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Evidence-based nutraceuticals for osteoarthritis: A review

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Abstract

Osteoarthritis (OA) is a major cause of disability worldwide. Alternative treatments are preferred due to the cardiovascular and gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs). Nutraceuticals help in balancing anabolic and catabolic processes in the joint tissue, improve redox balance, free-radical scavenging, thus provide cartilage protection. The anti-inflammatory, chondroprotection and antioxidant action of nutraceuticals help in the modification of OA pathophysiology and prevent destruction of articulate cartilage. In this current review, we have highlighted many existing nutraceuticals that have good efficacy, safety & easy accessibility.

Keywords: osteoarthritis, nutraceuticals, anti-inflammatory, chondroprotection, antioxidant

Introduction

Osteoarthritis (OA) of the knee is a major cause of disability in older adults worldwide, with a prevalence of 28.7% in India. It affects the hands, feet, spine, and large weight-bearing joints, such as the hips and knees. Elderly, women, obesity, sedentary people and heavy lifting are few risk factors associated with OA of the knee [1, 2]. The onset of OA is a consequence of synovial inflammation influenced 5-lipoxygenase (5-LOX) pathway, proinflammatory cytokines and matrix metalloproteinases (MMPs) enzymatically degenerate cartilaginous matrix substances thereby aggravating the condition [3-5]. Failure of NSAIDs, viscosupplementation and intra-articular corticosteroids and other non-pharmacological interventions is attributed to a lack of efficacy and more adverse effects [6-9]. Alternative treatments are preferred due to the cardiovascular and gastrointestinal side effects of NSAIDs [10]. The ideal treatment should consist of therapeutic agent with capacity to modify natural pathophysiology of OA and modify destruction of articular cartilage. Nutraceuticals are described as food substances with medical & health benefits accompanying disease modifying action without any serious side effects. Nutraceuticals have a broad mechanism by inhibiting TNF- α , IL-1 β , MMPs, NO, COX and caspases whereas NSAIDs only block arachidonic acid pathway and inhibit release of Cyclooxygenase [11].

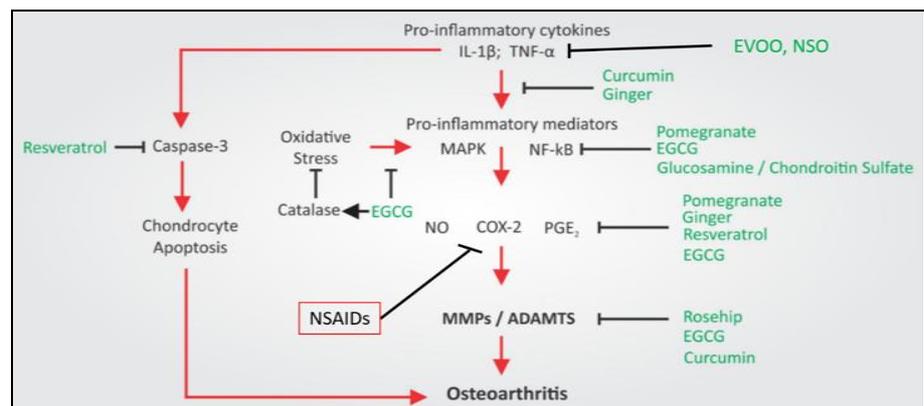


Fig 1: Mechanism of nutraceuticals in osteoarthritis [12]

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The objective of current review is to understand pathophysiology of OA and evaluated the efficacy and safety of nutraceuticals in their management.

Omega-3 fatty acid

Fish oil consists of omega-3 fatty acids, the most important ones being eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which are responsible for the variety of health benefits. Different *in vitro* & *in vivo* studies on fish oil displayed dose dependent decrease in inflammatory induced destruction of cartilage tissue. The mechanism of anti-inflammatory action involves competition of anti-inflammatory molecule resolvins; competition with receptors of pro-inflammatory molecules; interference in inflammatory signaling pathway; decline in lymphocyte proliferation; & gene expression of cyclo-oxygenase-2, cytokines [13].

