduction
Immune system of our body plays a crucial role, as an overactive immune system may lead to certain fatal disease because of various hypersensitive or allergic reactions which may cause numerous derangements; loss of normal capacity to differentiate self from non self resulting in immune reactions against our own's cells and tissues called autoimmune diseases. Certain common autoimmune diseases like myasthenia gravis, serum sickness, pernicious anemia, reactive arthritis etc., are the severe issues for medical and pharmaceutical community because of unknown etiology [1]. According to WHO, 0.3-1% of the world population is affected from rheumatoid arthritis (RA) and among them females are three times more prone to the disease as compared to males [2]. RA is a chronic, inflammatory, and systemic autoimmune disease [3]. The primary symptoms of RA include pain, swelling, and destruction of cartilage and bone as a result of which permanent disability occur. Although the exact etiology is unknown but several hypotheses said that it is triggered by the combination of genetic predisposition and exposure to environmental factors like viruses [4]. The exact pathophysiology is still unknown but release of certain free radicals such as nitrous oxide and superoxide radicals generated as by-products of cellular metabolism. The release of such free radicals may induce the production of interleukins (IL) and tumor necrosis factor (TNF-α) from T-cells which ultimately influence the production of growth factors, cytokines and adhesive molecules on immune cells as such factors may cause tissue destruction and inflammation [5]. Pathological changes in RA are hyperplasia of synovial membrane, infiltration of inflammatory cells and neovascularization, which results into cartilage erosion and articular destruction [6].

The goal of treatment for rheumatoid arthitic patients is to eliminate symptoms, slow disease progression, and optimize quality-of-life [7]. Therefore, before starting the treatment of RA certain goals must be kept in mind such as relief of analgesia, reduction of inflammation, protection of articular structure, maintenance of function, and control of systemic involvement [5]. Presently for the treatment of RA, strategies have changed from traditionally used non-steroidal anti-inflammatory drugs (NSAIDs) or disease modifying antirheumatic drugs (DMARDs) to novel biological agents, like TNF monoclonal antibody. Clinically, the treatment of RA includes five strategies. The foremost approach is the use of NSAIDs followed by mild doses of glucocorticoids to minimize the signs of inflammation as well as progression of disease. In chronic patients, the use of DMARDs such as methotrexate, sulfasalazine, gold salts or D-pencillamine can be included in the treatment. In certain cases, TNF-α neutralizing agents like infliximab, etanercept etc; IL-1 neutralizing agents like anakinra and the drugs which interfere with T-cell activation such as abatacept can also be included in treatment of chronic cases. Finally, immunosuppressive and cytotoxic drugs such as cyclosporine, azathioprine, and cyclophosphamide are used for the treatment of chronic patients [5, 7, 8]. The above-mentioned therapeutic agents reduce the inflammation and joint destruction but their long-term risks are still unknown. However, long-term risks of drugs include gastrointestinal ulcers, cardiovascular complications, hematologic toxicity, nephrotoxicity, pulmonary toxicity, myelosuppression, hepatic fibrosis, stomatitis, cirrhosis, diarrhoea, immune reactions, and local injection-site reactions. Moreover, higher costs and side effects which include high risks of infections and melagnancies reguires continous monitoring [8].

Herbal remedies for the treatment of arthritis
Herbal medicines are used for the treatment of various ailments from ancient times and it is not an exaggeration to say that the use of the herbal drugs is as old as mankind [9]. Herbal medicines are synthesized from the therapeutic

experience of generation of practicing physicians of ancient system of medicine for more than hundreds of years [10]. Nowadays, researcher shows a great interest in those medicinal agents that are derived from plants because the currently available drugs are either have certain side effects or are highly expensive [11]. Nature has blessed us with enormous wealth of herbal plants which are widely distributed all over the world as a source of therapeutic agents for the prevention and cure of various diseases [12]. According to WHO, world's 80% population uses herbal medicines for their primary health care needs. Herbal medicines will act as parcels of human society to combat disease from the dawn of civilization [13]. The medicinally important parts of these herbal plants are chemical constituents that produce a desired physiological action on the body [14]. Since ancient time India uses herbal medicines in the officially alternative systems of health such as Ayurveda, Unani, Sidha, Homeopathy, and Naturopathy [15]. In India, there are more than 2500 plants species which are currently used as herbal medicaments. For than 3000 years, the herbal medicines are used either directly as folk medication or indirectly in the preparation of recent pharmaceuticals [16]. Thus, from the knowledge of traditional plants, one might be able to discover new effective and cheaper drugs [17]. In this review article, we have tried to cover all the ayurvedic strategies that are followed for the treatment of RA without any possible side effects. The future treatment of RA should provide more effective relief [5].

