Potential of Nutraceuticals and Medicinal Plants in the Management of Osteoarthritis

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ABSTRACT

Osteoarthritis (OA), the most common form of joint disease in the elderly, is a progressive destructive process characterized by metabolic and structural changes in the cartilage, bone and articular surfaces. The management of OA involves both non-pharmacologic and pharmacologic approaches of therapy. Such modes of therapy may prove ineffective in some patients and moreover, have been found to be associated with serious side effects. Due to such problems, more patients have nowadays been found to resort towards complimentary/alternative medicines (CAM), which include the use of nutraceuticals as well as medicinal plants. Such approach has been reported to be not only effective at relieving the pain symptoms associated with OA but may also prove to be more safe and effective than conventional treatment options. In the present review, an attempt has been made to include the available literature on the effectiveness as well as molecular targets of nutraceuticals and medicinal plants in the management of OA.

Keywords: medicinal plants, NSAIDs, nutraceuticals, osteoarthritis, inflammation, CAM.

INTRODUCTION

Osteoarthritis (OA) is a chronic, painful and progressive debilitating disease that affects the elderly population. It mainly leads to thinning of joint cartilage in the knees, hips, spine and/ or hands [1]. It is one of the most prevalent causes of disability in the aging population of developing countries. OA results from the pathological imbalance between destructive and reparative processes, ultimately leading to the destruction of articular cartilage and subchondral bone. Due to its high prevalence and moderate-to-severe impact on daily life, OA poses to be a significant public health problem [2]. Despite its frequency in the population, the etiopathogenesis of OA remains poorly understood with few therapeutic options available.

In OA, the regions that are mainly affected include cartilage, synovium and the bone [3]. Although OA has been traditionally believed to be a non-inflammatory type of arthritis, recently inflammatory mediators of pain have been shown to be associated with it [4,5]. In response to various stimuli such as trauma, inflammation, age, obesity, mechanical stress, a cascade of molecular events occur that are responsible for articular cartilage degradation. These events include downregulation of anti-inflammatory cytokines (IL-4, -10 and -13), tissue inhibitors of matrix metalloproteinases (TIMPs) and growth factors (IGF-1, TGF-β, bFGF and BMPs); upregulation of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), IL-6, -8, -11, -17, -18) [6,7] and production of matrix metalloproteinases, collagenases, aggrecanases, nitric oxide (NO), prostaglandins (PGE2) and cyclooxygenase-2 (COX-2) (Figure 1).

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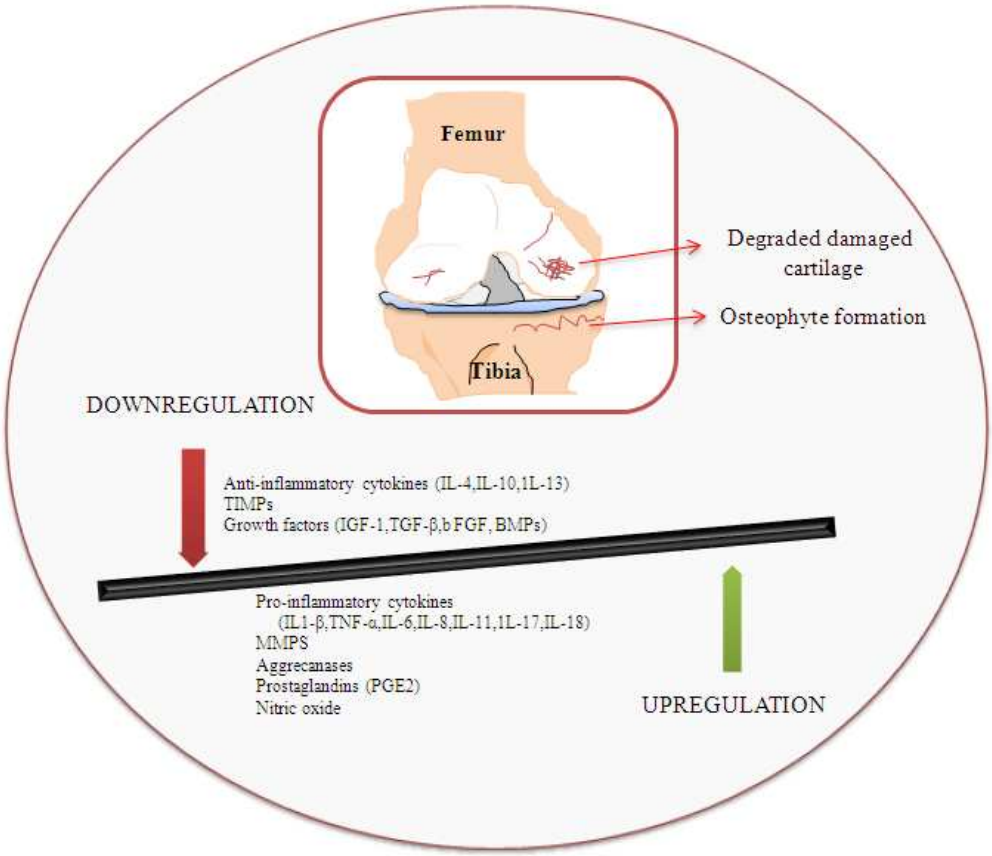

Figure 1. Pathophysiology of osteoarthritis knee.

The pro-inflammatory cytokines IL-1β and TNF-α activate mitogen activated protein kinase (MAPK), iNOS and nuclear factor κB (NFκB) pathways that ultimately lead to OA-related pathophysiology [8] including activation of MMPS (particularly, MMP-9, -13 and ADAMTS), COX-2, PGE_2, Lox5, LTB_4 and iNOS (Figure 2). All these cascade of events result into inflammation as well as swelling of the joints associated, apoptosis of chondrocytes as well as degradation of cartilage. Management of OA is primarily focused on alleviation of symptoms, using a combination of non-pharmacological and pharmacological interventions [9]. Such approaches have failed to prevent continued articular cartilage degeneration and have been often found to be associated with side effects. This has emphasized the need for safe and effective alternative treatments that would not only help to cure OA but would also prevent continued articular cartilage degeneration.

