Review Article

Herbal medicines and formulation approaches for the treatment of arthritis

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ABSTRACT

Current treatment of different types of arthritis such as osteoarthritis, rheumatoid arthritis, septic arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis involves the administration of nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatoid drugs, corticosteroids, and biological agents mainly by the oral, parenteral, or topical route. However, the frequent dosing and their side effects required often leads the patients to switch over to herbal medicines. Traditionally used herbal medicines, due to their anti-inflammatory and immunomodulatory properties, have potential to be a therapy of choice for arthritis patients and are now extensively being studied. However, only very few dosage forms of the effective plant sources are available in the market. The major category of formulations available in market is the oils. Hence, the research can be focused on various effective formulations with oral and external dosage forms. This review focused on the plant sources popularly used for the treatment of arthritis but still not available as an effective formulation. This review gives us an idea to direct the research toward the various formulations which will enhance the technologies. Furthermore, formulating the herbal actives into novel technologies such as liposomes, phytosomes, and transdermal drug delivery would be a potential area.

KEY WORDS: Arthritis, Formulations, Herbal, Inflammation, Nonsteroidal anti-inflammatory drugs

INTRODUCTION

Arthritis is a musculoskeletal system disorder following mechanical and biological events that destabilize normal coupling between degradation and synthesis within articular cartilage.[1] The most common form of arthritis is osteoarthritis (OA) while its other common rheumatic conditions are gout, fibromyalgia, and rheumatoid arthritis (RA).[2] Some forms of arthritis such as RA and lupus can infect multiple organs and cause widespread symptoms. Arthritis exhibits infection of the joint with age and causes severe pain or a trauma of the joint. Other arthritis forms are psoriatic arthritis, RA, and related autoimmune diseases. Septic arthritis is caused by joint infection. The symptoms can spread moderately or immediately.

Arthritis is commonly found in adults aged 65 years or older, but people of all ages' even children can be affected from severe joint pain. RA can affect people of all ages and disease may occur at any age, it usually begins after age 40.[3-5] It is the most common form of arthritis that affects both the largest and the smaller joints of the body including the hands, wrists, feet, back, hip, and knee.[6] Typically, this disease affects the weight-bearing joints such as the back spine and pelvis. The main risk factors for OA include prior joint trauma, obesity, and a sedentary lifestyle. It occurs as a result of injury. The disorder is much more common in women and more often affects joints in the fingers, wrists, knees, and elbows.

The disease is symmetrical and appears on both sides of the body. It leads to severe deformity if the treatment is not done. In children, the disorder appears due to genetic reasons and prevails skin rash, fever, pain, and disability in limbs and knee joints that limits the daily activities.[2]

CAUSES OF DISEASE

Due to changing mobility pressure and lifestyle, there will be a rapid increase in number of arthritis cases by year 2030 more than 25% of world population will be affected by any form of arthritis. Age, gender, and

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certain genes are among non-modifiable factors which are responsible for arthritis. Age is an important risk factor as the risk of developing most types of arthritis increases with age. Arthritis is mostly seen in women. Risk factors include overweight and obesity. Excess of weight is risky for progression of knee OA; it is also responsible for joint injuries. Many microbial agents can infect joints and potentially cause the development of various forms of arthritis. It is another severe form of arthritis that starts with sudden onset of chills, fever, and joint pain. The condition is caused by bacteria elsewhere in the body. Infectious arthritis must be rapidly diagnosed and treated promptly to prevent irreversible joint damage.[7-9]

Arthritis patients also show other comorbidities such as respiratory diseases, heart diseases, stroke, and diabetes. Important risk factors are included high blood pressure, physical laxity or inactivity, high cholesterol, obesity, and smoking. Gout is also pain-related disease that is caused by deposition of uric acid crystals in the joint with severe inflammation. In the early stages, the gouty arthritis usually occurs in one joint, but with time, it can occur in many joints and be quite crippling. The joints in gout can often become swollen and lose function. Gouty arthritis can become particularly painful and potentially debilitating when gout cannot successfully be treated. When uric acid levels and gout symptoms cannot be controlled with standard gout medicines that decrease the production of uric acid (e.g., allopurinol and febuxostat) or increase uric acid elimination from the body through the kidneys (e.g., probenecid), this can be referred to as refractory chronic gout or RCG.