1. Indian nettle *Acalypha indica* Linn.

Acalypha indica methanol extract was evaluated using three different *in vitro* models to explore antiarthritic potential such as inhibition of protein denaturation, proteinase inhibitory action and antihyaluronidase activity. Diclofenac was used as the positive control. All *in vitro* determinations were done in triplicate. A dose dependent increase in percentage inhibition was observed for all the three models. The inhibitory concentration (IC50) was found to be 52 µg/ml for protein denaturation assay, 37 µg/ ml in proteinase inhibitory action and 18 µg/ml for antihyaluronidase activity. Diclofenac offered protective activity at even much lower concentrations compared to *A. indica* methanol extract producing IC50 values of 40 and 13 µg/ml for protein denaturation and proteinase inhibitory assays. *A. indica* exhibited a very good anti-arthritic activity in all the methods checked confirming its traditional use.

2. Neelkanth Violet *Asystasia dalzelliana*

Anti-arthritic activity of ethanolic extract of *Asystasia dalzelliana* leaves was evaluated by Freund's adjuvant induced arthritis model in rats. Paw edema, changes in organ weight, serum parameters such as SGOT, SGPT and ALP were estimated. Hind paw of experimental rats were also subjected for radiographic and histopathological examination for assessing the anti-arthritis potential of ethanolic extract of *A. dalzelliana* leaves. The results of the current investigation concluded that extract of dose of 800mg/kg possess a significant anti-arthritic activity than the lower doses of 200mg/kg and 400mg/kg. The observed anti-arthritis activity of extract may be due to the presence of phytoconstituents such as alkaloid and flavonoids. 14 *A. dalzelliana* for its possible anti-arthritic activity by HRBC membrane stabilization and inhibition of protein denaturation method was evaluated.

3. Alfalfa

Alfalfa is a plant with a long history of nutritional and medicinal use, including as treatment for arthritis. It has a range of medicinal properties, including anti-fungal, anti-microbial, and anti-inflammatory effects. Its medicinal use has been studied mainly in atherosclerosis, diabetes, and hyperlipidemia (high cholesterol), but it has also been used traditionally for centuries as a treatment for arthritis, disorders of the bladder or kidney, menstrual irregularities, and for upset stomach.

4. Alstonia scholaris Linn. (Family-Apocynaceae)

Milky juice is mixed with oil and was applied in rheumatic pains.The plant shows immune-stimulatory, hepatoprotective, anti-cancer, anti-plasmodial, and anti-hypertensive activities. Extract of AS possess an anti-diabetic, anti-hyperlipidemic, anti-bacterial, anti-inflammatory, analgesic, antioxidant, immunostimulant, anti-cancer, anti-asthmatic, hepatoprotective, and anti-anxiety activity. The ethanolic extract of AS leaves at doses of 100 and 200 mg/kg confirmed anti-arthritic activity in male wistar rats. The anti-arthritic activity was mainly by reducing the total leukocyte migration as well as lymphocytes and monocytes/macrophages migration. It can be concluded that AS shows an anti-arthritic activity on male wistar rats.

5. Worm killer or kid Amari

Aristolochia bractaeta Lam. Family-Aristolochiaceae

The studies of extract have shown anti-pyretic, anti-allergic, anti-inflammatory, anti-arthritic, anti-ulcer, anti-fungal, anti-microbial, antioxidant, wound healing [anti-implantation, and abortificient activities. The petroleum ether, methanol, and chloroform extract of whole plant of AB possess comparable anti-arthritic activity at doses of 100, 200, and 400 mg/kg body weight. AB revealed anti-arthritic activity by maintaining the synovial membrane and vascular permeability thus inhibiting cytokines and leukotriene infiltration. In conclusion, AB possesses an anti-arthritic effect on wistar albino rats of either sex [1].

6. Arnica

The active components in Arnica are sesquiterpene lactones, which are known for their anti-inflammatory and pain reduction properties. Arnica also contains thymol (an essential oil), flavonoids, inulin, carotenoids and tannins which stimulate blood circulation. Arnica works by stimulating the activity of white blood cells that perform much of the digestion of congested blood, and by dispersing trapped fluids from bruised tissue, joints and muscle. Arnica has also been shown to improve the health and conductivity of certain nerves.

7. Ashwagandha *Withania somnifera* Linn. solanaceae

Phytoconstituents: Alkaloids- withanine, withanine, pseudo-withanine, tropine, pseudo-tropine, somniferine, somnine lycosides- sitoindoside-7 and sitoindoside-8.Oral

administration of root powder showed the anti-arthritic effect in adjuvant induced arthritic rats. Related effects on cytokines and transcription factors, and suppression of nitric oxide has also been seen.

8. Banyan Tree *Ficus benghalensis* Linn. Moraceae

Phytoconstituents: α-L rhamnoside and leucocynidin 3-0-α-D galactosyl cellobioside, glucoside, beta glucoside, pentatriacontan-5-one, beta sitosterolalpha-D glucose19-20. Anti rheumatic activity of the methanolic extract of the bark of *Ficus bengalensis* (MFB) were studied using Freund's complete adjuvant induced arthritis model, the formalin induced arthritis model and the agar induced arthritis model. The extract produced marked inhibitory effect on edema especially on secondary immunological arthritis and caused graded inhibition of both phases of formalin- induced pain.

