

Anti-arthritic potential of plant natural products; its use in joint pain medications and anti-inflammatory drug formulations

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Abstract

The present review explains reasons of arthritis a disease related to chronic joint pain and inflammation. It also emphasizes the use of bioactive principles of plant origin to be used to relieve from arthritic pain, aching, stiffness, and swelling. These plant natural products can finish rheumatic pain if they are used regularly according to physician's advice. There are so many active crude extracts and pure compounds which show anti-arthritic activity in Freund's complete adjuvant induced animal models. Certain Ayurvedic formulations also assist to relieve from rheumatic arthritic pain and tone up immune system to function normally. This article shows an overview of medicinal suggestions on the basis of experimental advances made in the herbal medicinal researches in recent years for the treatment of arthritis. There are various dietary supplements which could also provide for management of severe pain of joints, and mitigation of inflammation. It is also suggested that early diagnosis, proper treatment, and healthy dietary habits can reduce the disease spectrum and chronic inflammatory pain.

Key words: Arthritis, herbal medicines, inflammation, joint pain, plant natural products

INTRODUCTION

Arthritis is a disease related to chronic joint pain and inflammation. More than 200 rheumatic diseases or severe disorders are known^[1,2] which are related to tissues, joints, and other connective tissues.^[3,4] There occurs a constant pain that becomes localized in the joint affected, which is the main feature of arthritis. The pain increases with the daily wear and tear of joint, muscle strains caused by forceful movements against stiff painful joints and fatigue. Typically arthritis shows heavy morbidity of pain, aching, stiffness, and swelling in and around one or more joints characterize rheumatic conditions. The most common form of arthritis is osteoarthritis (OA) while its other common rheumatic conditions are gout, fibromyalgia, and rheumatoid arthritis (RA).^[4] Some forms of arthritis such as RA and lupus, can affect multiple organs and cause widespread symptoms. Arthritis displays severe pain or a trauma of the joint, infection of the joint with the age. Other arthritis forms are RA, psoriatic arthritis, and related autoimmune diseases. Septic arthritis is caused by joint infection. The symptoms can develop gradually or suddenly. 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. The majority of adult population is reported to have a form of arthritis, i.e., RA, gout, lupus or fibromyalgia.

OA is a progressive degenerative joint disease that has a major impact on joint function and quality of life. RA can affect people of all ages and disease may occur at any age, it usually begins after age 40. It is the most common form of arthritis^[5] that affects both the largest and the smaller joints of the body including the hands, wrists, feet, back, hip, and knee. This disease typically 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 also 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. Unlike the wear-and-tear damage of OA, RA affects the lining of your joints, causing a painful swelling that can eventually result in bone

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Received: 27-03-2016

Revised: 02-07-2016

Accepted: 14-07-2016

erosion and joint deformity. It is a chronic inflammatory disorder that typically affects the small joints in hands and feet. In RA body's own immune system starts to attack body tissues and severe damage occurs to the joint lining and cartilage which eventually results in erosion of two opposing bones. In beginning disease remains undifferentiated and does not detected but as soon as pain increases it appears.^[6] Certain rheumatic conditions also involve the immune system and various internal organs of the body.^[7] The disease is symmetrical and appears on both sides of the body. It can lead to severe deformity if no treatment is done. In children, the disorder appears due to genetic reasons and prevail skin rash, fever, pain and disability in limbs and knee joints that limits the daily activities.

CAUSES OF DISEASE

Due to changing lifestyle and mobility pressure, there is a sharp 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 certain genes are among non-modifiable factors which are responsible for arthritis. Age is important risk factor as the risk of developing most types of arthritis increases with age. Arthritis is mostly seen in women. Overweight and obesity are among some modifiable risk factors. 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.^[8]

Arthritis patients also show other co-morbidities such as heart diseases, chronic respiratory diseases, diabetes, and stroke. High blood pressure, physical laxity or inactivity, high-cholesterol, obesity and smoking are important risk factors. 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.^[9] When uric acid levels and gout symptoms cannot be controlled with standard gout medicines that decrease the production of uric acid (e.g., allopurinol, 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.^[10]

RA, induced by the prolonged inappropriate inflammatory responses, is one of the most prevalent of all chronic inflammatory joint diseases.^[11] 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 present in Th17 cells and osteoblasts.^[12] 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.^[13] This adaptive immune response is initiated in part by CD4+ T helper (Th) cells, specifically Th17 cells.^[5] 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).^[14] 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. But 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. 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 and lesser side effects [Table 1]. It may eventually lead to the development of a new class of anti-inflammatory agents for the treatment of arthritis.^[15] This review article presents an overview of recent advances in reasons and medications of arthritis. There are several classes of traditional anti-arthritis formulations available in Ayurvedic, Siddha, and Chinese traditional medicine which are used for the treatment of severe joint pain and inflammation.