RA, induced by the prolonged inappropriate inflammatory responses, is one of the most prevalent of all chronic inflammatory joint diseases. Bone erosion is a central feature of RA. It begins in the joints with the inflammation of the synovium. It is caused in part by the production of pro-inflammatory cytokines and receptor activator of nuclear factor kappa B (NFκB) ligand (RANKL), a cell surface protein presents in Th17 cells and osteoblasts. The "rheumatoid factor" is an antibody that can be found in the blood of 80% of people with RA. Osteoclast activity can be directly induced by osteoblasts through the RANK/RANKL mechanism. This adaptive immune response is initiated in part by CD4+T helper (Th) cells, specifically Th17 cells. Th17 cells are present in higher quantities at the site of bone destruction in joints and produce inflammatory cytokines associated with inflammation such as interleukin-17 (IL-17). Due to the production of inflammatory cytokines, local activation of NFκB and the subsequent expression of NFκB-regulated genes mediate joint inflammation and destruction. Bone continuously undergoes remodeling by actions of bone-resorbing osteoclasts and bone-forming osteoblasts. There is no cure available for RA. However, rest and slow but continuous exercise provide relief in joint pain. However, regular medications and surgery be needed at later stage. Oxygen-derived free radicals are known to play an important role in the etiology of tissue injury in RA.[10-12]

DRUGS USED IN TREATMENT OF ARTHRITIS

The goals of currently used antirheumatic drugs are to reduce pain and swelling, delay the progression of disease, minimize the disability, and ultimately improving patient life and expectancy. Most of these objectives are achieved by combination of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs, corticosteroids, and biological agents. In addition to conventional therapies, some unconventional therapies such as superoxide dismutase, antisense oligonucleotide, boron neutron capture therapy, and radioisotopes have been explored for the management of arthritis.[13] NSAIDs are medications that reduce inflammation and relieve pain. They can relive joint pain and reduce swelling. Commonly used NSAIDs for the treatment of RA include diclofenac, ibuprofen, and naproxen. Celecoxib and etoricoxib are two other relatively common NSAIDs. The different NSAIDs are basically equally effective, but their effect will vary from person to person.

NSAIDs can cause stomach ulcers when used over a long period of time. Stomach ulcers are usually felt as a pain in the upper abdomen. The pain is particularly noticeable just after eating when the stomach produces more acid. Stomach ulcers or bleeding occurs in about 1–2 out of 100 people who take NSAIDs over a period of 1 year. People are at higher risk if they are over 65 years old, already had a stomach ulcer in the past, taking certain antidepressant medication (a selective serotonin reuptake inhibitor), and taking steroids also taking several NSAIDs at the same time, for example, if they also take acetylsalicylic acid (the drug in medicines like aspirin) for the prevention of cardiovascular disease. With the exception of acetylsalicylic acid, NSAIDs can also increase the risk of cardiovascular diseases such as heart attacks. Naproxen has the lowest risk of all of the NSAIDs, so it is recommended for people who have cardiovascular disease in addition to RA. NSAIDs can sometimes be a problem for people who have kidney disease too.[14]

Steroid injections are one of the most effective ways to decrease pain and improve function, yet they generally do not cure the illness. In rare instances, the following side effects might occur: Infection, allergic reactions, bleeding into the joint, rupture of a tendon, skin discoloration, weakening of bone, ligaments, and

tendons (from frequent, repeated injections into the same area). Not everyone will develop side effects and side effects vary from person to person. If steroid injections are infrequent (less than every 3–4 months), it is possible that none of the listed side effects will occur.[15-18]

Steroids on oral treatment side effects are more common with a higher dose and longer treatment. Side effects are much more common with oral drugs. Some side effects are more serious than others. Common side effects of oral steroids include acne, blurred vision, cataracts or glaucoma, easy bruising, difficulty sleeping, high blood pressure, increased appetite, weight gain, increased growth of body hair, insomnia, lower resistance to infection, muscle weakness, nervousness, restlessness, osteoporosis, stomach irritation or bleeding, sudden mood swings, swollen, puffy face, water retention, swelling, and worsening of diabetes may happen. Allopathy focuses only on ailments and organs and not on the person as a whole. Furthermore, it revolves around only curing a given ailment and completely ignores the much broader aspect of individual health.[19-21]

IMPORTANCE OF USING HERBAL DRUGS IN ARTHRITIS

The worsening condition of arthritis requires proper therapy for arthritis along with better economical consideration for chronic treatment. As synthetic molecules have not been proven to provide adequate therapy due to toxicity, side effects, or reappearing of symptoms on discontinuation, there is urgent need to have alternative options for arthritis.[22] Research has indicated that people suffering from chronic pain and those dissatisfied with current treatment are very likely to seek alternative treatments, and an estimated 60–90% of persons with arthritis use complimentary alternative medicine (CAM). Among the various CAM in the last few years, there has been an exponential growth in the field of herbal medicine, and these drugs are gaining popularity in both developing and developed countries because of their natural origin, reduced risk of side effects, effective with chronic conditions, lower cost, and widespread availability [Table 1]. It may eventually lead to the development of a new class of anti-inflammatory agents for the treatment of arthritis and also many herbal products are already available in the market in the form of tablets, capsules, oils, lotions, and liniments.