9. Orchid tree *Bauhinia variegata* L.

The anti-inflammatory activity of the leaf extract of *B. variegata*, using three *in vivo* animal models the carrageenan induced rat paw edema, cotton pellets induced granuloma formation, and adjuvant induced arthritis in rat was evaluated. Both the ethanol extract and the petroleum ether fraction obtained from this extract demonstrated activity in all the three bioassays. The activity was found to be more pronounced in the petroleum ether fraction. These bioactivities compared favorably with diclofenac sodium, which was used as positive control, and confirms the traditional usefulness of this plant for the treatment of both acute and chronic inflammatory conditions.

10. Raktapurna *Boerhaavia diffusa* Linn. (BD) (Family-Nyctagineae)

A paste made up of roots together with Colchicum, Solanum nigrum, Tamarind stone, Stag's horn and dried ginger, all in equal parts, are used in rheumatic and gouty painful joints. Root is used as powder in drachm doses or decoction or infusion for the treatment of inflammatory disorders like arthritis. Chakradatta used it in the treatment of chronic alcoholism and various other ailments i.e. phthisis, insominia, and rheumatism. The air-dried plant was found to contain large quantities of potassium nitrate and also contains an alkaloid, panarnavine, present in very small quantity of 0.01%.The petroleum ether extract of roots at dose 1000 mg/kg has been evaluated as anti-arthritic using CFA model and showed 81.5% response as compared to indomethacin.

11. Borage Borago officinalis

The seeds of the plant borage are a source of gamma-linolenic acid (GLA), which has been shown to inhibit the synthesis of certain immune system chemicals (leukotrienes). Seed oils are a source of GLA, and borage seed oil has one of the highest concentrations of GLA among various seed oils, including evening primrose and black current seed oils. Preliminary evidence indicates that GLA may have anti-inflammatory properties that make it beneficial in RA. However, more research is needed to determine the proper dosage of GLA, especially when taken in the form of an herbal supplement such as borage seed oil.

12. Bromelain

Bromelain is a digestive enzyme extracted from the stem and fruit of pineapple and other plants in the same family. It assists in digestion and has anti-inflammatory properties. There is some evidence showing that bromelain is as effective as the prescription NSAID diclofenac in relieving knee pain associated with osteoarthritis. There has been one small study of bromelain in patients with RA. In the study, bromelain resulted in reduced swelling in a majority of patients. Other evidence for the effectiveness of bromelain in RA comes from several case reports.Bromelain should be used with caution in patients with stomach ulcers, bleeding disorders, heart disease, or liver or kidney disease. It should be stopped at least 2 weeks before and after surgery or other procedures where there is increased risk for bleeding. Bromelain should be avoided by women who are pregnant or breastfeeding.

13. *Cinnamomum zeylanicum* L.

The efficacy of the polyphenol fraction from *Cinnamomum zeylanicum* bark (CPP) in animal models of inflammation and rheumatoid arthritis was evaluated. Dose-response studies of CPP (50, 100, and 200 mg/kg) used in a separate set of *in vivo* experiments were conducted in acute (carrageenan-induced rat paw edema), subacute (cotton pellet-induced granuloma), and subchronic (AIA, adjuvant-induced established polyarthrtis) models of inflammation in rats and the acetic acid-induced writhing model of pain in mice. CPP showed a strong and dose-dependent reduction in paw volume, weight loss reversal effects against carrageenan-induced paw edema, and cotton pellet-induced granuloma models in rats. CPP (200 mg/kg p.o. for 10 days) showed a significant reduction in elevated serum TNF-α concentration without causing gastric ulcerogenicity in the AIA model in rats. CPP also demonstrated mild analgesic effects during acute treatment as evidenced by the reduction in the writhing and paw withdrawal threshold of the inflamed rat paw during the acetic acid-induced writhing model and Randall-Selitto test. CPP was found to inhibit cytokine (IL-2, IL-4, and IFNγ) extracted from Cinnamon bark evaluated in animal models of inflammation and rheumatoid arthritis in rats. Carrageenan-induced rat paw edema (CPE) and adjuvant induced established arthritis (AIA), in rats were used as the experimental models for inflammation and arthritis respectively. Analgesic activity was evaluated in Randall–Selitto assay in AIA rats. TAPP showed significant anti-inflammatory effect at dose of 4, 8 and 25 mg/kg, p.o. but not at 2 mg/kg, p.o. dose in CPE model. The dose of 8 mg/kg, p.o. was selected for the evaluation of anti-arthritic activity in AIA model. TAPP (8 mg/kg, p.o., daily from day-12 today-21) treatment in established arthritic rats showed significant reversal of changes induced in AIA with respect to body weight drop (cachexia), ankle diameter, arthritic score, serum C-reactive protein (CRP) levels.