THERAPEUTICS

Use of Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor (TNF) alpha inhibitors, IL-6 inhibitors, T-cell activation inhibitors, B-cell depleters, JAK inhibitors, immunosuppressants, and steroids are used in the treatment of RA. Light aerobics, physical exercise, yoga and proper medication can provide better relief to osteoarthritic weight-bearing joint pains with defects. The patients can also provide different drug regimens depend on the type of arthritis and its severity. For treatment of inflammatory arthritis non-steroidal anti-inflammatory drugs like ibuprofen is provided. Acetaminophen (paracetamol) is provided as first-line treatment. Opioids and NSAIDs are less well tolerated.^[5] RA is autoimmune disorder that generates high pain, hence, anti-inflammatory drugs called DMARDs [Table 1]. These drugs act restore immune functions and slow down the progression of RA. Methotrexate and remicade drugs are provided to improve quality of life. Corticosteroids and monoclonal

Table 1: Important anti-arthritic ingredients isolated from various plant species

Plant	Part	Active ingredients	Chemical group	Biological activity
Flax seed oil, chia seeds, walnuts	Seafood sources like salmon and sardines	Omega-3 fatty acids	Fatty acid, ALA, DHA and EPA	Management of inflammatory disorders
<i>Linum usitatissimum</i>		Fixed oil	Mixed and multi-component	Anti-arthritic
Chili peppers	Genus capsicum flower bud and seed	Capsaicin	8-methyl-N-vanillyl-6-nonenamide, phenol group, alkene and nitrogen group	Antioxidant and anti-inflammatory
<i>Curcuma longa</i>	Zedoary roots	Curcumin	The aromatic ring systems, which are phenols, are connected by two α , β -unsaturated carbonyl groups	Antioxidant and anti-inflammatory
Plant-based foods	Such as oils, nuts, and seeds	Dietary n-3 fatty acids		Antioxidant and anti-inflammatory
<i>Allium sativum</i>	Bulbs and leaves	Ajoene	Sulfoxide and disulfide functional groups	Anti-inflammatory properties
Plant based foods	Nuts seeds, leafy vegetables, sunflower oil	Vitamin E	Tocopherols and tocotrienols. Of the many different forms of vitamin E, γ -tocopherol	Antioxidant and anti-inflammatory
<i>Camellia sinensis</i>	Leaves	Green tea	Four major epicatechin derivatives namely, EC, EGC, ECG, and EGCG	Antioxidant and anti-inflammatory
<i>Ocimum sanctum</i>	Leaves	Indian holy basil	Volatile constituents in oil from different plant parts of methyl eugenol-rich, ocimumosides A and B	Antioxidant and anti-inflammatory
<i>Syzygium cumini</i>	Fruit and seeds	Alkaloid, jambosine, and glycoside jambolin or antimellin	Anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol and myrecetin	Inhibit formation of oxygen derived free radicals. Provide relief in RA
<i>Clerodendrum phlomidis</i>	Roots	Flavonoid glycosides	β -(4-hydroxyphenyl)-ethyl- O - α -l-rhamnopyranosyl (1 \rightarrow 3)- β -D-(4- O -2'	Displays considerable potency in anti-inflammatory action and has prominent anti-arthritic effect on adjuvant induced arthritis
<i>Strychnos potatorum</i> Linn	Seeds	Alsogavebrucine, strychnine, novacine, icajine	Oleanolic acid and its glycoside	Loganiaceae seeds show effect on the FCA induced arthritic rat paw edema, body weight changes
Ginger (<i>Zingiber officinale</i>)	Essential oils	Nongingerol	Terpene are sesquiterpene hydrocarbons and phenolic compounds	Show significant joint-protective effect
<i>Withania somnifera</i>	Leaves and root	Twelve alkaloids, 35 withanolides, and several sitoindosides	C28 steroidal nucleus with C9 side chain, with a six membered lactone ring	Anti-inflammatory activity
<i>Chenopodium album</i> L.	Leaves and roots	Polyphenolic and flavonoid, Roots contain ecdysteroids, β -ecdysone and polypodine B	Albuminoids and other nitrogenous compounds, carotene and vitamin C. Oxalic acid	Anti-inflammatory activity

(Contd...)