This review article presents an overview of the various herbal plants used in the treatment of arthritis and their benefits. Furthermore, the various herbal formulations effectively used for the treatment of severe joint pain and inflammation.[22,23]

Curcuma Longa

It belongs to a family Zingiberaceae commonly known as curcumin and possesses various biological activities such as anti-inflammatory, hepatoprotective, antibacterial, antidiabetic, antidepressant, analgesic, and anticarcinogenic. The anti-inflammatory action of curcumin is attributed to inhibition of lipoxygenase LOX, suppression of activation of NF-β, tumor necrosis factor-alpha (TNF-α), molecular adhesion, and inhibition of upregulation of matrix metalloproteinase (MMP-9) mRNA. It also promotes suppression of expression of TNF-α-induced MMP-13 in chondrocytes.[24] Various *in vivo* and *in vitro* studies have been carried out to explore the antiarthritic potential of curcumin. *In vivo* evaluation of curcuminoid was found to reduce both acute and chronic inflammation by 75% and 68%, respectively.[25] Oral administration of curcumin provides symptomatic relief in exercise-induced muscle damage due to its anti-inflammatory property.

M. Akram and his team evaluated that animal studies in rats with Freund's adjuvant-induced arthritis, oral administration of *C. longa* significantly reduced inflammatory swelling compared to controls.[26]

Withania Somnifera

It is commonly known as Ashwagandha and is reported to have analgesic, anti-inflammatory, antibacterial, immunomodulatory, anticancer, diuretic, antiulcer, antidiabetic, and antiarthritic properties. The *in vivo* antiarthritic potential of aqueous extract of *W. somnifera* roots was evaluated in rats and was found to reduce anticyclic citrullinated peptide antibody, collagen type II antibody (a-CII), and inflammatory marker such as C-reactive protein, lipid peroxidation, and glutathione-S-transferase activity with anolides also inhibit NF-κB and NF-κB-regulated gene expression. The clinical evaluation of *W. somnifera* extract at two different doses (250 mg and 125 mg) has been found to reduce inflammation significantly in dose-dependent manner and was devoid of any side effects.[27]

Boswellia Serrata

It belongs to the family Burseraceae, pentacyclic terpenes are found in plants in the forms of various derivatives such as acetyl-11-keto-BA and 11-keto-BA. Therapeutically, BA and its derivatives are used in various ailments such as ulcerative colitis, cancer, hepatitis, inflammation, pain, cough, bacterial infection, and OA. In preclinical evaluation, BA was reported to reduce cartilage loss, synovitis, and osteophyte formation and, hence, has beneficial role in OA and other joint disorders. Clinical investigation of *B. serrate* extract was found to provide statistically significant improvement in patients suffering OA and was well tolerated with minor gastric disturbance.[28]

Table 1: Formulation of herbal drugs available in market for treating arthritis[46]]

Product name	Plant source	Manufacturer	Dosage form
Mahanarayana thailam	Abutilon indicum Premna corymbose Paederiafoetida	Ayusearch drugs and laboratories	Oil
Arthrella	Indian senna Boswellia serrata Vitex negundo Oroxylum indicum Cyperus rotundus	Charak Pharma	Tablets
Orthovita oil	Cinnamomum camphora Gaultheria fragrantissima	Planet Ayurveda	Oil
Cart fit	Allium sativum Boswellia serrata Boerhaavia diffusa Zingiber officinale Commiphora mukul	Streamline Pharma Pvt. Ltd	Oil
Pinda Thailam	Sesamum indicum Rubia cordifolia Vateria indica Honey bee wax Hemidesmus indicus	Global Ayucare	Oil
Joint care capsule	Borhavia diffusa Ptychotis ajowan Trigonella foenum graceum Smilax glabra Boswellia serrata Winthania somnifera Zingiber officianlis Commiphora wightii	Amulya Herbs Pvt. Ltd	Capsule
Rumaxel	Sesamum indicum Eucalyptus globulus	Trio Healthcare Pvt. Ltd	Oil
Pain niwaran churna	Terminalia chebula Holarrhena antidysenterica Curcuma longa Sphatika bhasma	Rajasthan Aushadhalaya Private Limited	Oil
Ezofen	Linum usitatissimum	Estrellas Life Sciences Pvt. Ltd	Oil
Pain well plus	Strychnos nux-vomica Crocus sativus Syzygium aromaticum Sesamum indicum	Indian Herbo Pharma	Oil
Muscle and joint rub	Ricinus communis	Himalaya	Cream
Arthronil	Aconitum ferox Piper nigrum Colchicum luteum Operculina turpethum	Nirogam Pvt. Ltd	Capsule
Flexi joint	Salix alba	Vee Excel Drugs And Pharmaceuticals Private Limited	Oil
Rheumartho gold	Commiphora wightii Strychnos nux-vomica	Global Ayucare	Capsule
Balcodol	Mustard oil Datura stramonium Peppermint Curculigo orchioides	Alna Care	Oil
Vat Mantra	Linseed oil Camphor oil Peppermint oil Cheed oil	Tansukh Herbals Pvt. Ltd	Oil
Mafrince	Strychnos nux-vomica Aconitum ferox Litsea glutinosa	Success pharmaceuticals	Oil
Pain away cream	Rosemary oil Lavender oil Eucalyptus oil Emu oil	Divyanjay herbal enterprises	Cream

(Contd...)