14. *Caesalpinia sappan* Linn. Family-Leguminosae

The heartwood of the CP is bitter, astringent, sweet, acrid, refrigerant, constipating, sedative, and hemostatic. In Yunani system, the decoction of wood was useful in rheumatism. CP is reported to have an anti-anaphylactic, anti-coagulant, anti-bacterial, anti-fungal, anti-inflammatory, anti-tumor anti-viral,

immunostimulant, and semen coagulating activities. CP also causes the inhibition of phosphodiesterase and stimulation of glutamate pyruvate transaminase and tyrosinase enzymes. The study concluded that CP possesses an anti-arthritic activity on rats.

15. *Cannabis sativum* Linn. Family-Urticaceae

Oil extracted from seeds is used in rheumatism. The chief chemical constituent is a resin volatile oil composed of canabene, canabene hydride, canabinon, and canabin; which consist of cannabinol, pseudo-cannabinol, cannabinin, and several terpenes. Around more than 166 research papers confirm that cannabis and related therapies will be helpful in relieving the pain associated with arthritis. Moreover, cannabinoid component of cannabis shown to possess anti-arthritic activity. It has been claimed to use as anxiolytic, antidepressant in schizophrenia and RA. The active moiety of CT i.e. cannabidiol at a dose of 10 and 25mg/kg, orally, administered in collagen-induced arthritic ratssignificantly decreases the arthritic score and inhibits the release of inflammatory mediators. Thus, it was concluded that the cannabidiol have an anti-arthritic activity by possessing anti-inflammatory and immunosuppressive action.

16. *Coriander sativum* Linn. Family-Umbelliferae

Oil is very useful for rheumatism in a dose of 1-4 minims on sugar or in emulsion. Coriander oil which contains linalool/coriandrol, geraniol, and boborneol, extracted from its fruit, is volatile and essential. Externally seeda can be used as a lotion or have been bruised and used as a poultice for the treatment of arthritis. Cineole, one of the 11 components of the essential oils, and linoleic acid, present in coriander, possess antirheumatic and anti-arthritic properties. CS possesses an antibacterial, anti-spasmodic, antioxidant, anticarcinogenic, and hypolipidemic activities. The hydroalcoholic extract of seeds at doses of 8, 16, and 32 mg/kg showed reduction in paw swelling induced by formaldehyde and CFA methods in male wistar rats by inhibiting the pro inflammatory cytokines and TNF-α. In conclusion, the extract of CS shows a potent anti-arthritic activity on rats.

17. Chamomile

The flowers of chamomile contain 1–2% volatile oils including alpha-bisabolol, alpha-bisabolol oxides A & B, and matricin (usually converted to chamazulene and other flavonoids which possess anti-inflammatory and antiphlogistic properties.A study in human volunteers demonstrated that chamomile flavonoids and essential oils penetrate below the skin surface into the deeper skin layers. This is important for their use as topical antiphlogistic (anti-inflammatory) agents. One of chamomile's anti-inflammatory activities involve the inhibition of LPS-induced prostaglandin E(2) release and attenuation of cyclooxygenase (COX-2) enzyme activity without affecting the constitutive form, COX-1. Iranian researchers divided 84 people suffering from osteoarthritis of the knee into groups that received three different treatments: chamomile (*Matricaria chamomilla*) oil, diclofenac (an anti-inflammatory drug typically used to treat arthritis) or placebo. They were instructed to apply the chamomile preparation to their knee and surrounding tissue three times a day for three weeks, and not to massage it into the affected area. They were also allowed to take acetaminophen as an analgesic if needed. Every week, the researchers assessed subjective levels of pain, physical function and stiffness. Analysis revealed that the chamomile oil significantly reduced the patients' need for acetaminophen compared to the diclofenac or placebo groups. In addition, the chamomile preparation showed some beneficial effects on pain, stiffness and physical activity in patients and no adverse effects were reported.

18. Cocoa

Inflammation occurs in the joints due to the damage associated with cartilage breakdown or from the immune system attacking the thin membrane that lines the joints, causing a buildup of fluid and inflammation. Symptoms vary from person to person but may include swelling, pain or a decreased range of motion in the affected joints. Depending on the type of arthritis, inflammation may not be limited to the joint itself. It can affect the body as a whole, which can lead to systemic side effects like fatigue and a decreased appetite. Cocoa influences the immune system, in particular the inflammatory innate response and the systemic and intestinal adaptive immune response. Preclinical studies have demonstrated that a cocoa-enriched diet modifies T cell functions that conduce to a modulation of the synthesis of systemic and gut antibodies. In this regard, it seems that a cocoa diet in rats produces changes in the lymphocyte composition of secondary lymphoid tissues and the cytokines secreted by T cells.