Clinical evidence: A randomized double blind clinical trial was conducted to compare efficacy of high dose & low dose of fish oil in 202 patients with knee osteoarthritis. At the end of the study, low dose fish oil found to be more efficient than high dose fish oil in terms of WOMAC score & functional score [14]. More clinical studies are required to support the use of fish oil in treatment of OA.

Olive Oil

Phenolic compounds & monounsaturated fatty acids (MUFAs) are the bioactive ingredients of olive oil responsible for anti-inflammatory action. Preclinical studies showed improved cartilage recovery in olive oil fed rats after anterior cruciate ligament transection [15].

Clinical evidence: In a randomized, double blind clinical trial, olive water extract evaluated for 8 weeks and found significant improvement in terms of Health assessment questionnaire disability index & disease activity score with 28-joint count index [16]. Furthermore, the study was performed on Female (40-85 years) Iranian OA patient to examine effect of topical application of olive oil in comparison to 1 gm of piroxicam gel (0.5%). Piroxicam & olive oil decreased WOMAC score but olive oil found superior in the treatment after second week of treatment. The study had a high dropout rate, but rate was not significant between treatment and control group. In addition, the study was performed for short duration therefore long-term effect of olive oil needs to be evaluated further [17].

Methionine

Also known as essential amino acid as it is not synthesized inside the body & therefore needs to be consumed through diet. S-adenosylmethionine (SAME) which is active form of methionine has antioxidant properties & provides antioxidant enzyme glutathione peroxidase in the joint [18, 19]. Furthermore, SAME also inhibits the enzyme system which degrades cartilages thereby protects proteins and proteoglycans. Research studies displayed that SMEs regulate cartilage regeneration by promoting anabolic process of cartilage [20].

Clinical evidence

The long-term use of SAME have produced more prominent effect in OA patients than NSAIDs [21]. Also, OA patients with liver & kidney disease have difficulty in methionine activation but supplementation with SAME proved to be effective [22]. The effect of methionine for symptomatic

management of OA was evaluated in double blind cross over study involving sixty-one patient. The study compared of methionine (200mg) & celecoxib (200mg) for pain control, functional improvement & reduced side effects. Methionine displayed slower onset of action, but efficacy is similar to celecoxib in terms of pain reduction, improvement from the baseline & joint function test. However longer duration study required as onset of methionine action was allow compared to celecoxib [23]. Konig B 1987 performed a long term (24 months) multicenter trial to evaluate efficacy & tolerance of methionine in 108 OA patient. Methionine was well tolerated and showed good clinical efficacy in OA patient. Non-specific side effects occurred in 20 patients were disappeared during the therapy [24]. The clinical data suggest the use of methionine in the management of OA, however more clarity needed to understand molecular mechanism.

Undenatured Type II Collagen

It's a nutritional supplement derived from sternum cartilage of chicken which increases mobility & functionality of joints with reduced pain in OA patient. [25, 26] It affects humoral and cellular immune response through T-cell thereby secreting cytokines which constrain response to collagen type II present in articulate cartilage. Undenatured type II collagen thereby inhibits over-reaction of pro-inflammatory immune system I OA patients [27, 28]. Despite of its efficacy in OA as it reduces pain and block inflammatory markers, still further investigation is recommended for safe use in human.

Curcumin

Curcumin is a polyphenol extracted from curcuma longa (Turmeric) known for its anti-inflammatory action since ancient time [29]. Curcumin exerts its anti-inflammatory action by interaction with NF-kB signaling pathway & reduces expression of inflammatory markers such as IL-1 β , TNF-alpha, COX-2 and MMP [30]. Furthermore, Curcumin upregulates the production of collagen-II and decreases MMP13 expression, thus inhibiting NF-kB pathway [31, 32]. Curcumin also exert its anti-inflammatory and antioxidant effect by acting on pathways involving reactive oxygen species, Nrf2 and its target genes such as superoxide dismutase (SOD2), HO-1, and glutamate cysteine ligase catalytic subunit. It also promotes autophagy by attenuating Akt/mTOR pathway leading to reduced apoptosis and matrix degradation [33].