Recently, nutraceuticals and medicinal plants have become the focus of current medical research in the treatment/prevention of various diseases [10,11]. Nutrition has been shown to provide long-term rather than short-term health benefits with no adverse side effects. It could be used as an effective alternative to pharmacological intervention since the nutritive components could target multiple pathways involved in the pathogenesis of OA [12]. Besides nutrition, use of herbs/medicinal plants in the management of OA has been recently on the rise. Herbal medicine is the basis of various traditional medicine systems around the world. Plants are the source of ~25% of

currently used crude drugs, with another 25% obtained from chemically altered natural products [13]. The aim of the present article is to review the recent available literature on the current treatment modalities for OA with a special thrust towards the use of complementary and alternative medicine (CAM) including nutraceuticals and herbals in the management of OA.

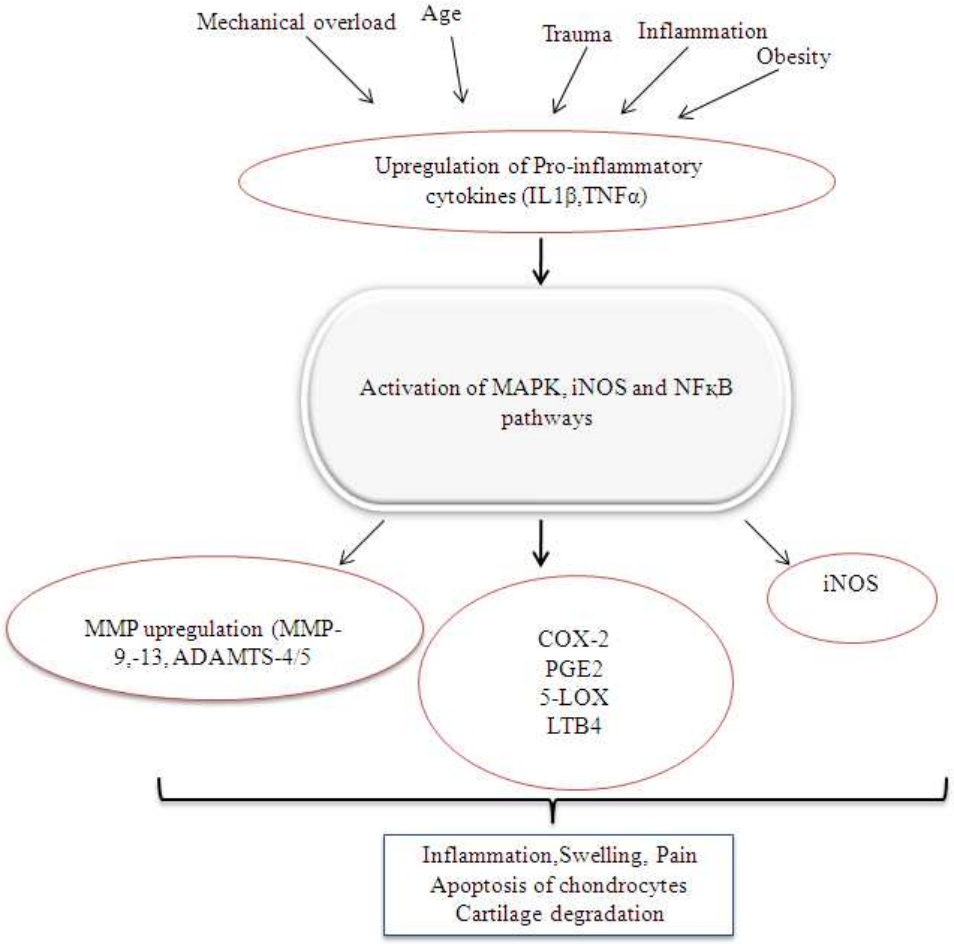

Figure 2. Molecular mechanisms underlying pathophysiology of osteoarthritis.

CONSERVATIVE APPROACHES IN THE MANAGEMENT OF OSTEOARTHRITIS

The current treatment options for the treatment of OA mainly aim at reducing the symptoms of pain and inflammation, maintenance of joint mobility and prevention of loss of function [14]. These options include a combination of non-pharmacological and pharmacological therapeutic modalities [15-17] (Figure 3).

Non-Pharmacological Intervention

Non-pharmacological approaches have been mostly recommended to combat pain in osteoarthritis. Such interventions do not involve drugs and thus could reduce drug consumption and toxicity or even could help in delaying the need for joint replacement surgery. Non-pharmacological interventions include patient education and self-management [14], exercise, weight reduction, acupuncture and physical therapy, the latter involving thermotherapy, transcutaneous electrical nerve stimulation (TENS) and short wave diathermy. Patient education is an important component of arthritic pain management. It has been proved that through lifestyle modification, particularly inclusion of exercise and weight reduction programs, it is possible to manage the arthritic pain [18,19]. Acupuncture is also used as an adjunctive therapy for pain relief in osteoarthritic patients [20,21]. Physical therapy is the backbone of OA treatment. It includes muscle strengthening programmes specific for certain joints and general aerobic conditioning [22]. These regimens have been shown to decrease pain and prevent disability in knee OA. Thermotherapy and sound wave diathermy that are a part of physical therapy have also been used for relieving the symptoms of osteoarthritis. TENS involves non-invasive safe nerve stimulation intended to relax the pain associated with osteoarthritis and has been shown to relieve the pain by almost by 50-67% in OA [23,24].