Table 1: (Continued)

Plant	Part	Active ingredients	Chemical group	Biological activity
<i>Cissampelos pareira</i>	In roots	Alkaloids	Saponins	Anti-inflammatory activity
<i>Semecarpus anacardium</i>	Leaves roots and fruits	Biflavonoids, phenolic compounds, bhilawanols, minerals, vitamins and amino acids	Mixed functional groups	Antiarthritic effect by retarding lipid peroxidation and causing a modulation in cellular antioxidant defense system
<i>Pterodon pubescens</i>	Seeds	Geranylgeraniol	6 α -Acetoxy-7 α -Hydroxy-Vouacapan	Anti-arthritis activity
<i>Curcuma zedoaria</i> Rosc	Roots	Curcumin (CC1) and demethoxycurcumin, one gingerdione: 1-dehydrogingerdione (CC3), together	With four sesquiterpenes: Germacrone (CC4), (+)-germacrone -4,5-epoxide (CC5), zederone (CC6) and	Anti-arthritis activity
<i>Azadirachta indica</i>	Leaves and fruit	Tetranortriterpenes	Nimbidin	Inhibit inflammatory stimuli and also phagocytosis
<i>Kalopanax pictus</i> bark	Leaves	Saponins	Hyperoside, 3,5-di-O-caffeoyl quinic acid, methyl 3,5-dicaffeoyl quinate, and 3-O-feruloylquinic acid	Good antioxidant
<i>Psammrusosilene tunicoids</i>	Roots	Saponins	Saponins	Decrease arthritis index and regulate down the content of IL-1beta and TNF alpha in the inflammatory tissue, use to treat RA
<i>Capparis spinosa</i> L.	Fruits and flowers	P-hydroxy benzoic acid; 5-(hydroxymethyl) furfural; bis (5-formylfurfuryl) ether; daucoesterol	α -D-fructofuranosides methyl; uracil; and stachydrine	Anti-arthritis effects
<i>Aloe vera</i>	Leaves	Aloin and vitamin B12, folic acid, and <i>choline</i>	Amino acids, anthraquinones, enzymes, minerals, vitamins, lignins, monosaccharide, polysaccharides, salicylic acid, saponins, and sterols	Laxative properties
<i>Semecarpus anacardium</i>	Nut	Siddha formulation constituting nut milk extract (SA)	Biflavonoids, phenolic compounds, bhilawanols, minerals, vitamins and amino acids	Shows antiarthritic effects
<i>Emblica officinalis</i>	Nut	Vitamin C and polyphenolic compounds	(poly) phenolic analytes, e.g., ellagic and gallic acids and corilagin	Shows antiarthritic effects
<i>Ginkgo biloba</i> leaves	Leaves	Ginkgetin, a biflavone, flavonol and flavone glycosides, lactone derivatives (ginkgolides), bilobalide, ascorbic acid, catechin, iron-based superoxide, 6-hydroxykinuretic acid, protocatechuic acid, shikimic acid, sterols and vanillic acid	Both ginkgetin and indomethacin are potential antiarthritic agents inhibitor of Group II phospholipase A2	Ginkgetin consistently inhibits the production of leukotriene C (4) (LTC (4) and shows a dual cyclooxygenase -2/5-lipoxygenase inhibitory activity

(Contd...)

Table 1: (Continued)

Plant	Part	Active ingredients	Chemical group	Biological activity
Triphala <i>Emblica officinalis</i> Gaertn (Amla), <i>Terminalia chebula</i> Retz (Haritaki) and <i>Terminalia bellerica</i> Roxb (Bibhitaki) in equal proportions	Ayurvedic herbal formulation by using various plant parts	Gallic acid, chebulagic acid, chebulinic acid	Corilagin, sitosterol, bellericanin, Vitamin C and quercetin	Promising anti-inflammatory activity and antiarthritic effect

ALA: Alpha-linolenic acid, DHA: Docosahexaenoic acid, EPA: Eicosapentaenoic acid, EC: Epicatechin, EGC: Epigallocatechin, ECG: Epicatechin gallate, EGCG: Epigallocatechin Gallate, RA: Rheumatoid arthritis, FCA: Freund's complete adjuvant, SA: *Semecarpus anacardium*, Interleukin 1: IL-1: TNF: Tumor necrosis factor

antibodies are administered intravenously. In the early stage, joint surgery provides some relief but as soon as pain prevails in many other parts of body, it becomes very difficult to treat the patient. There are several types of medications, and drug regimens are used for the treatment of arthritis [Table 1]. But mostly those drugs are used which show fewest side effects and minimum complications to the immune system.^[14]