Table 1: ***(Continued)***

Product name	Plant source	Manufacturer	Dosage form
Myaxyl oil	Tabernaemontana divaricata Cedrus deodara Alpinia galangal	Kerala Ayurveda	Oil
Rheuma off oil	Thymus vulgaris Pinus roxburghii oil	Virgo UAP Pharma Pvt. Ltd.	Oil
Rumacure	Gaultheria fragrantissima	Dharmani's international	Capsule
Zeotone	Commiphora mukul Hordeum vulgare	Nirogam Pvt. Ltd	Soft gel capsule
Rumogin 5	Boswellia serrata Piper longum	Planet Ayurveda	Capsule
Rhumasyl gel	Maha mash taila	Zandu Ayurveda	Gel
Peedantak kwath	Argyreia speciosa Cassia fistula	Divya pharmacy	Powder
Aamvatantak churna	Withania somniferum Colchicum luteum	Planet Ayurveda	Powder
Mardana gel	Ricinus communis	Vasishta Pharmaceuticals	Gel
Ortho veda	Piper longum Ricinus communis	LA nutraceuticals	Oil/capsule
Arth-9	Curcuma longa Gum Resin	Rx vitamins	Capsule
Valeria	Zingiber officianlis Curcuma longa	Ayusya naturals	Capsule

The antiarthritic activity of BA is due to inhibition of NF-κB, COX-2, and LOX-5.

Aman Upaganlawar and his team studied on mycobacterium adjuvant-induced polyarthritic in rats, Salai guggal showed 34% and 49% inhibition of paw swelling with 50 and 100 mg per kg −1 (p.o.) doses, respectively, as compared to controls.[29]

Cinnamomum Zeylanicum

It belongs to a family (Lauraceae), a polyphenol derivative has been explored in various pharmacological conditions such as atherosclerosis, diabetes, fungal infection, inflammation, Alzheimer disease, and arthritis. Type-A procyanidine polyphenols are reported to have immunomodulatory and anti-inflammatory potential without analgesic activity in both *in vitro* and *in vivo* studies. In another study, *C. zeylanicum* extract was found to reduce inflammation and arthritis in rats by suppressing intracellular release of TNF-α in dose-dependent manner and, hence, is an effective remedy for treating RA.[30]

Pasupuleti Visweswara Rao and his team studied that ethanolic extract of *C. zeylanicum* showed significant anti-inflammatory effects by reducing the activation of Src/spleen tyrosine kinase (Src/Syk)-mediated NF-λB.

Achyranthes Aspera

A. aspera belongs to the family Amaranthaceae, it is an annual stiff erect herb and found commonly as a weed throughout India. *A. aspera* is commonly called in Tamil as Nayuruvi and in Hindi as Circita. The whole plant is traditionally used as diuretic, expectorant, and anthelmintic. It is a useful remedy for asthma, bronchitis, cardiac disorders, anemia, leprosy, skin diseases, and also for inflammations. The plant juice and ash are used for treating bleeding piles. An alkaline powder of the plant is used in preparing kshar sutra of Ayurvedic medicine, which is recommended for treating fistula-in-ano. *A. aspera* is reported to possess antimicrobial, diuretic, antilithiatic, anxiolytic, anti-inflammatory, hepatoprotective, antidiabetic, and antioxidant. The whole plant contains alkaloids achyrathine and betaine. Achyranthes shows spasmodic effects on the rectus muscle of frog, diuretic, and purgative action in albino rats. A study revealed a significant potential of *A. aspera* in slowing down the arthritic progression and reversing the pathological changes resulting from arthritic development.[31]

The ethanolic extract of *A. aspera* was investigated for its anti-inflammatory activity using protein inhibition assay method. The seven concentrations of the extract and diclofenac sodium were used in this study as standard drug. The extract at the dose of 800 µg and 1000 µg/ml showed potent action on comparison with the standard diclofenac sodium. The results of the present study empirically indicated that *A. aspera* was effective in the treatment of RA and that can support the common belief prevailing international medicines worldwide.