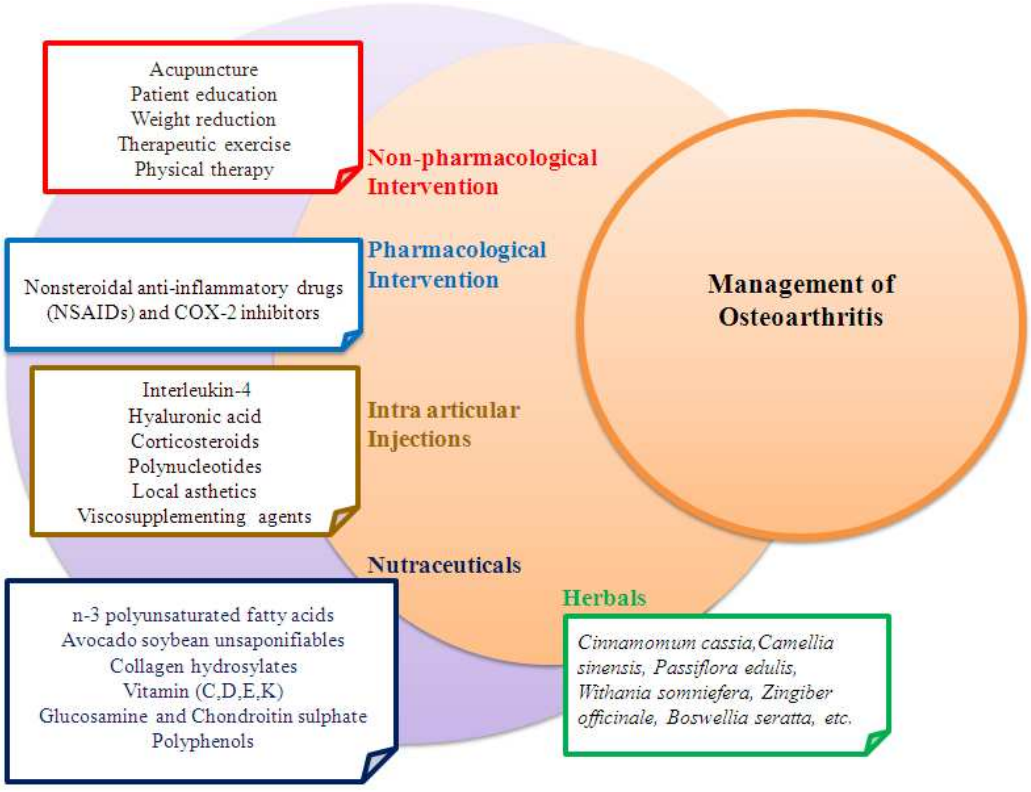

Figure 3. Treatment options in the management of osteoarthritis.

Pharmacological Intervention

The pharmacological management of OA mainly focuses on the relief of symptoms associated with OA. It has been mainly dominated by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics [25]. It also includes topical treatment and intra-articular therapy.

NSAIDs and analgesics

NSAIDs are effective analgesic and anti-inflammatory drugs that are mainly used in the treatment of OA related symptoms, the major one being the OA-related pain. Oral analgesic medications commonly used to reduce arthritic pain include acetaminophen, ibuprofen, diclofenac and intra-articular corticosteroids which are cyclooxygenase type 2 (COX-2) inhibitors [26]. Though NSAIDs provide short-term pain relief in OA, but there are several side effects associated with their long term use [27]. Excessive use of NSAIDs have been reported to be associated with upper and lower gastrointestinal harm, acute renal failure and congestive heart failure.

Topical treatment

Topical treatment is an additional treatment option and is available in the form of creams so that less drug is absorbed systemically into the body [28,29]. Topical treatment modalities include the use of capsaicin, topical lidocaine and topical nonsteroidal anti-inflammatory drugs (NSAIDs). The topical application of NSAIDs reduces adverse effects of oral drugs by maximizing local delivery while minimizing systemic toxicity.

Intra-articular therapy

Corticosteroids

Intrarticular injections of corticosteroids are being used frequently for the management of OA. These have been reported to show significant reduction in the pain and stiffness associated with hip osteoarthritis [30,31]. The major preparations include methylprednisolone acetate (MPA), triamcinolone hexacetonide (TAH), triamcinolone acetonide (TA), betamethasone acetate/betamethasone sodium phosphate (Celestone Chronodose) and betamethasone dipropionate/betamethasone sodium phosphate (Diprospan).

Interleukin-4

IL-4 is one of the anti-inflammatory cytokines and has been reported to inhibit the expression of inducible nitric oxide synthase (iNOS) mRNA as well as the production of nitric oxide (NO) by indirectly inhibiting the production and activity of pro-inflammatory cytokines IL-1β and TNF-α in synoviocytes [6,32-34]. IL-4 has also been shown to be chondroprotective *in vitro* [6].

Hyaluronic acid

Hyaluronic acid (HA) or hyaluronan is a linear polysaccharide found in extracellular matrix and is an important component of synovial fluid. It is essential for maintaining the viscoelastic properties of synovial fluid and acts both as a lubricant and shock absorber [35-37]. Intra-articular injections of HA are being approved worldwide for the treatment as well as for the viscosupplementation of the osteoarthritic joints [37-42]. Currently, only five FDA-approved injectable preparations of HA are

available for clinical use that include Synvisc®, Hyalgan®, Supartz®, Orthovisc® and Euflexxa® [38]. HA viscosupplementation has been found to decrease the concentration of inflammatory mediators such as prostaglandins, fibronectin and cyclic AMP37 [42-44]. HA has been reported to increase the synthesis of chondroitin sulfate and proteoglycans and decrease the expression of MMPs and ADAMTS in human chondrocytes [36,37,45,46]. Hyaluronan has also been shown to modulate the plasminogen activator (PA) system in articular joints that plays a key role in fibrinolysis, a major pathological condition associated with OA [36,47].

Polynucleotides

Polynucleotides isolated from natural sources (fish sperm) are effectively being used for the management of OA. These are composed of polymeric molecules which have the ability to bind to a large amount of water and to modulate the organization of water molecules to form a 3D gel-like network that can retain the moisturizing and viscoelastic properties of articular cartilage [48]. A clinical trial has reported intra articular polynucleotides to be more effective in relieving the pain in knee OA as compared to the hyluronan supplementation and could be a good alternative [48].

Inhibition of cartilage degradation

Matrix metalloprotease inhibitors

Matrix metalloproteases (MMPs) play a major role in the pathologic breakdown of the joint extracellular matrix in OA. A number of hydroxamic and non-hydroxamic acid containing compounds have been shown to have high potency for MMP inhibition. For example, an *in vivo* study has reported the potential of hydroxamate-based MMP inhibitors in inhibiting the activity of MMP-9 and -13 in a significant way [49,50].