There must be drugs which could significantly increase lysosomal membrane integrity and show stabilizing action on lysosomal membranes. Drug administration should prevent local activation of NFκB and the subsequent expression of NFκB-regulated genes mediating joint inflammation and destruction including chemokines, cyclooxygenase 2 (COX-2), and RANKL. The levels of lysosomal enzymes, tissue marker enzymes, glycoproteins, and paw thickness should be increased in arthritis affected patients. Ginkgetin strongly reduces arthritic inflammation when administered via intraperitoneal injection, while prednisolone showed 79% reduction. Total saponins of *Psammruosilene tunicoids* (TSPT) could effectively inhibit articular swelling, decrease arthritis index and regulate down the content of IL-1 beta, and TNF alpha in the inflammatory tissue soak of AA rats. There are numerous plant species whose organic solvent extracts show anti-inflammatory activity in animal model^[12] and restores level of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP) levels with pro-inflammatory cytokines, plasma lysosomal enzymes, and protein-bound carbohydrates. These can be potentially used arthritis to treat arthritis.

NUTRACEUTICALS

Nutraceuticals and dietary supplements derived from herbs have long been used in traditional medicine, and there is considerable evidence that nutraceuticals may play an important role in inflammation and joint destruction in OA. Food sources rich in omega-3 fatty acids have been

valued for their beneficial effect in the management of inflammatory disorders [Figure 1].^[15] *Linum usitatissimum* fixed oil (LUFO) shows antiarthritic and immunomodulatory activity in experimental models. The LUFO produced a dose-dependent reduction in joint swelling and circulating TNF alpha level in both preventive and curative protocols of arthritis induced by complete Freund's adjuvant (CFA). Expression of TNF-R1 and IL-6 proteins in the arthritic paw was also significantly reduced in the LUFO-treated animals. LUFO shows antiarthritic and disease modifying activity and its dietary incorporation may be beneficial in the prevention and management of RA and other chronic inflammatory disorders.^[15] Omega-3 fatty acid and phenolic anti-oxidant interventions are important dietary constituents which show antioxidant activity and anti-inflammatory responses.^[16,17] Three important additions to the diet, i.e., capsaicin, curcumin (CM), and dietary n-3 fatty acids cause decrease in generation of reactive oxygen species in peritoneal macrophage [Figure 1].^[17] Onions is used for arthritis treatment.^[18] Ajoene, a natural product isolated from *Allium* shows anti-inflammatory properties.^[19] There are so many dietary supplements which are used in different parts of the world such as turmeric, garlic, salad, green wet moong, cat's claw, ginger, fish oil, omega-3 fatty acids, vitamin E, vitamin C, Baikal skullcap, barberry, Chinese goldthread, green tea, Indian holy basil, Hu Zhang, oregano, and rosemary. These dietary supplements show antioxidant and anti-inflammatory and are used to manage OA and RA and make conclusions about their place in therapy. Omega-3 fatty acids, vitamin E; vitamins A, C, and E in combination; ginger; turmeric are used for the treatment of OA [Table 1]. These supplements can be effectively and safely recommended to reduce nonsteroidal anti-inflammatory drug or steroid usage is unclear and requires more high-quality research.^[16]

Use of Organic Solvent Extracts

Different organic solvent extracts of various plant species show anti-inflammatory activity. *Clerodendrum phlomidis* active crude extract shows antiarthritic activity in Freund's