19. Dong quai Dong quai

(Also known as angelica, Chinese angelica, or female ginseng) Family Apiaceae, which includes parsley, celery, anise, caraway, and carrots. It has been used for thousands of years in China, Japan, and Korea. Medicinal uses of dong quai include menstruation pain, cardiovascular conditions, and inflammation. It has been used traditionally to treat arthritis. However, there is little data supporting its benefits in either osteoarthritis or RA.

20. Devil's Claw

Devil's claw is made from roots of the plant Harpagophytum procumbens, which grows in savannah and desert regions of Southern Africa. Devil's claw is mainly used as an anti-inflammatory and pain medication and there is a growing body of evidence suggesting that it is as effective as non-steroidal anti-inflammatory drugs (NSAIDs) (Advil, Motrin) for short-term relief of pain associated with osteoarthritis. However, many existing studies have been small and limited in design. It has not been studied in RA. Devil's claw should be used with caution in patients with stomach ulcers, bleeding disorders, diabetes, heart disease, a history of stroke, gout. It should be stopped at least 2 weeks before and after surgery or other procedures where there is increased risk for bleeding. Devil's claw should be avoided by women who are pregnant or breastfeeding.

21. Flax Seed

Flaxseed oil contains alpha-linolenic acid (ALA), an omega-3

essential fatty acid that's important for maintaining a joint's cell structure and function. ALA is made into two important compounds within your body – docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Both DHA and EPA play a significant role in making anti-inflammatory substances in your blood called prostaglandins. Flaxseed oil also contains some chemicals called lignans, which have antioxidant properties Flax seeds have natural anti-inflammatory benefits, which makes them beneficial for arthritis sufferers. The Omega-3 fatty acids found in flax seeds are used by the body to produce prostaglandins. These are hormone-like substances which help reduce inflammation.

22. Fenugreek

The anti-inflammatory and anti-arthritic activities of petroleum ether extract of fenugreek seeds. Fenugreek seed powder can be extracted in petroleum ether by cold maceration. This fenugreek seed petroleum ether extract (FSPEE) was tested on rats against carrageenan and formaldehyde-induced paw edema, complete Freund's adjuvant (CFA)-induced arthritis and cotton pellet-induced granuloma. Changes in serum glutamic oxaloacetic tansaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), and alkaline phosphatase (ALP) activities in liver and serum were also studied in cotton pellet-induced arthritic rats. Data were analyzed by Student's *t*-test. P <0.05 was considered statistically significant. GLC of FSPEE showed oleic (33.61%), linoleic (40.37%), and linolenic (12.51%) acids. With 0.5 mL/kg FSPEE treatment, there was 37% (P < 0.05) and 85% (P < 0.05) reduction in inflammation of the paw in carrageenan and formaldehyde-induced paw edema. In CFA-induced arthritis, a biphasic increase in paw volume followed by decrease was seen. There was 42.5% (P < 0.01) reduction in the weight of cotton pellets and significant (P < 0.01) reductions in the elevated SGPT and ALP activities in serum and liver of FSPEE (0.5 mL/kg) treated rats.

23. Garlic *Allium sativum* family liliaceae

Research in recent decades has shown widespread pharmacological effects of *A. sativum* and its organosulfur compounds especially Allicin. Studies carried out on the chemical composition of the plant show that the most important constituents of this plant are organosulfur compounds such as allicin, diallyl disulphide, S-allylcysteine, and diallyl trisulfide. Allicin represents one of the most studied among these naturally occurring compounds.

Turpentine induced arthritis: Albino rats of either sex weighing between 120-160 gms were used and divided into three groups of six each. One of the groups served as control and the other two groups served as the drug treated groups. The control group received 2% plain gum acacia suspension orally (without drugs) only, while the other two groups received piroxicam & Garlic powder respectively, in the dose of 100 mg/Kg body weight, in 2% of gumacacia suspension, by mouth; joint oedema was provoked by injection of 0.01 ml turpentine oil into the synovial cavity of the right knee joint one hour after the administration of gum acacia and drugs, in the control and drug treated groups respectively. Here the parameter for assessment is the lateral diameter of the knee joint and accordingly knee joint lateral diameter was measured by using screw gauge immediately after the injection of turpentine oil in to the knee joint cavity (Zero hour reading) and after six hours). Thus the mean increase in joint diameter in the control group was compared with that in the drug treated groups.

24. Ginger *Zingiber officinale* Family Zingiberaceae

Volatile oil, starch, fat, fibre, inorganic material, residual moisture. Ginger oil contains monoterpine, sesquiterpine hydrocarbons, oxygenated mono and sesquiterpines. They decrease inducible nitric oxide synthase (iNOS) and tumor necrosis factor alpha (TNF-α) expression through suppression of I-kappaB alpha (IkBα) phosphorylation, nuclear factor kappa B (NFk -B) nuclear translocation. A potent inhibitor of cyclooxigenase-2 expression and acts by blocking the activation of p38 mitogen-activated protein kinase (mapk) and NF- kB.