Abhijit dey reported that ethanolic plant extract has shown antiarthritic activity.[32]

Girardinia Diversifolia

G. diversifolia, commonly known as the Himalayan nettle or Nilgiri nettle, is found abundantly in open forest land and riversides. It grows naturally at

elevations between 1200 and 3000 m (3900–9800 feet). It is a shade tolerant, tall, stout, and erect herb growing up to 3 m height with perennial rootstock. The plant grows as a clump, and each clump has many stem. The stem contains bast fiber of unique quality which is strong, smooth, and light. It is also known as Himalayan "Giant" stinging nettle (*G. diversifolia*), also known as Allo or bichu buti is a perennial plant which grows wild throughout the moist mountainous regions of Nepal and India. Himalayan nettle is possibly best known as a source of strong, lightweight, and sustainable natural fibers. However, this herb's benefits encompass the entire plant from roots to crown and everything in between! Nettle has traditionally been used as a natural diuretic and laxative. It can help to soothe nausea and eliminate internal parasites. Nettle has a positive effect on the pancreas, helping to prevent diabetes by balancing blood sugar, and it assists in regulating blood iron levels. It can be used to ease a headache and to relieve joint pain such as that caused by arthritis. It is known to improve urinary tract health and prevent gout flare-ups by cleansing uric acid from the joints, as well as for promoting respiratory health, bolstering the immune system by stimulating the lymph and endocrine systems.[33]

Anemone Vulgaris

It belongs to Ranunculaceae *A. vulgaris* also known as "windflower" growing along the water channels and grasslands, plants of 20–100 cm in height, silky pubescent herbs with basal leaves with rounded blade of 7–15 cm, deeply 3-lobed, shallowly toothed, flower 1.3–3 cm, white. The whole plant is dried and made powder which is taken orally to cure asthma. However, scientific evidence of using this plant for arthritis was not obtained.[34]

Gaultheria Fragrantissima

The genus Gaultheria (Ericaceae) comprises about 200 species, and *G. fragrantissima* is a bushy evergreen shrub of higher elevation, growing in shaded woodland and margin of forests. The plant grows in sandy (light), loamy (light), and acidic soils. This aromatic plant has long been valued for its wintergreen oil. The bruised leaves have powerful camphor-like smell. The essential oil rich in methyl salicylate is extracted by distillation of leaves. The oil has high demand in pharmaceutical and perfumery industries.[35,36]

The plant has been used as an antiseptic, carminative, flavoring agent and condiment and also in rheumatic and arthritis treatments. Methyl salicylate is a natural precursor of pharmaceutical aspirin. It is also an active ingredient to treat various kinds of external pains.

Toddalia asiatica

T. *asiatica* (Rutaceae), also known as Wild Orange tree, is a green leafy climber growing in the evergreen forests and is vastly distributed in the tropical regions of Africa, India, and Madagascar. It contains coumarins, quinoline, and benzophenanthridine alkaloids. The alkaloids of the crude extract have been shown to have anti-inflammatory effects in rats using the carrageenan test and to inhibit the auricle swelling caused by xylol and joint swelling caused by agar in rats. It has also been shown to have antimalarial and antileukemic properties. The central and peripheral antinociceptive effects of T. *asiatica* have been demonstrated using mice. Roots as well the leaves are used in parts of East Africa for the management of neuropathic and inflammatory pain. Roots have been shown to be potent in antinociception than leaves. Most of the folkloric uses of the genus T. *asiatica* evolve around pain, inflammation, and microbial infections. T. *asiatica* (L.) Lam. has been utilized traditionally for medicinal purposes such as the treatment of rheumatism. Currently, the extract is considered to be a good source of pharmacological agents for the treatment of bone-related diseases, but the active compounds have yet to be identified.[37]

Akio Watanabe and his team have investigated that whether toddaculin, derived from T. *asiatica* (L.) Lam., affects both processed by inhibiting bone resorption and enhancing bone formation. Thus, toddaculin is beneficial for the prevention and treatment of osteoporosis.[38]

Artocarpus Heterophyllus

A. heterophyllus belonging to family Moraceae is an integral part of common Indian diet and is freely available in Indian and adjoining continents, its medicinal properties are also mentioned in Ayurveda. The plant is reported to possess antibacterial, anti-inflammatory, antidiabetic, antioxidant, and immunomodulatory properties. *A. heterophyllus* is an important source of compounds such as morin, dihydromorin, cynomacurin, artocarpin, isoartocarpin, cyloartocarpin, artocarpesin, oxydihydroartocarpesin, artocarpetin, norartocarpetin, cycloartinone, betulinic acid, artocarpanone, and heterophylol which are useful in fever, boils, wounds, skin diseases, convulsions, diuretic, constipation, ophthalmic disorders, and snake bite.[39]

Om Prakash and his team studied that *in vitro* anti-inflammatory effects of phenolic compounds isolated from the ethyl acetate extracts of the fruits of *A. heterophyllus*. Three phenolic compounds were characterized as artocarpesin (5,7,2',4'-tetrahydroxy-6-β-methylbut-3-enyl) flavone) (1), norartocarpetin (5,7,2',4'-tetrahydroxyflavone) (2), and oxyresveratrol (trans-2,4,3',5'-tetrahydroxystilbene) (3) by spectroscopic methods and through comparison with data reported in the literatures. The anti-inflammatory effects of the isolated compounds[1-3] were evaluated by

determining their inhibitory effects on the production of pro-inflammatory mediators in lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophage cells. These three compounds exhibited potent anti-inflammatory activity. The results indicated that artocarpesin[1] suppressed the LPS-induced production of nitric oxide (NO) and prostaglandin E 2 (PGE 2) through the downregulation of inducible NO synthase (iNOS) and cyclooxygenase 2 (COX-2) protein expressions. Thus, artocarpesin[1] provides a potential therapeutic approach for inflammation-associated disorders.