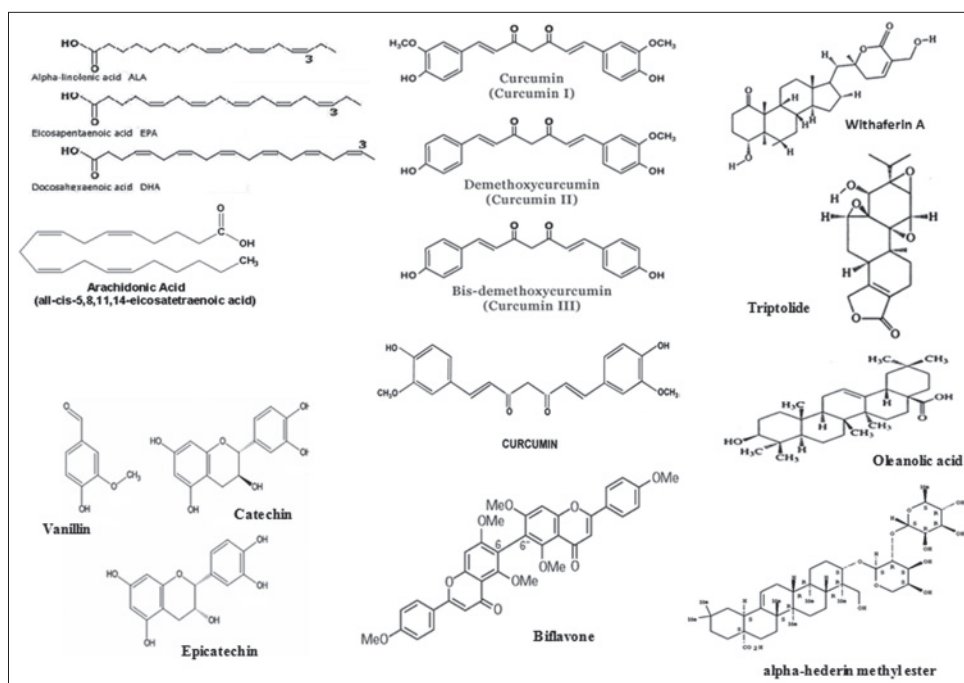


Figure 1: Plant origin bio-organic components which show anti-arthritis potential

complete adjuvant (FCA) induced animal model.^[12] Its ethanolic extract restores level of serum SGOT, SGPT, ALP levels with pro-inflammatory cytokines, plasma lysosomal enzymes, and protein-bound carbohydrates of FCA arthritic animals. *C. phlomidis* displays considerable potency in anti-inflammatory action and has prominent anti-arthritis effect on adjuvant-induced arthritis.^[12] Similarly, aqueous extract and the whole seed powder of *Strychnos potatorum* Linn Loganiaceae seeds show the effect on the FCA induced arthritic rat paw edema, body weight changes, and alterations in hematological and biochemical parameters in both developing and developed phases of arthritis.^[20]

Ginger (*Zingiber officinale*) essential oils and more polar compounds were found more effective. Nongingerol components were found highly active and show significant joint-protective effect.^[21] Similarly, infusions of Indian black tea (BTI), when administered orally, produced significant inhibition of rat paw edema, induced with carrageenin (pre and post treatment) and arachidonic acid. BTI was also found to inhibit peritoneal capillary permeability and caused a marked reduction of lipopolysaccharide (LPS) induced prostaglandin E(2) (PGE2) generation.^[22] Similarly, *Plumeria alba* L. has protective activity against arthritis, mainly rheumatism and other inflammatory diseases. There was significant ($P < 0.05$) improvement in thymus weight in EAPA treated rats, whereas significant ($P < 0.01$) improvement was also seen in hemoglobin level in diclofenac-treated group. Motor incoordination and nociceptive threshold were also significantly ($P \leq 0.05-0.01$) improved.^[23] Aqueous extracts of *Withania somnifera* (Ashwagandha) root and glucosamine sulfate significantly decreased nitric oxide (NO) release by explants from one subset of patients (anti-inflammatory

response) and significantly increased levels of NO and glycosaminoglycans (GAGs) released and significantly increased levels of NO and GAGs released by explants from the second subset ("non-responders").^[24]

Chenopodium album L. (Bathua: Chenopodiaceae) is used for the treatment of rheumatism.^[25] It has a role in inhibition of NF κ B activity and increase antioxidant potential. The polyphenolic and flavonoid content of different extracts were in the range of $14.56 \pm 0.21-42.00 \pm 0.2$ mg (gallic acid equivalent/g extract) and $2.20 \pm 0.003-7.33 \pm 0.5$ mg (rutin equivalent/g extract), respectively. Similarly, *Mesua ferrea* Linn. (Clusiaceae), Cobra's saffron, found in tropical climates is prescribed in the Ayurvedic medicine for the treatment of pain, inflammation, and rheumatic conditions [Table 1].^[26] *M. ferrea* exerts a potent protective effect against formaldehyde and adjuvant-induced arthritis in rats.^[26] Similarly, aqueous ethanolic extract of *Cissampelos pareira* (Menispermaceae) roots showed the dose-dependent significant protective effect against CFA induced arthritis.^[27] Solvent extract decreased lysosomal enzymes (acid phosphatase and N-acetyl glucosaminidase) by 50% ($P < 0.01$) and 26.26% ($P < 0.05$). *C. pareira* vindicated its medicinal value in the treatment of pain and arthritis.^[27]

Avocado and soya un-saponifiables (ASU) are plant extracts used as a slow-acting antiarthritic agent.^[28] ASU stimulate the synthesis of matrix components by chondrocytes, probably by increasing the production of transforming growth factor-beta (TGF-beta). TGF-beta is expressed by chondrocytes and osteoblasts and is present in cartilage matrix.^[28] ASU treatment caused an increase in TGF-beta1 and TGF-beta2 levels in the joint fluid when compared to controls.^[28]

Similarly, administration of *Semecarpus anacardium* (SA) nut extract brings back the altered antioxidant defense components to near normal levels. It exerts antiarthritic effect by retarding lipid peroxidation and causing a modulation in cellular antioxidant defense system. Aqueous-alcoholic extract of *Pterodon pubescens* (HEPp) seeds shows anti-arthritis activity in collagen-induced arthritis (CIA) in DBA1/J mice after treatment with daily oral doses of HEPp in different schedules.