Cytokine inhibition

In OA patients, chondrocytes produce increased levels of inflammatory cytokines, such as IL-1β and TNF-α. These cytokines decrease collagen synthesis and increase the expressison of MMPs and other inflammatory mediators, such as IL-8, IL-6, prostaglandin E2 and nitric oxide. In clinical trials, it has been shown that oral diacerein significantly improved the symptoms of patients with hip and/or knee OA [51-55]. Rhein, the active metabolite of diacerein has been shown to inhibit the synthesis and activity of IL-1β. Even though pharmacological approaches provide a short-term relief for the management of OA, but these have been criticized due to their failure to prevent continued articular cartilage degeneration. Moreover, certain NSAIDs, have led to an increased progression of osteoarthritic conditions due to inhibition of prostaglandins synthesis [56]. Thus, for the past few years, lot of research is being focussed towards alternative treatment options that include the use of nutraceuticals and herbals for not only the improvement of OA related pathology but also towards chondroprotection.

COMPLEMENTARY AND ALTERNATIVE MEDICINES FOR THE MANAGEMENT OF OSTEOARTHRITIS

Osteoarthritis therapeutic modalities mainly focus towards either pain or inflammation reduction. However, the focus should be more towards the prevention of cartilage degeneration as well as towards the regeneration of the cartilage. Recently, people are resorting towards CAM that mostly includes chondroprotective drugs, either in the form of nutraceuticals or in the form of herbals.

Nutraceuticals

The term 'nutraceutical' is coined from the combination of 'nutrition' and 'pharmaceutical'. It refers to food or food products that provide health and medical benefits in terms of prevention and/or therapy [57]. Nutraceuticals can protect the cartilage from oxidative damage caused by the generation of reactive oxygen species (ROS) [57,58]. A large number of nutraceuticals have been reported to be effective in the management of osteoarthritis that have been detailed out in this section (Table 1).

Table 1. Nutraceuticals used in the management of OA.

Nutraceuticals	References
n-3 polyunsaturated fatty acids (n-3PUFAs)	[14,59-63]
Glucosamine and chondroitin sulphate (CS)	[64-76]
Avocado soybean unsaponifiables (ASUs)	[14,77-80]
Collagen hydrosylates (CHs)	[14,81-85]
Vitamin D	[14,86-89]
Vitamin C	[89,90]
Vitamin E	[91]
Vitamin K	[89,92-94]
Polyphenols	[14,95-132]
Capsaicin	[133,134]
Jelly fish mucin	[135]

n-3 or omega 3 polyunsaturated fatty acids (n-3 PUFAs)

Omega 3 fatty acids are the essential fatty acids that our body cannot synthesize and are available in soybean and canola oils, flaxseeds, walnuts, and fish oils. Omega-3 fatty acids are known to modulate cellular signaling events, membrane protein function as well as gene expression [14,59]. Various studies have shown the anti-inflammatory effects of the polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and their role in cartilage metabolism [60]. They have been shown to reduce inflammatory mediators such as IL-1β, COX-2, 5-lipoxygenase (LOX) as well as the catabolic factors such as MMPs or ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) that contribute to the inflammatory cascades in osteoarthritis [61,62]. Recently, an *in vivo* study has reported the role of omega 3 in the regulation of osteoarthritis. Dietary intake of omega 3 increased the cartilage GAG content, reduced denatured type II collagen (NS), and reduced pro- and activated MMP-2 production, all indicative of reduced disease severity [59]. Clinical administration of omega-3 has also been found to reduce the stiffness and pain associated with osteoarthritis [63].

Glucosamine and chondroitin sulphate (CS)

Glucosamine, chondroitin sulphate (CS) and hyaluronic acid (HA) form the backbone of cartilage and synovial fluid. They are not only formed naturally by the body but can also be provided through dietary supplementation. Glucosamine is an aminosaccharide which acts as a preferred substrate for the biosynthesis of glycosaminoglycan and for the production of aggrecan and other proteoglycans [64]. Chondroitin sulphate is a major component of the extracellular matrix of many connective tissues, including cartilage, bone, skin, ligaments and tendons. CS, glucosamine sulfate (GS) or both together affect the major bone biomarkers, osteoprotegerin (OPG), receptor activator of nuclear

factor-kappa B ligand (RANKL) and the proresorptive activity of OA osteoblasts [65-67]. Glucosamine and CS have been shown to stimulate collagen synthesis and reduce the expression of iNOS, COX-2 and phopholipase-2, thereby inhibiting the inflammatory cascades at the molecular level [65-69]. Studies on humans have shown that CS supplements may have an effect in relieving pain and stiffness caused by arthritis [69]. Moreover, combination of glucosamine and chondroitin was shown to be effective in relieving pain in OA patients [70] in a Glucosamine/Chondroitin Arthritis Intervention Clinical Trial. Oral administration of glucosamine and intra-articular administration of n-acetyl glucosamine in knees of animals with experimentally induced osteoarthritis have also been demonstrated to reduce the progression of osteoarthritis lesions [67,71-76].

Avocado soybean unsaponifiables (ASUs)

These are derived from unsaponifiable residues of avocado and soybean oils. ASUs have been shown to promote the synthesis of anabolic factors that would normally feedback on the cell and will shut down the catabolic pathways [14,77,78]. These have been shown to reduce the expression of inflammatory mediators such as IL1-β, TNF-α, COX-2 and PGE_2 [78]. Moreover, clinical studies have revealed the disease modifying effects of ASUs in OA [79,80].

Collagen hydrosylates (CHs)

These are obtained by the process of enzymatic hydrolysis of collagen tissue present in the mammalian bone, hide or hide split. CHs are the main source of glycine and proline, the two essential amino acids that can regenerate and stabilize the damaged osteoarthritic cartilage [14,81-84]. *In vitro* studies have shown the role of CHs in stimulating the synthesis of extracellular matrix macromolecules by chondrocytes [85].

Vitamin D

It is known to play an essential role in calcium absorption by the body and helps to build cartilage and strong bones. Low serum levels of vitamin D have been shown to increase the progression of knee OA [14,86-88]. Deficiency of Vitamin D has been found to have adverse effects on calcium metabolism, osteoblast activity, matrix ossification and bone density [14,89].