25. Ginkgo

The Ginkgo biloba extract, EGb 761, contains flavonoid glycosides and unique terpene lactones as major active components. In this study, we determined the anti-inflammatory effect of the water-soluble portion (GH415) of the EGb 761 on the inflammation caused by Candida albicans, a major ethiological agent that causes fungal arthritis. For inflammatory induction, an emulsified mixture of C. albicans cell wall and Complete Freund's Adjuvant (CACW/CFA) was injected into BALB/c mice by the hind footpad route once a day for 3 days. Twenty-four hours after the final injection, mice having the swollen footpad were given the GH415 (2 mg/dose) intraperitoneally to the mice once every 3 days for 15 days.Results showed that the GH415 treatment reduced the swelling. In the same animal model, this effect was enhanced by treatment with the GH415 entrapped within liposome (Lipo-GH: 200 micro/dose). Further analysis revealed that terpene, not flavone portion, was responsible for such therapeutic anti-inflammatory effect. Treatment with the terpene (7.4 microg/dose) by liposomal delivery method had similar effects as the treatment with indomethacin at 30 microg/dose. Addition of the terpene to lipopolysaccharide-treated macrophages showed suppression of nitric oxide (NO) production. These results suggest that blockage of the NO production from the macrophages that infiltrated to the inflamed site may be a possible mechanism for the therapeutic anti-inflammatory effect. Antioxidant activities of plant derived flavonoids are found to be beneficial in arthritis treatment. Research shows that kaempferol, hesperitin and naringin- flavonoids present in grapefruit inhibit the activity of inflammatory enzyme COX-2 and hence can aid in treatment of rheumatoid arthritis research shows that high doses of Vitamin C could be beneficial in reducing inflammation and oxidative damage in patients suffering from inflammatory diseases.

This proves that ascorbic acid does play a significant role in cartilage regeneration and swelling reduction in arthritis. Synovial fibroblasts are type of cells present in the lubricating fluid between the joints that in rheumatoid arthritis start secrete inflammatory substances and destroy bones and cartilage. Research shows that kaempferol inhibits the growth of synovial fibroblasts in rheumatoid arthritis, prevents them

from releasing inflammatory chemicals like prostaglandins, COX enzyme and this in turn inhibits degradation and inflammation of joints and bone tissue. Kaempferol can be a novel therapeutic agent in rheumatoid arthritis. Hesperidin is another flavonoid found in grapefruit. It can help in reducing inflammation and inflammation related pain. It possess antioxidant and anti-inflammatory activity that benefits in treatment of rheumatoid arthritis.

26. Guduchi *Tinospora cordifolia* Linn. Menispermacea.

Tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furanolactone tinosporidine, columbin and b-sitosterol. It is used in the treatment of rheumatoid arthritis. At the dose of 100 mg/kg it shows reduction of paw volume in collagen induced arthritic rats

27. Ginseng

Ginseng biologically active compounds found in the herb ginseng, have strong anti-inflammatory effects. The research demonstrates that ginsenosides can reduce inflammation in septic shock, rheumatoid arthritis, and dermatitis including psoriasis. In the laboratory, researchers have applied this knowledge by creating a new ginsenoside called G-Rp1. This ginsenoside, made from the ginsenosides G-Rg5 and G-Rk1 found in ginseng root, exhibits an even stronger anti-inflammatory effect than naturally occuring ginsenosides. Further, all of the aforementioned ginsenosides have important immunosuppressive effects in fighting autoimmune diseases

28. Jasmine *Ncytanthes arbortristis* Linn. Oleaceae

Phytoconstituents: mannitol, b-amyrin, b-sitosterol, benzoic acid and benjoic ester of longanin, nycthanic acid. Action: inhibited the acute inflammatory edema produced by different phlogistic agents, viz. carrageenin, formalin, histamine, 5-hydroxytryptamine and hyaluronidase in the hindpaw of rats. Acute and chronic phases of formaldehyde induced arthritis are significantly inhibited. Nyctanthes arbortristis Linn., also found to inhibit the inflammation produced by immunological methods, viz. Freund's adjuvant arthritis

29. Marigold

Calendula has a high content of flavonoids, chemicals that act as anti-oxidants in the body. Anti-oxidants are thought to protect body cells from damage caused by a chemical process called oxidation. Oxidation produces oxygen free radicals, natural chemicals that may suppress immune function. Calendula has been considered beneficial in reducing inflammation and promoting wound healing. It has been used to treat a variety of skin diseases and has been seen effective in treatment of skin ulcerations, eczema, juvenile acne and dry phthiriasis.