Clinical evidence: Safety & efficacy of curcumin in OA was compared with diclofenac in a randomized open label study. At the end of study, patient receiving curcumin exhibited similar improvement to that of diclofenac in pain & Knee Injury and Osteoarthritis Outcome Score. In addition to that, none of the curcumin treated patient required H2 blockers. Also, low side effects were observed in curcumin group when compared with diclofenac. The study suggest curcumin can be used as an alternative treatment in OA patient with side effects of NSAIDs [34]. In another study, Horyan *et al.* 2018 evaluated combination of curcumin & boswellic acid extract in 201 OA patients. After 12-week study, combination found to be effective in pain reduction & improves physical function of participants [35].

Quercetin

It is a circulating aglycone form of rutin widely available in vegetables with strong ROS scavenging activity [36]. The Chinese traditional medicine identified quercetin as herbal

treatment in OA patient. Different *in vivo* studies evaluated the role of quercetin in OA & found beneficial by both routes using topical application as well as oral supplementation. [37, 38] The polyphenols act by promoting mitochondrial biogenesis and efficiency by improving potential of membrane, oxygen consumption, ATP production, glutathione levels & decreasing oxidative stress. These effects found to be mediated by phosphorylation of AMPK & increased expression of SIRT-1 which leads to attenuation of ER stress in rat OA models thereby improves maintenance of cartilages & chondrocyte survival. [39] Quercetin also found to reduce accumulated synovial M1 macrophages which endure OA exacerbation in human and animal. [40] Furthermore, quercetin also improves TGF- β and insulin like growth factor expression which stimulate prochondrogenic environment & CAF synthesis in chondrocytes thereby improves repairing capacity of cartilage [41].

Glycosaminoglycans (CAGs)

Chondroitin Sulfate (CS), Glucosamine Sulfate (GS) and hyaluronic acids are glycosaminoglycans (CAGs) produced by chondriocytes and synoviocytes and are vital component of extracellular matrix and synovial fluid. Growing evidence suggest that supplementation with CAGs protects joints from trauma or wear and ultimately protect from OA progression. Supplementation with glucosamine sulfate stimulate cartilage regeneration along with improvement in joint function and reduces pain which help in OA treatment. [42] Although not all clinical papers are in favor of beneficial role of glucosamine in OA but large number of studies revealed that its low toxicity makes it able option in the treatment of OA [43].

Clinical evidence: In a randomized controlled trial, glucosamine sulfate & chondroitin sulfate improved catabolic & degenerative process in OA patient owing to their antioxidant & anti-inflammatory action [44, 45]. Jackson *et al.* in a pharmacokinetic study evaluated synergistic effect of glucosamine & chondroitin and found that both has no synergistic effect as they compete for intestinal absorption. Therefore, different time is used for ingestion of these two CAGs depend on individual clinical cases [46]. Glucosamine sulfate & chondroitin sulfate improves pain and stiffness in OA patient when administered with fish oil containing n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [47-49]. Another CAGs, hyaluronic acid have showed beneficial effect in joint pain. During *in vitro* study hyaluronic acid improved mechanical properties of synovial fluid. It is generally used as local injection into the joint which reduces pain and improves function of OA patient. [50, 51] Clinical evidence suggests the efficacy of CAGs in the OA treatment, however further investigation is required to understand its anti-inflammatory action at the molecular level. The safety & efficacy of chondroitin sulfate (400 mg) & glucosamine hydrochloride (500 mg) was evaluated in knee osteoarthritic patient for 6 months. Combination possess similar potency as that of celecoxib (200 mg) & reduced joint swelling, pain, stiffness in OA patient. The combination has comparable efficacy to celecoxib with excellent safety profile [52]. In another two-year randomized follow-up study, 605 knee OA patients were evaluated for reduction in joint space narrowing (JSN) and pain after administration of glucosamine sulfate & chondroitin sulfate combination. These dietary supplements when administered in combination found to be effective significantly in reduction of JSN [53].