Zingiber Officinale

Ginger is obtained from rhizomes of *Z. officinale*. The plant belongs to Zingiberaceae family. Since ancient times, it has been widely used as a medicinal herb and spice. As it contains various phytochemical ingredients as beneficial therapeutic agent, *Z. officinale* has been contributing pivotal roles against a broad range of diseases like asthma, diabetes, stroke, constipation, and others. It is reported that 100,000 tons of gingers are annually produced, and 80% of this is produced in China.

The activity of *Z. officinale* as an anti-inflammatory agent was investigated by Thomson and his group in rats. Experimental rats were treated with aqueous extract of *Z. officinale* either orally or intraperitoneally daily for 4 weeks. Although at low-dose ginger did not reduce PGE 2 concentrations, at high doses it significantly lowered PGE 2 levels. Therefore, ginger could reduce inflammation associated with RA.

Recently, *in vitro* anti-inflammatory effect of ginger was carried out by Ribel-Madsen *et al*. where they isolated synovial cells from synovial membrane or synovial fluid. Cells were stimulated by TNF-α. Ginger-treated cells showed similar inhibitory effect to betamethasone by inhibiting production of cytokines IL-1 and IL-6 indicating anti-inflammatory effect.[40]

Strobilanthes Kunthianus and Strobilanthes Tuspidata

The plants *S. kunthianus* and *S. cuspidate* are belongs to the family Acanthaceae. Brahma Srinivasa Rao and his team investigated the *in vitro* anti-inflammatory and antiosteoarthritic activities of these plants extracts and compared with the marketed herbal formulation Shallaki which contains *B. serrata* extract. The results were found to be positive.[41]

In vitro anti-inflammatory and antiosteoarthritic effects of ethanolic extracts of *S. kunthianus* and *S. cuspidate* were studied using "human RBC membrane stabilization method" and "rabbit cartilage explants culture method," respectively. Shallaki (50 µg/ml), diclofenac (50 µg/ml), and celecoxib (50 µg/ml) were used as reference drugs for comparison.[42] The results revealed that both the plants have anti-inflammatory and antiosteoarthritic activity. Moreover, the extracts showed equipotent activity to diclofenac and higher activity than Shallaki.[43]

Camellia Sinensis

It belongs to the family Theaceae *C. sinensis* commonly called tea and is largely used since ancient times and this plant of scientific interest for its numerous therapeutic properties. It is an evergreen shrub or small tree, native to mainland China, South and Southeast Asia, now cultivated across the world in tropical and subtropical regions. The active constituents of *C. sinensis* are polyphenols (catechins and flavonols). Other constituents are caffeine and essential oils. The most important catechin in green tea is (-) epigallocatechin that is a potent antioxidant. The reduced collagen-induced arthritis incidence and severity was reflected in a marked inhibition of the inflammatory mediators COX-2, IFNγ, and TNFα in arthritic joints of green tea-fed mice. Total immunoglobulin's G (IgG) and Type II collagen-specific IgG levels were found to be lower in serum and arthritic joints of green tea-fed mice. Nadia M El-Beih and his team evaluated and compared the elevated effects of two doses of green and black tea aqueous extracts on articular/extra-articular complication in rat adjuvant-induced arthritis. The results showed that green tea may be highly useful in the management of RA complications.[44]

Leucas Aspera

L. aspera is a small erect, branched annual herb. It is distributed throughout India from the Himalayas down to Ceylon. The plant is used traditionally as an antipyretic and insecticide. Medicinally, it has been proven to possess various pharmacological activities such as antifungal, antioxidant, antimicrobial, antinociceptive, and cytotoxic activity. It contains triterpenoids, oleanolic acid, ursolic acid and b-sitosterol, nicotine, sterols, glucoside, diterpenes, and phenolic compounds. Ethanolic extract of *L. aspera* shows anti-RA effect in complete Freund's adjuvant induce arthritis.

Navin patil and his team studies on evaluation of anti-inflammatory activity of alcoholic extract of leaves of *L. aspera* in albino rats. In his study, the alcoholic extract of leaves of *L. aspera* was tested for anti-inflammatory activity in three different doses and all the three test doses did exhibit anti-inflammatory activity.[45]

Others

In addition to above-discussed natural products, several other herbal compounds are found to have antiarthritic activity. Clinical trials have been carried

out with several natural products and their combination preparation. The anti-inflammatory activity of extract of 10 herbs including Japanese creeper, Chinese honeylocust spine, datchmanspipe herb, pubescent angelica, garden balsam, cantonese buttercup, giant typhonium tuber, euphorbia, semen hyoscyami, and sesame oil was investigated in oxazolone-induced inflammation in mice. It has been observed that extract of these herbs has ability to reduce inflammation by inhibiting TNF-α level.