Vitamin C

It is also known as ascorbic acid and has been shown to play an essential role in biosynthesis of cartilage molecules. Vitamin C participates in the synthesis of glycosaminoglycan as well as collagen. Its deficiency can impair the production as well as the biomechanical quality of cartilage [89]. Ascorbic acid serves as a cofactor for enzymes that are crucial in collagen synthesis. It has been shown that ascorbate and ascorbic acid increased the protein and proteoglycan synthesis by articular chondrocytes as well as the mRNA levels of type I and II collagen, aggrecan and α-prolyl 4-hydroxylase [90].

Vitamin E

Alpha-tocopherol or vitamin E is the only significant lipid-soluble, chain-breaking antioxidant present in plasma and red blood cells. The richest food sources of vitamin E are edible plant oils. In

OA, vitamin E has been found to decrease the synovial inflammation by blocking the formation of arachidonic acid from phospholipids and inhibit the lipoxygenase activity, without having much effect on cyclooxygenase. Vitamin E has also been reported to promote the synthesis of glycosaminoglycan, involved in synthesis of proteoglycans in cartilage [91].

Vitamin K

Vitamin K or phylloquinone plays an essential role in the synthesis of proteins involved in the regulation of bone metabolism [92]. Deficiency of vitamin K can result in abnormal cartilage and bone mineralization [93]. Vitamin K has been shown to inhibit apoptosis in chondrocytes and its role in chondrocyte development and maturation in OA has been reported [89,91,94].

Polyphenols

Polyphenols are important chemical constituents present in food, either vegetables or fruits. These are secondary metabolites of plants and have been found to possess excellent anti-inflammatory activities [14,95]. Polyphenols are generally divided into hydrolyzable tannins and phenylpropanoids such as lignins, flavonoids and condensed tannins. Several reports have suggested that due to their rich antioxidant potential, polyphenols could reduce bone loss in men and women [96-98]. Literature study has revealed the anti-inflammatory potential of a wide variety of polyphenols. Pycnogenol®, a standardized polyphenolic extract from the bark of the French maritime pine *Pinus pinaster* (family Pinaceae), has been studied for its anti-inflammatory, anti-oxidant as well as inhibitory effects on MMPs and iNOS [14,99,100]. It has been well-documented to relieve the OA-associated pain and physical stiffness in patients. Quercetin, a plant-derived flavonoid has been found to decrease the expression of TNF-α and monocyte chemoattractant protein-1 (MCP-1) in human synovial cells14. Its anti-inflammatory and anti-oxidant properties have been reported.

An *in vitro* study has investigated the anti-inflammatory effect of prodelphinidins (polymeric tannin found in the pomegranate and green tea leaves) on human chondrocytes [14]. The study showed that prodelphinidins have the potential to increase PG (proteoglycan) and type II collagen and inhibit PGE2 synthesis by acting on COX-2 [14,101]. Nobiletin, a citrus polymethoxyflavone, has been studied *in vitro* in synovial fibroblasts and articular chondrocytes. It was reported to inhibit the production of PGE_2, MMP-3, MMP-9, ADAMTS-4 and 5 in rabbit and human synovial fibroblasts [14,102-104]. Nobiletin was also shown to activate the MMP inhibitor, TIMP-1 in rabbit articular chondrocytes as well as to inhibit cartilage degradation. Epigallocatechin-3-Gallate (EGCG) is the major polyphenolic component of green tea. It has been shown to to inhibit the production of PGE_2, NO, COX-2 and iNOS as well as decrease the expression of MAPK and NFκB signaling pathways in osteoarthritic chondrocytes [14,105-115].

Resveratrol, a natural polyphenol present in grape skin and red wine, has been found to have anti-oxidant as well as anti-inflammatory properties. It has been demonstrated to inhibit MMPs, PGE2 and COX-2 and stimulate the synthesis of matrix components (PG, GAG, type II collagen), thereby preventing cartilage degradation [14,108,110,111]. Intra-articular injection of resveratrol in anterior cruciate ligament transaction OA model and LPS-induced arthritis model in rabbit showed its chondroprotective activity [116]. Curcumin, an active component of *Curcuma longa*, commonly known as turmeric, is used as a spice, flavoring agent, food preservative as well as a coloring agent. Curcumin has been extensively studied for its anti-cancer [117,118], anti-oxidant [119,120], anti-inflammatory [120] and analgesic activities. Its potential in OA has been widely studied *in vitro*. Curcumin inhibits the activation of NF-κB in human articular chondrocytes. Recently, the anti-apoptotic effect of curcumin on osteoarthritic chondrocytes has also been demonstrated. It has been

found to inhibit IL-1β, TNF-α, MMP-1, MMP-3, MMP-9, and MMP-13 as well as to restore the type II collagen and GAG synthesis [121-132].

Capsaicin

Capsaicin (8-methyI-N-vanillyl-6-nonenamide) is the pungent vanilloid found in red peppers [133]. It exerts its analgesic effect exhaustion of transmitters and desensitization resulting into silencing of the afferents. The efficacy of capsaicin cream has been reported in osteoarthritis, diabetic neuropathy and psoriasis at clinical level [134].

Jellyfish mucin (Qniumucin)

It is a glycoprotein isolated from jelly fish and clinical studies have demonstrated its potential to reduce the articular cartilage degeneration in OA [135].

Herbals used in the management of Osteoarthritis

Medicinal plants have been used from time immemorial for the prevention as well as treatment of various disease conditions. Currently, the research on herbals is at its peak and more attention is being focussed towards elucidation of molecular mechanisms underlying the action of herbal drugs. Some of the herbals that have been proven to be effective in the management of osteoarthritis alongwith their molecular targets have been discussed in table 2. *Harpagophytum procumbens* (devils' claw) belongs to the family Pedaliacea and is a plant found in Kalahari region of South Africa. Its main active compound is harpagoside that has been shown to inhibit the IL-1β induced production of MMP-1, MMP-3 and MMP-9 in human chondrocytes [136]. *Passiflora edulis* is a vine belonging to the family Passifloraceae and is widely grown in almost all parts of world. The antioxidant and anti-inflammatory properties in the bioflavonoids of *P. edulis* have been reported [137-141]. Plant flavonoid attenuates inflammation through inhibition of regulatory enzymes (lipoxygenase and cyclooxygenase) involved in arachidonic acid metabolism [141,142].