Milk extract of SA nuts effect on glycolysis and lysosomal stability in adjuvant-induced arthritis in rats.^[29] Phenolic constituents found in flowers of *Aloe barbadensis* show anti-oxidative capacity.^[30] *P. alba* L.,^[23] *Cynodon dactylon*,^[31] and *Boswellia serrata* leaf extract showed anti-arthritis activity and attenuates mediators and oxidative stress in collagen-induced arthritis.^[32] Similarly, Swertiamarin attenuates inflammation mediators via modulating NFκB/IκB and JAK STAT3 transcription factors in adjuvant-induced arthritis,^[33] Celery seeds also show anti-arthritis activity.^[34] *Tinospora cordifolia*,^[35] *Terminalia chebula* Retz,^[36] and *Ajuga bracteosa* Wall ex Benth^[37] and Lakshadi Guggul showed strong anti-arthritis potential in albino rats [Table 1].^[38] A regular treatment significantly reduces both the arthritic index (AI) and the CIA incidence.^[39]

AYURVEDIC MEDICINES

Polyherbal Ayurvedic formulations/preparations showed anti-inflammatory and anti-arthritis effects.^[40] Prominently, BV-9238, a proprietary formulation of *W. somnifera*, *B. serrata*, *Z. officinale*, and *Curcuma longa*, inhibits LPS-induced TNF alpha and NO production from mouse macrophage and reduces inflammation in different animal models. BV-9238 is found potential, safe and well-tolerated anti-inflammatory formulation.^[40] *Curcuma zedoaria* (family Zingiberaceae) ethanolic rhizome extract shows anti-inflammatory activity.^[41] Turmeric is an Ayurvedic medicine practiced for centuries for the treatment of inflammatory disorders including arthritis. It is used as a dietary supplement to treat arthritis treatment [Table 1].^[42] A turmeric fraction depleted of essential oils profoundly inhibited joint inflammation and periarticular joint destruction in a dose-dependent manner. *In vivo* treatment, it prevents local activation of NFκB and the subsequent expression of NFκB-regulated genes mediating joint inflammation and destruction, including chemokines, COX-2, and RANKL. It significantly inhibits inflammatory cell influx, joint levels of PGE2, and periarticular osteoclast formation.^[43]

Curcuminoid-containing turmeric extracts showed protective effects against RA. AI, a clinical measure of joint swelling, was used as the primary endpoint for assessing the effect of extracts on joint inflammation. An essential oil-depleted turmeric fraction containing 41% of the three major curcuminoids was efficacious in preventing joint

inflammation.^[43] *In vivo* treatment prevents local activation of NFκB and the subsequent expression of NFκB-regulated genes mediating joint inflammation and destruction, including chemokines, COX-2, and RANKL. Turmeric extract treatment inhibited, inflammatory cell influx, joint levels of PGE2, and periarticular osteoclast formation.^[43]

CM

CM is an orange-yellow hydrophobic polyphenol (diferuloylmethane) derived from the herb turmeric or curry powder [Figure 1]. This is a natural product isolated from the rhizome of the plant *C. longa*.^[44] CM, the active principle of turmeric used in Indian curry is known for antioxidant, antiarthritic, anti-ischemic and anti-inflammatory properties [Table 1].^[45] It is used as a food-coloring agent and easily available for medication. CM shows antiarthritic, anti-amyloid, antioxidant, and anti-inflammatory properties. It does regulation of various molecular targets including transcription factors (such as NFκB), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, IL-1 and IL-6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt), and other enzymes (such as COX-2 and 5 lipoxygenase).^[44] CM was found to be a potential therapeutic agent for the prevention and/or treatment arthritis, and other inflammatory illnesses [Table 1].^[44]