DISCUSSION

The above-mentioned plants are been commonly used for the treatment of arthritis. A number of inexpensive herbal medicines have been reported in literature to be useful for treating arthritis due to their anti-inflammatory and immunosuppressive potential. The herbal medicines majorly available in market are oils when compared to other dosage forms such as tablets, capsules, creams, gels liniments which can also be an effective source of remedy [Table 1]. So plant based such formulations can be developed.

Therefore, there is a need to identify the active principles of these medicines as potential chemotherapeutic agents and monitor the safety of these active constituents.[34] There has been, thus, a need of scientific approach toward phytotherapeutics to deliver the components in a sustained manner so as to increase patient compliance and minimize the need for repeated administration.

A possible way to achieve this is designing novel drug delivery systems for herbal constituents such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transfersomes, ethosomes, and transdermal drug delivery. Novel drug delivery systems help to the reduce toxicity and increase the bioavailability, thereby improving the therapeutic value of the active constituent.

Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach.

CONCLUSION

There are many plants that have antiarthritic and anti-inflammatory properties when compared to allopathic drugs. Due to various side effects and adverse effects always, there is a thirst for the herbal formulations from the patient's side. From our study, we have reported some plants which are been effectively used for treating arthritis. With above-mentioned few plants formulations are available for treating arthritis but for many plants formulations are not available. Hence, a large number of plants described in this review clearly demonstrate the importance of herbal plants in the treatment of various types of arthritis and also to consider one of good source for a new drug or lead to make a new drug formulation were it can be treated globally.

REFERENCES

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
2. Barrera P, Blom A, van Lent PL, van Bloois L, Beijnen JH, van Rooijen N, *et al.* Synovial macrophage depletion with clodronate-containing liposomes in rheumatoid arthritis. Arthritis Rheum 2000;43:1951-9.
3. Furst DE. Anakinra: Review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther 2004;26:1960-75.
4. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002;4 Suppl 3:S265-72.
5. Marks WH. Tripterygium wilfordii hook F. Versus sulfasalazine in the treatment of rheumatoid arthritis: A well-designed clinical trial of a botanical demonstrating effectiveness. Fitoterapia 2011;82:85-7.
6. Quan LD, Thiele GM, Tian J, Wang D. The development of novel therapies for rheumatoid arthritis. Expert Opin Ther Pat 2008;18:723-38.
7. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol 2014;10:581-92.
8. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: Potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237-47.
9. Darlington G, Linda G. Diet and Arthritis: A Comprehensive Guide to Controlling Arthritis through Diet. New Delhi, India: Random House Publishers, India Private Limited; 1998. P. 110001.
10. Upadhyay RK. Anti-arthritic potential of plant natural products; Its use in joint pain medications and anti-inflammatory drug formulations. Int J Green Pharm 2016;10:120-8.
11. Reid MC, Shengelia R, Parker SJ. Pharmacologic management of osteoarthritis-related pain in older adults. Am J Nurs 2012;112:S38-43.
12. Ali S, Lally EV. Treatment failure gout. Med Health R I 2009;92:369-71.
13. Wadekar JB, Sawant RL, Patel UB. Rheumatoid arthritis and herbal drugs: A review. J Phytopharmacol 2015;4:311-8.
14. Zheng Z, Sun Y, Liu Z, Zhang M, Li C, Cai H. The effect of curcumin and its nano formulation on adjuvant-induced arthritis in rats. Drug Des Devel Ther 2015;9:4931-42.
15. Chabaud M, Garnero P, Dayer JM, Guerne PA, Fossiez F, Miossec P, *et al.* Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. Cytokine 2000;12:1092-9.
16. Won HY, Lee JA, Park ZS, Song JS, Kim HY, Jang SM, *et al.* Prominent bone loss mediated by RANKL and IL-17 produced by CD4+ T cells in tally Ho/JngJ mice. PLoS One 2011;6:e18168.
17. Kurebayashi Y, Nagai S, Ikejiri A, Koyasu S. Recent advances in understanding the molecular mechanisms ofthe development and function of Th17 cells. Genes Cells 2013;18:247-65.
18. Atmakuri LR. Dathi S. Current trends in herbal medicine. J Pharm Res 2010;3:109-13.
19. Brownstein D. Overcoming Arthritis. West Bloomfield, MI: Medical Alternative Press; 2001. p. 4173.
20. Schett G. Pathophysiology of subchondral bone erosions in rheumatoid arthritis. Arthritis Res Ther 2012;14:1-14.
21. Singh S, Nair V, Gupta YK. Linseed oil: An investigation of its ant arthritic activity in experimental models. Phytother Res 2012;26:246-52.
22. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H,