Table 2. List of herbals used in the management of osteoarthritis alongwith their molecular targets.

Medicinal Plants	Molecular Targets	References
Harpagophytum procumbens	MMPs (1,3,9)	[136]
Passiflora edulis	COX, LOX	[137-142]
Rosa canina	NO, PGE_2, IL-1β, TNF-α, MMPS (MMP 1,-3,-13)	[149-154]
Camellia sinensis	iNOS, NFκB, COX-2	[155,156]
Boswellia seratta	GAG (glycosaminoglycan)	[157-159]
Zingiber officinale	NFκB,COX-2	[160-164]
Uncaria tomentosa	NFκB, TNF-α	[165,166]
Emblica officinalis	GAG, Hyaluronidase and Collagenase type II inhibition activity	[167-171]
Withania somniefera	MMPs	[172-178]
Triphala guggulu	MMPs (1, 3 and 8), hyaluronidase and collagenase type-II inhibition activity	[176,179-184]
Willow bark	NO, TNF-α, IL-16	[186,187]
Punica granatum	MAPK, NFκB	[192-194]
Humulus lupulus	PEG_2, COX-2	[195-197]
Tripterygium wilfordii	COX-2, PGE2, MMP-3, MMP-13, AP-1, NFκB	[200,201]

Lonicera japonica is a Chinese herb belonging to the family Caprifoliaceae. Its flowers are of high medicinal value and have been found to have anti-bacterial [143] and anti-inflammatory [144] properties. The anti-nociceptive and anti-inflammatory activity of *L. japonica* in osteoarthritic animal models has been reported [144,145]. *Anemarrhena asphodeloides* is a Chinese herb belonging to the family Agavaceae. In traditional medicine, its rhizome is used as an anti-inflammatory [145], anti-diabetic [146] and antidepressant [147]. The anti-inflammatory as well as protective effect of *A. asphodeloides* in osteoarthritic cartilage has been reported [148]. *Rosa canina* belongs to the family Rosaceae and is widely cultivated in Europe, Northwest Africa and Western Asia. Hyben vital is a phytomedicinal preparation of rose-hip powder, the fruit from a subtype of *R. Canina*. Some reports have shown safety and efficacy of Hyben vital for the treatment of OA [149]. *R. canina* has also been reported to have anti-inflammatory and antioxidant properties [150,151]. It has been reported to inhibit the production of NO and PGE2 and reduce the secretion of cytokines (TNF-α, IL-1β), chemokines (RANTES) and various MMPs such as MMP-1, -3 and -13 in OA [152]. Several clinical studies have reported the use of *R. canina* in the management of OA pain [153,154].

Camellia sinensis is commonly known as green tea and belongs to the family Theaceae. It is available in the form of fresh or dried leaves and has been reported to inhibit iNOS, COX-2 as well as NF-kB pathways [155]. It has also been shown to inhibit cartilage degradation and provide protection to proteoglycans and collagen II. It has been shown to suppress the aggrecanases ADAMTS-1, -4, and -5 [156]. *Boswellia seratta* belongs to the family Burseraceae and is widely found in Rajasthan and Madhya Pradesh in India. It is a moderate-to-large branching tree found in India, Northern Africa, and the Middle East. Extracts of this gummy exudate have been traditionally used in the Ayurvedic system of medicine in arthritis [157]. *Boswellia seratta* extract has been shown to inhibit the glycosaminoglycan degradation thereby preventing the destruction of articular cartilage [158]. It has been shown to relieve the symptoms of OA in a randomized placebo-controlled trial in OA knees [158,159].

Zingiber officinale is commonly known as ginger, belonging to Zingiberaceae family, and is a very popular spice in cuisine. Ginger has been used traditionally in Japanese, Indian and Chinese medicine as an anti-inflammatory agent for musculoskeletal disorders [160]. Ginger extract has been shown to decrease IL1β- and LPS-induced production of NO and PGE_2 in osteoarthritic cartilage samples [161]. In synoviocytes, ginger has been shown to decrease the IL1β- or TNF-α-induced expression of TNF-α mRNA and protein as well as the expression of COX2 and NF-κB by reducing IκB [162,163]. Clinically, *Z. officinale* has been proven to be effective in reducing the symptoms associated with osteoarthritis [164]. *Uncaria tomentosa* (Cat's claw) is a medicinal plant from the Amazon River basin that has been used for the treatment of chronic inflammation, including arthritis by indigenous civilizations for centuries. Several *in vitro* and *in vivo* studies have demonstrated the role of cat's claw in inhibiting TNF-α and NFκB in OA [165]. Clinical studies have reported its use in improving the joint function in OA [166]. *Emblica officinalis* is also known as *Phyllanthus emblica* and belongs to Euphobiaceae family. It has been shown to exhibit immunomodulatory [167], anti-cancer [168], antiulcer [169] and antioxidant activities [170]. The chondroprotective activity of aqueous extract of *P. emblica* fruit powder has been reported wherein the extract was shown to strongly inhibit the activities of hyaluronidase and collagenase type 2 enzymes *in vitro* on human cartilage explants. Moreover, *P. emblica* fruit extract caused a statistically significant, long-term decrease in levels of glycosaminoglycans released from human cartilage explants in a subset of OA patients [171].