CM, a natural polyphenolic compound present in turmeric, exhibited multiple pharmacological activities including anti-inflammatory, antiarthritic and antioxidant properties.^[46] CM has various pharmacological activities against many chronic diseases and acts by inhibiting cell proliferation and metastasis and downregulating various factors, including NFκB, IL-1β, and TNF alpha.^[11] It shows anti-inflammatory, antiarthritic and antioxidant properties.^[46] It shows therapeutic effect when administer via intravenous and show low oral bioavailability.^[11] Petroleum ether, chloroform, and methanol root extracts of *C. zedoaria* Rosc (Family: Zingiberaceae) showed significant recovery on behavioral and radiology aspects of FCA-induced monoarthritis in left ankle joint of rats using open-field test. Traditionally, *C. zedoaria* root has been used as anti-inflammatory and antiarthritic drug.^[47] CM is also used in various systems of indigenous medicine and is helpful in preventing arthritis and has therapeutic potential in combating RA disorder [Table 1].^[45]

Infusions of BTI, produced significant inhibition of rat paw edema, induced with carrageenin (pre- and post-treatment) and arachidonic acid if administered orally. BTI was also found to inhibit peritoneal capillary permeability and caused a marked reduction of LPS induced PGE2 generation.^[48] BTI was found to scavenge superoxide and hydroxyl radicals and also protected rat erythrocytes from the damaging effects

of hydrogen peroxide. BTI inhibited granuloma formation along with the reduction of both lipid peroxidation and hydroxyproline content (in the granuloma tissue). Chronic treatment with BTI (in arthritic rats) resulted in a decrease of paw diameter and tissue lipid peroxidation, along with a restoration of GSH, catalase, and superoxide dismutase levels.^[48] Some medicinal fruits and herbs - pomegranate, green tea, cat's claw, devil's claw, ginger, Indian olibaum, turmeric, and ananas can set pivotal molecular targets involved in inflammation and the joint destruction process and can be used as adjunct therapy for OA management.^[49]

NIMBIDIN

Nimbidin is a mixture of tetranortriterpenes and found the major active principle of the seed oil of *Azadirachta indica* A. Juss (Meliaceae) possess potent anti-inflammatory and anti-arthritic activities. Nimbidin significantly inhibited some of the functions of macrophages and neutrophils relevant to the inflammatory response following both *in vivo* and *in vitro* exposure [Table 1].^[50] Oral administration of 5-25 mg/kg nimbidin to rats for 3 consecutive days significantly inhibited the migration of macrophages to their peritoneal cavities in response to inflammatory stimuli and also inhibited phagocytosis and phorbol-12-myristate-13-acetate (PMA) stimulated respiratory burst in these cells. *In vitro* exposure of rat peritoneal macrophages to nimbidin also inhibited phagocytosis and PMA stimulated respiratory burst in these cells. Nimbidin also inhibited NO and PGE2 production in LPS stimulated macrophages following *in vitro* exposure, whereas IL-1. Nimbidin ameliorated the induction of inducible NO synthase without any inhibition in its catalytic activity. In addition, nimbidin also attenuated degranulation in neutrophils assessed in terms of release of beta-glucuronidase, myeloperoxidase, and lysozyme.^[50]

SAPONINS

Kalopanax pictus bark extract contains saponin components which showed inhibition of adjuvant-induced arthritis in rats [Table 1]. From *K. pictus* alpha-hederin, alpha-hederin methyl ester, and kalopanaxsaponin I were isolated which antiarthritic activity, and inhibit vascular permeability in mice. When alpha-hederin methyl ester alone is provided, it showed anticarrageenan activity in rats and antiarthritic activity in rats and mice.^[51] Similarly, TSPT showed anti-RA effects and effectively inhibited articular swelling, decrease arthritis index and regulate down the content of IL-1beta and TNF alpha in the inflammatory tissue soak of AA rats.^[52] TSPT has good antiarthritic effects because of down-regulation of IL-1beta and TNF alpha.^[52] Ethanol and ethanol-water extracts of *Capparis spinosa* L. (Capparidaceae) fruits showed anti-arthritic effects due to the presence of few important chemical constituents such as P-hydroxy benzoic

acid; 5-(hydroxymethyl) furfural; bis (5-formylfurfuryl) ether; daucosterol; α -D-fructofuranosides methyl; uracil; and stachydrine.^[53] Few plant species such as *Aloe vera* is used to treat arthritis. Regular use of its crude juice and gel is very efficient for relieving arthritic pain. It helps to eliminate pain and provides easy mobility. It contains sterols such as lupeol and campesterol. If *A. vera* gel is mixed with crushed aspirin and is applied topically for instant relief from pain in joints. If it is applied as a poultice with a warm, moist wash cloth or gauze pad provides instant relief and reduces swelling. Latex from the *A. vera* plant contains aloin that contains laxative properties.^[54] Latex of *C. procera* shows anti-arthritic activity and cut down arthritic pain in joints [Table 1].^[55] Korean red ginseng saponin fraction rich in gensenoside-Rb-1, Rc, and Rb2 attenuates the severity of mouse collagen-induced arthritis.^[56]