30. Spirulina

The study was carried out to evaluate the anti-inflammatory effect of Spirulina fusiformis on adjuvant-induced arthritis in mice. Arthritis was induced by intra dermal injection of complete freund's adjuvant (0.1 ml) into the right hind paw of Swiss albino mice. Spirulina fusiformis (800 mg/kg/b.wt) was orally administered for 8 d (from 11th to 18th day) to arthritic animals after adjuvant injection. The anti-inflammatory activity of Spirulina fusiformis was assessed by measuring paw volume, body weight, levels of lysosomal enzymes, tissue marker enzymes and glycoproteins in control and experimental animals. In adjuvant-induced arthritic animals, the levels of lysosomal enzymes, tissue marker enzymes, glycoproteins and the paw volume were increased significantly. However the body weight was found to be reduced when compared to control animals. Oral administration of Spirulina fusiformis (800 mg/kg/b.wt) significantly altered these above physical and biochemical changes observed in arthritic animals to near normal conditions. Hence results of this study clearly indicate that Spirulina fusiformis has promising anti-inflammatory activity against adjuvant-induced arthritic animals. Spirulina is a type of simple one-celled microscopic fresh-water blue green algae that grows naturally in warm climates and has been taken as supplement in human and animal food. Spirulina is known to have a diverse biological activity due to its high content of minerals, fatty and amino acids, vitamins and it also contains phenolic acids, tocopherols and beta-carotene that are known to exhibit antioxidant properties.

31. Willow bark *Salix Alba*

Evidence has shown that the active ingredient in willow, salicin, reduces the production of pain inducing chemicals in nerves; *Salix* species are credited as the natural source of aspirin.

Studies show inconclusive evidence of the benefits of this bark for RA patients. A slight reduction in pain was noted in two UK trials, but conclusive results as to the bark's efficacy have not been substantiated. As with aspirin, willow bark can interact with certain drugs, including anti-inflammatories and anticoagulants. Additionally, willow bark can lead to stomach upset and an allergic reaction.

32. Liquorice Family-Fabaceae

Roots in the form of infusion, decoction, extract or lozenge are useful as a demulcent in inflammatory affections. The clinical trials reveal that glycyrrhizin has favorable effects on RA, when administered along adrenocorticotropic hormone or cortisone, in comparison, when administered alone. In male wistar rats by inhibiting the leukocyte migration and auto antigens production and exhibit anti-protinase activity. The study concluded that GY possess a significant anti-arthritic activity.

33. *Lantana camara* Linn. Family-Verbinaceae

Traditionally, LC is used in the treatment of sores, chicken pox, measles, fever, cold, rheumatism, asthma, ulcers, and high blood pressure. In Asian countries like India, the decoction of leaves of the plant LC was used traditionally for the treatment of rheumatism. In Ghana, the infusions of whole plant are used against arthritis.

34. *Phyllanthus amarus* Schum and Thomm. Family-Euphorbiaceae

The aqueous extract of whole plant at a dose of 100, 200, and 400 mg/kg shows anti-arthritic activity in male wistar rats.

The extract at various doses reduced the levels of aspartate transaminase and alanine transaminase and thus maintains its anti-arthritic activity.

35. Pomegranate *Punica granatum* Linn. Family-Lythraceae

In Iranian Traditional Medicinal system, the seeds and juice are considered as a tonic for the treatment of rheumatism. Pomegranate fruit consumption reduced composite disease activity index in RA patients, and this effect could be related to the anti-oxidative property of pomegranates. Dietary supplementation with pomegranates may be a useful complementary strategy to attenuate clinical symptoms in RA patients. Some of the major chemical constituents present in the PG aregallic acid, anthocyanins, ellagitannins, flavones, flavonoids, antocyanidins, sterols, quercitin, rutin, and other fatty acids. The plant is of high value due to its anti-inflammatory, anti-carcinogenic, antioxidant, hypotensive, hypolipidaemic anti-artheroseclerotic, and anti-diabetic activities. The fruits of PG show an anti-arthritic activity at doses of 13.6-34 mg/kg by inhibiting the spectrum of signal transduction pathway in male wistar rats. Thus, it can be concluded that PG have potent anti-arthritic activity.

36. *Ruta graveolens* Linn. Family-Rutaceae

It is traditionally used as antiseptic, anthelminthic, antispasmodic, stimulant, abortificient, expectorant, and anti-rheumatic. The major chemical constituents isolated from the RG are rutin, quercitin, rutacridone, rutacridone epoxide, graveoline, and gravacridonodiol. RG is reported to have anti-inflammatory, analgesics, antiandrogenic, antihyperglycemic, antihyperlipidemic, anticancer activity, and anti-rheumatic properties. The polyphenolic fraction of aerial parts of RG at a dose of 10 mg/kg, b.w. showed an anti-arthritic activity in male wistar rats induced by CFA model. The polyphenolic fraction revealed its activity by inhibiting the prostaglandins synthesis, decreasing CRP level, ceruloplasmin, lipid peroxidation and release of other inflammatory mediators. In conclusion, RG possess anti-arthritic activity.