Withania somniefera is commonly known as *Ashwagandha* and belongs to the family Solanaceae. It has been reported to exhibit anti-inflammatory, antitumor [172], antistress [173], antioxidant [174], immunomodulatory, hematopoietic and rejuvenating properties [175,176]. It has been mentioned in the Indian Ayurvedic medicine as herbal tonic and health food with rejuvenating

properties. Among all the parts of this plant, the root has been considered to be most active for therapeutic purposes. The chondroprotective activity of aqueous extract of *W. somniefera* root powder has been reported wherein the extract was shown to strongly inhibit the activities of the gelatinase and collagenase type 2 enzymes *in vitro* on OA cartilage explants [176,178]. Moreover, *W. somniefera* root extract caused a significant decrease in levels of glycosaminoglycans released from human cartilage explants in a subset of OA patients [177]. *Triphala guggulu* is an ayurvedic formulation prepared through a combination of three powdered fruits, namely *Phyllanthus emblica* (amala), *Terminalia chebula* (haritaki) and *Terminalia belerica* (bibhitaki), *Commiphora wightii (guggulu*). It has been shown to possess anti-inflammatory [179], hypoglycaemic, anti-oxidant [180], anti-cancer [181], radioprotective [182] as well as anti-microbial [183] properties. *Triphala guggulu* has been reported to have chondroprotective activity [184]. It has been found to inhibit the activities of hyaluronidase and collagenase type 2 enzymes *in vitro* on OA cartilage explants [184].

Urtica dioica (Stinging nettle) belongs to the family Uricaceae and is widely found in European, Asian and African countries. It has been reported to have potent anti-inflammatory properties. Clinical studies have reported the use of *U. dioica* in providing mild to moderate relief in OA symptoms [185]. Willow bark belongs to the family Salicaceae is widely found in European, Asian and African countries. Willow bark has been reported to have potent anti-inflammatory properties. *In vivo* studies have demonstrated the potential of willow bark in reducing nitric oxide, TNF-α, IL-1β and IL-6 in OA [186]. Clinically, it has been proven to alleviate the symptoms associated with OA [187]. *Clerodendrum phlomidis* belongs to the family Verbinaceae and is widely found in some parts of South India. In the Indian system of medicine, it has been reported to have anti-inflammatory, anti-microbial and anti-flatulence properties [188,189]. *In vivo* studies have demonstrated the potential of *C. phlomidis* in reducing the swelling associated with OA [189]. *Perna canaliculus* (Green-lipped Mussel) belongs to the family Mytilidae and is widely found in New Zealand. It has been reported to have anti-inflammatory properties [190]. *In vivo* studies have demonstrated the potential of *P. canaliculus* in alleviating the pain associated with osteoarthritis [191].

Punica granatum belongs to the family Punicaceae and is widely found in Persia. It has been reported to have anti-oxidant and anti-inflammatory properties [192,193]. *In vitro* studies have demonstrated the potential of *P. granatum* in reducing the expression of MAPK and NFκB in OA chondrocytes [194]. *Humulus lupulus* (Common hop) belongs to the family Cannabaceae and is widely found in Northern hemisphere. It has been reported to have anti-oxidant and anti-inflammatory properties [195,196]. *In vivo* studies have demonstrated the potential of *H. lupulus* in inhibiting PEG_2 and COX-2 production in OA [197]. *Arnica Montana* belongs to the family Asteraceae and is widely found in Europe. It has been reported to have anti-inflammatory properties [198]. *In vitro* studies have demonstrated the potential of *A. montana* in reducing the symptoms associated with OA [199]. *Tripterygium wilfordii* belongs to the family Celastraceae and has been reported to have anti-inflammatory properties [200]. *In vitro* studies have demonstrated the potential of *T. wilfordii* in reducing the expression of COX-2, PGE_2, MMP-3, MMP-13, AP-1 and NFκB in OA chondrocytes [201].

Herbals with anti-inflammatory potential proposed for use in Osteoarthritis

Osteoarthritis is a chronic inflammatory disease and is the major cause of disability in the elderly population. Inflammation may be a primary event in osteoarthritis progression. It can occur around the affected joint leading to the oxidative stress as well as generation of reactive oxygen species (ROS) that may ultimately contribute to articular cartilage degradation as well as chondrocyte apoptosis. Considerable evidence suggests the role of cytokines IL-1β and TNF-α in OA that get upregulated in OA synovium and cartilage [202]. These induce a catabolic cascade of events

involving generation of high levels of arachidonic acid from damaged cell membranes by phospholipase A2 [203,204]. This is followed by further metabolism of arachidonic acid by COX-2 into the prostaglandins (PGs) and thromboxanes (TXA2). On the other hand, 5-Lox metabolizes arachadonic acid to Leukotienes (LTB4) (Figure 2). It has been shown that long-term inhibition of COX-2 could lead to a shunt to the 5-lipoxygenase (5-LO) pathway, leading to the formation of leukotrienes (LTs), which can induce gastric lesions and ulceration [204]. Although it is well known that PGE_2 is intimately involved in inflammation, byproducts of the 5-LOX pathway, more specifically LTB4, have been shown to play a direct pathogenic role in OA. It has also been found that in the synovial membranes of OA patients, LTB_4 upregulates the synthesis of the IL-1β and TNF-α as well as MMPs [205].

Non-steroidal anti-inflammatory drugs (NSAIDs) are used as the first line of treatment for the pain relief in OA. However, their long term use leads to various side effects that have drawn attention towards alternative treatment options. Thus, more research is being focussed towards identification of natural products that would not only target the inflammatory mediators in OA but would also prevent the further deterioration of the affected regions. In the previous section, we have enlisted herbals that have been specifically tested for OA, but a large number of plants have been investigated for their anti-inflammatory potential *in vitro* using macrophage and chondrocytic cell lines. These plants have been shown to modulate the inflammatory mechanisms via inhibition of key enzymes (COX, LOX), as well as pathways (MAPK, NFκB). In table 3, based on the available literature, we have attempted to enlist majority of medicinal plants that have been shown to exhibit anti-inflammatory potential by targeting various molecular mechanisms involved in the process of inflammation. Such plants could be explored further for their potential in the management of OA at clinical level.

Table 3. List of herbals shown to possess anti-inflammatory potential along with their molecular targets.