Deyo RA, *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the united states. Part II. Arthritis Rheum 2008;58:26-35.
23. Gossell M, Simon OR, West ME. The past and the present use of plants for medicines. West Indian Med J 2006;55:217.
24. Usmanghani K, Hannan A, Mohiuddin E, Asif M. Curcuma longa and curcumin: A review article. Rom J Biol Plant Biol 2010;54:321.
25. Revathy S, Elumalail S, Benny M, Benny A. Isolation, purification and identification of curcuminoids from turmeric (*Curcuma longa* L.) by Column Chromatography. J Exp Sci 2011;2:21-5.
26. Appelboom T, Maes N, Albert A. A new curcuma extract (flexofytol®) in osteoarthritis: Results from a Belgian real-life experience. Open Rheumatol J 2014;8:77-81.
27. Singh D, Aggarwal A, Maurya R, Naik S. *Withania somnifera* inhibits NF-kappaB and AP-1 transcription factors in human peripheral blood and synovial fluid mononuclear cells. Phytother Res 2007;21:905-13.
28. Upaganlawar A, Ghule B. Pharmacological activities of *Boswellia serrata* Roxb. Mini review. Int J Ethnobotanical Res 2009;13:4.
29. Siddiqui MZ. *Boswellia serrata*, a potential anti-inflammatory agent: An overview. Indian J Pharm Sci 2011;73:255-61.
30. Balekar N, Bodhankar S, Mohan V, Thakurdesai PA. Modulatory activity of a polyphenolic fraction of *Cinnamomum zeylanicum* L. Bark on multiple arms of immunity in normal and immunocompromised mice. J Appl Pharm Sci 2014;4:114-22.
31. Neogi NC, Rathor RS, Shrestha AD, Banerjee DK, Studies on the anti-inflammatory and anti-arthritic activity of achyranthine. Indian J Pharm 1969;1:37-48.
32. Srivastav S, Singh P, Mishra G, Jha KK, Khosa RL. *Achyranthes aspera*-an important medicinal plant: A review. J Nat Prod Plant Resour 2011;1:1-14.
33. Nath KK, Deka P, Borthakur SK. Traditional remedies of joint diseases in Assam. Indian J Tradit Knowl 2011;10:568-71.
34. Shaikh MR, Maleka B, Naqvi S. Partial purification and arthritic studies of extracts from *Anemone vulgaris*. Pak J Sci Ind Res 1994;37:279-80.
35. Joshi S, Subedi PC. Phytochemical and biological studies on essential oil and leaf extract of *Gaultheria fragrantissima* wall. Nepal J Sci Technol 2013;14:59-64.
36. Liu WR, Qiao WL, Liu ZZ, Wang XH, Jiang R, Li SY. Gaultheria: Phytochemical and pharmacological characteristics. Molecules 2013;18:12071-108.
37. Rajkumar M, Chandra RH, Asres K, Veeresham C. Plant review *Toddalia asiatica* (Linn.) Lam. A comprehensive review. Phcog Rev 2008;2:386-97.
38. Bose SN, Sepaha GC. Herbal observation on the anti-arthritic properties of *Toddalia asiatica*. J Indian Med Assoc 1956;27:388-91.
39. Asmaliani I, Immaculata M. The effect from methanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lam) in rheumatoid arthritis rat induced collagen Type II. Der Pharmacia Lett 2016;8:180-4.
40. Funk JL, Frye JB, Oyarzo JN, Timmermann BN. Comparative effects of two gingerol-containing *Zingiber officinale* extracts on experimental rheumatoid arthritis. J Nat Prod 2009;72:403-7.
41. Gupta GS, Sharma DP. Triterpenoid and other constituents of Strobilanthes cuspidate flowers. Phytocognosy 2013-2014;13:1974.
42. Preethi F, Suseem SR. A comprehensive study on an endemic Indian genus-strobilanthes. Int J Pharm Phytochem Res 2014;6:459-66.
43. Sarpate R, Tupkari S. Evaluation of the anti-arthritic potential of the Genus *Strobilanthus*. Int J Drug Develop Res 2012;4:230-6.
44. Vishnoi H, Bodla RB, Kant R. Green tea (*Camellia sinensis*) and its antioxidant property: A review. Int J Pharm Sci Res 2018;9:1723-36.
45. Patil N, Somashekar HS, Reddy SR, Nayak V, Narendranath S, Bairy KL, *et al*. Evaluation of anti-inflammatory activity of alcoholic extract of leaves of *Leucas aspera* in Albino rats.Int J Pharm Pharm Sci Res 2014;6:716.
46. Available from: https://www.dir.indiamart.com/impcat/arthritis-oil.html. [Last accessed on 2018 Jan 24].

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