37. *Saussurea lappa* Clarke. Family-Compositae

Roots in the form of infusion with little cardamoms are used in chronic rheumatism. The ethanolic extract of SL at dose levels of 50-400 mg/kg showed potent anti-arthritic activity. A sesquiterpene lactone "cynaropicrin" isolated from SL strongly inhibited TNF-α release from lipopolysaccharide (LPS) - stimulated murine macrophage cell line and dose-dependently suppressed the proliferation of lymphocytes stimulated. Another sesquiterpene lactone "dehydrocostus lactone" from SL suppressed LPS-induced nitric oxide production. The investigation concluded that the SL shows a significant anti-inflammatory and anti-arthritic activity.

38. *Sida rhombifolia* Linn. Family-Malvaceae

The reported activities of plant include cytotoxic, antimicrobial, antibacterial, anti-inflammatory, antipyretic and anti-arthritic. The aqueous and ethanol extract of aerial parts of the SR at doses 30 and 100 mg/kg reduced the paw edema induced by CFA method. Thus, it is concluded that the plant possess a potent anti-arthritic activity.

39. Sarsapareilla

A vine plant sarsapareilla has been used in Chinese medicine for centuries as a treatment for various inflammatory conditions. It has anti-bacterial, anti-inflammatory, and antioxidant properties. There have been no studies of the use of sarsapareilla as a treatment for RA. However, there is a theoretical basis for the use of the plant in arthritis. Sarsapareilla contains a flavanoid called astibin which has been shown to suppress lymphocyte functions in animals with possible benefits in some forms of arthritis.

40. *Terminalia chebula* Retz. Family-Combrataceae

It is reported to have an immunomodulatory, radioprotective, cytoprotective, cardioprotective, and hepatoprotective activity. Moreover, the hydroalcoholic extract of TC produces a significant inhibition of joint swelling in formaldehyde induced arthritis and CFA induced arthritis models. The anti-arthritic potential of the extract was due to significant reduction in the levels of TNF-α, IL-6, and IL-1β.

41. Burdock datura *Xanthium strumarium* Linn. Family-Compositae

Oral doses (200 and 400 mg/kg) ofethanolic extract of XS when administered exhibited anti-arthritic activity by inhibiting the release of inflammatory mediators.

42. Evening primrose oil

Evening primrose is a yellow-flowered plant that produces seeds from which a medicinal oil is made. Several small clinical trials of evening primrose oil have been conducted in patients with RA. While some of these trials have reported benefits, including patient-reported improvement in symptoms and decreased NSAID use, findings from these studies have been inconsistent and there is currently insufficient evidence to make definitive conclusions concerning the benefits of evening primrose oil in RA. Evening primrose oil should be avoided by patients with seizure disorders and used cautiously in patients who are receiving drugs to treat psychiatric illness. It should be stopped 2 weeks before surgery and should not be used by women who are pregnant or nursing.

Conclusion

Since Neanderthal times, the plants had been used for the prevention and cure of various ailments such as RA and other inflammatory diseases. Natural sources such as plants have been considered as the safest and valuable treatment for the disease. From the ethno botanical knowledge, we included the plants that are used in Indian traditional systems such as herbalism, folklore and shamanism.

For the treatment of RA, various parts of plants are used such as leaves, roots, fruits, rhizomes, and seeds in distinguished dosage forms like extract, decoction, juice, infusion, paste, oil etc. The most potent anti-arthritic plants such as Aconitum ferox, Balsamodendron mukul, BD, Boswellia serrata, CS, CL, PL, Ricinus communis, Plumbago zeylanica, SL, SR, and Strychnos nux vomica have been elaborated in the review article. Among these listed plants, certain plants have been used in acute attack or in chronic pain or chronic rheumatism. Traditional medicines used for the treatment of arthritis are used in various tribal/rural cultures worldwide. At present,

investigation of anti-arthritic activity of traditional medicine has led to the development and studies of many herbal remedies employed for such purpose. The information that has been gathered from various sources is helpful in preserving folk indigenous knowledge as well as discovery of potential compounds having promising anti-arthritic activity. In conclusion, about 485 plant species mentioned in the list would have a promising anti-arthritic activity in humans.

The collection of plants in this review will be a remarkable tool for the researcher who involve in research in this area. The persons, seeking a better treatment for rheumatoid arthritis will also benefitted by this fruitful article. In this review, we mainly deal with the safety profile, mechanism of action, and toxicity studies of plant extracts. The plant extracts and polyherbal formulations would be served as an alternate therapy for the treatment of arthritis with lesser side effects. Moreover, current knowledge can be helpful in materializing the commercial products, where the evidence can be quite limited can further research may pave a way for effective alternative therapy.

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