Medicinal plants	Molecular targets	References
Xiexin decoction	Nitric oxide, iNOS COX-2, pro-inflammatory cytokines(IL-1β,TNF-α), PGE2	[206]
Seabuckthorn	Nitric oxide, iNOS	[207]
Rhizoma coptidis	MCP-1/CCL2, AP-1, NFκB	[208]
Cudrania tricuspidata	Nitric oxide, iNOS COX-2, PGE2, pro-inflammatory cytokines (IL-1β, TNF-α)	[209]
Lilium lancifolium	Nitric oxide, iNOS COX-2, NFκB, pro-inflammatory cytokine (IL-6, TNF-α)	[210]
Jeju endemic seaweeds: *Acer pictum, Viburnum dilatatum, Melia azedarach, Lonicera japonica, Osmun japonica, Alnus firma, Lindera erythrocarpa, Platycarya strobilacea, Rhododendron werrichii, Weigela subsessilis, Salix koreensis, Magnolia kobus, Corylus sieboldiana, Cornus walteri, Ulmus parvifolia, Morus bombycis, Aria alnifolia, Neoshirakia japonica, Actinodaphne lancifolia, Triadica sebifera, Elaeagnus umbellata, Oenothera glazioviana, Ficus erecta* var. *sieboldii, Rubus buergeri, Orixa japonica, Cnidium japonicum*	Nitric oxide, iNOS	[211]
Laurencia okamurae, Grateloupia elliptica,	Nitric oxide, iNOS COX-2, NFκB,	[212]

Sargassum thunbergii, *Gloiopeltis furcata* and *Hizikia fusiformis*	PGE2, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)	
Dioscorea batatas	Nitric oxide, iNOS, NFκB, ERK1/2	[213]
Acanthopanax senticosus	Nitric oxide, iNOS, NFκB	[214]
Glycyrrhiza glabra	Nitric oxide, iNOS, NFκB, COX-2, pro-inflammatory cytokines (IL-1β, IL-6)	[215]
Cinnamomum cassia, *Cinnamomum zeylanicum*	TNF-α, Nitric oxide, iNOS COX-2, PGE2	[216]
Pleurospermum kamtschatidum	TNF-α, Nitric oxide, iNOS COX-2, PGE2, NFκB	[217]
Dictyota dichotoma	Nitric oxide, iNOS COX-2, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)	[218]
Alpinia officinarium	pro-inflammatory cytokines (IL-1β, IL-8, TNF-α), TLR2	[219]
Daphne genkwa	Nitric oxide, COX-2, PGE2, NFκB	[220]
Chrysopogon aciculatis	Nitric oxide, iNOS, COX-2, PGE2, NFκB, JNK/p38 MAPK	[221]
Sargassum micracanthum	Nitric oxide, iNOS, COX-2, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)	[222]
Citrus reticulata	Nitric oxide, iNOS, NFκB	[223]
Phellinus linteus	Nitric oxide, iNOS, MAPK(JNK)	[224]
Vietnamese oriental medicine: *Crinum latifolium*, *Evodia rutaecarpa*, *Polygonum cuspidatum*, *Perilla ocymoides*, *Rubia cordifolia*, *Scutellaria barbata*, *Sparganium stenophyllum*	NF-κB	[225]
Mume fructus	Nitric oxide, PGE2, IL-6, iNOS, COX-2, p38 MAPK	[226]
Moutan cortex	Nitric oxide, PGE2, iNOS, COX-2, p-IkB, NFkB, TNF-α, IL-1β, IL-6	[227]
Pistacia terebinthus	LTB4, 5-LOX	[228]
Artemisia copa	PGE-2, COX-2	[229]
Capparis spinosa	PGE-2	[230]
Juniperus communis	PG release	[231]
Hypericum perforatum	5-LOX	[232]
Humulus lupulus	PGE-2	[233]
Salvia aethiopis	5-LO	[234]
Rosmarinus officinalis	COX, LOX	[235]
Plantago lanceolata	Nitric oxide, COX-2, PGE-2	[236]
Scrophularia auriculata	iNOS, COX-2, PGE-2	[237]
Smilax china, *Smilax glabra*	IL-1β, TNF-α, NO, COX-2	[238]
Physalis peruviana	Nitric oxide, iNOS, COX-2, PGE-2	[239]
Pinus sylvestris	Nitric oxide, iNOS, COX-2	[236]
Plantago lanceolata	Nitric oxide, iNOS, COX-2	[240]
Daphne oleoides	IL-1β, IL-1α, TNF-α	[241]
Medicago sativa (alfalfa sprouts)	TNF-α, IL-6, IL-1β, NFkB	[242]
Aloe vera	Nitric oxide	[243]
Chrysanthemum indicum	IL-1β, TNF-α	[244]
Sophora flavescens	iNOS, COX-2, PGE-2	[245]
Eucalyptus globules	iNOS	[246]
Tanacetum parthenium (Feverfew)	PGE-2, TNF-*α*, IL-2, IFN-*γ*, IL-4	[247]
Commiphora myrrha	PGE-2	[248]

Silybum marianum	iNOS, COX-2	[249]
Pimpinella corymbosa	NFkB	[250]
Physalis alkekengi	NFκB (IKKβ)	[251]
Silybum marianum	TNF-α, TGF-β, MAPK (JNK)	[252]
Ocimum sanctum	Nitric oxide, iNOS, IL-1β, TNF-α	[253]
Cymbopogon giganteus	Prostaglandin H synthase (PGHS), 5-LOX	[254]

CONCLUSION AND FUTURE PERSPECTIVES

OA is a heterogeneous group of skeletal disorders characterized by common structural and functional changes in overall joint tissues, including cartilage loss, synovium inflammation and bone sclerosis and is associated with chronic pain. The etiology of OA is multifactorial and current research attributes it to a complex network of biochemical factors such as proteolytic enzymes, cytokines, chemokines, and adhesion molecules [6,8]. Even though OA is the most common type of arthritis encountered worldwide, the development of effective disease-modifying treatments has lagged behind compared to other types of arthritis. The current modalities for treating arthritis are symptomatic and have not been shown to recover the cartilage degradation and joint destruction. Despite some relief offered by current anti-inflammatory treatments for OA, the side effects associated with these treatments, particularly the COX-2 specific NSAIDs, are becoming increasingly recognized [27]. Thus alternative methods of treatment that include nutraceuticals and complementary medicines have come to the forefront in the recent times that offer better options for the management of OA. Moreover, the elucidation of underlying molecular mechanism(s) for the anti-inflammatory and chondroprotective activity of nutraceuticals and medicinal plants would authenticate their use for health benefits and may help to develop new and better modalities for treating degenerative and inflammatory joint diseases.

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