GINKGETIN

Ginkgetin, a biflavone isolated from *Ginkgo biloba* leaves, is a potent inhibitor of group II phospholipase A2.^[57] It shows potent anti-arthritic activity in rat adjuvant-induced arthritis as well as analgesic activity. Ginkgetin inhibits COX-2 dependent phases of prostaglandin D(2) generation in bone marrow-derived mast cells in a concentration-dependent manner. Ginkgetin consistently inhibits the production of leukotriene C(4) and shows a dual COX-2/5-lipoxygenase inhibitory activity.^[58] A 1:1 mixture of ginkgetin and isoginkgetin, from *G. biloba* leaves, inhibit production of PGE2 from LPS-induced RAW 264.7 cells.^[59] Ginkgetin and the biflavonoid mixture (100-1,000 microg/ear) dose-dependently inhibited skin inflammation of croton oil-induced ear edema in mice by topical application. Ginkgetin from *G. biloba* leaves down-regulates COX-2 induction *in vivo* and this down-regulating potential is associated with an anti-inflammatory activity against skin inflammatory responses.^[59] Both ginkgetin and indomethacin are potential antiarthritic agents [Table 1].^[59] Ginkgetin strongly reduced arthritic inflammation in an animal model of rat at a dose of 10-20 mg/kg/day. It also shows ant-analgesic activity.

TRIPHALA

Herbal products reduce inflammation-induced bone damage in arthritis.^[60] Triphala is an Ayurvedic herbal formulation that shows antiarthritic effect in adjuvant-induced arthritis in mice. Its oral treatment restores levels of lysosomal enzymes, tissue marker enzymes, glycoproteins and paw thickness in adjuvant-induced arthritic animals. Oral administration of Triphala (1 g/kg/bwt) reduces body weight, restore both physical and biochemical changes in rthritic animals and shows promising anti-inflammatory activity [Table 1].^[61]

SIDDHA FORMULATION

Kalpaamruthaa (KA) is a modified indigenous Siddha formulation constituting SA nutmilk extract, *Embllica officinalis*, and honey shows anti-inflammatory activity. KA exhibited enhanced effect on anti-inflammatory and antiarthritic properties than sole SA treatment, and the collective effect of KA might be due to the combined interactions of the phytochemicals such as flavonoids, tannins, and other compounds such as vitamin C present in KA.^[62] Lysosomal acid hydrolases are thought to play an important role in inflammation associated with RA. KA treatment has significantly increased total and free activity of lysosomal enzymes in arthritic rats with a concomitant increase in plasma levels of protein-bound carbohydrates. Significantly increased lysosomal membrane fragility as observed in arthritic condition was reduced in drug-treated animals [Table 1].^[63] Similarly, milk extract of SA (Serankottai Nei), a Siddha preparation from nut, shows anti-arthritic effects. It shows a significant modification in lysosomal enzyme release and total carbohydrate components of glycoprotein. After administration of the extract the lysosomal enzyme activity and protein-bound carbohydrate, component levels were significantly normalized.^[64] Polyherbal Unani formulation showed anti-rheumatic activity.^[65] Celastrus and its bioactive celastrol protect against bone damage in autoimmune arthritis by modulating osteoimmune cross-talk.^[66]

CONCLUSION

To control the severity of pain and inflammation due to Arthritis change of lifestyle, regular exercise, diet, and proper medication are important. There are drug formulae which are commercially available in the market which prevents local activation of NFκB and the subsequent expression of NFκB-regulated genes mediating joint inflammation and destruction, including chemokines, COX-2, and RANKL but this is treatment is costly and is non-affordable to most of the patients due to economic reasons. Hence, plant natural products can be used as sources of herbal medicines for the treatment of arthritis affected people. Phytochemicals, nutritional and mineral constituents of different plant species will definitely assist clinicians and pharmacists to prepare anti-arthritis drug formulation with an establishment of non-toxic herbal drugs. These could be used as a source of nutrients, and as replacements for synthetic antibiotics which impose many side effects. No doubt indigenous medicinal plants can be used to maximize the production of economically feasible drugs as an alternative of synthetic antibiotics to treat not only arthritis but also other chronic pain-related diseases and disorders.

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Source of Support: Nil. **Conflict of Interest:** None declared.