Wogonin

It is O-methylated flavone obtained from *Scutellaria baicalensis* and used in Chinese traditional medicine in the treatment of different disorder. Anti-inflammatory action of wogonin evaluated and found to be useful in reduction of MMP-3 expression in IL-1 β treated articular chondrocytes. [54] It also suppresses IL-1 β induced activator protein-1 (AP-1) thereby controls chemokine expression [55]. Wogonin also have ability to reduce reactive oxygen species generation in OA chondrocytes and induces Nrf2 and enzymes involved in antioxidant pathways [56]. From *in silico* molecular docking study, it was observed that wogonin intercalates between guanine & cytosine bases as ethidium bromide and prevents denaturation of DNA and contribute to DNA stability [57]. This evidence has been evaluated for topical application of wogonin in DMM mouse model of OA and found that topical wogonin improves joint health by reducing pathological scores which is mediated through MMP-13, NF-kB [58]. More extensive long term clinical trials are required to determine safety & efficacy of wogonin in human.

Botanical extracts

Various botanical extract and their active components possess anti-inflammatory action and are currently evaluated for their action in OA.

Avocado & soybean

Avocado/soy unsaponifiable (ASU) components of avocado & soybean possess anabolic as well as anti-inflammatory on chondrocytes. *In vitro* studies revealed ASU blocks inflammatory cytokines such as IL-1, IL-8, IL-6 and prostaglandin E2 [59]. It also helps in stimulation of growth factor production, synthesis of collagen and aggrecan. Daily administration of 300 mg of ASU improves OA symptoms, however further study required for better understanding of its mechanism in OA [60].

Green tea

It is non-fermented & one of the most consumed hot beverage which mainly consists of catechin, a powerful antioxidant. Polyphenols such as Epigallocatechin-3-gallate (EGCG) present in green tea significantly decreases advanced glycation end products responsible for pro-inflammatory responses in chondrocytes [86, 87]. EGCG also prevents expression of TNF-alpha, NF-kB, MMP-13 and proved its ability of inhibition of inflammatory response of OA by modulating RNA expression [63]. Currently sufficient data is available for green tea's action as an anti-inflammatory & anti-arthritis agent in preclinical model however further clinical research required to establish its efficacy in OA treatment.

Clinical evidence: Green tea is a dietary supplement and novel functional food with high polyphenol contents responsible for anti-inflammatory & bone repair action. The safety & efficacy of green tea extract was evaluated in 50 patients of OA & found significant reduction in VAS pain, total WOMAC & WOMAC physical function score [64].

Boswellia

Boswellia showed efficacy against different disease like cancers, inflammatory, wound healing etc. It is a gum resin extracted from *Boswellia serrate* & possess potent anti-inflammatory, analgesic & anti-arthritis activity [65]. Studies revealed that 3-O-Acetyl-11-keto-beta-boswellic acid

(AKBA) which is active constituent of Boswellia extract inhibit 5-lipoxygenase and associated cellular inflammatory reactions. It also inhibits generation of pro-inflammatory cytokines which are involved in the process of cartilage damage. [66] In another study, Blain *et al* showed that Boswellia not only reduces MMP-9 & MMP-3 mRNA levels but also inhibit expression of MMP9. Furthermore, Boswellia also decreases production of nitrite, prostaglandin E2 and cyclooxygenase-2 [67]. The novel Boswellia extract called as 5-Loxin consists of 30% of 3-O-acetyl-11-keto-beta-boswellic acid (AKBA) found efficient and safe in OA patient. It significantly reduced MM-3 of synovial fluid in OA patient. [68] Belcaro G *et al.* found that in OA patient WOMAC score for pain, stiffness and physical function is significantly improved after 4 weeks in Boswellia group when compared with control [69]. In randomized double blind controlled study, 5-Loxin & Aflapin from Boswellia showed substantial improvement in pain and physical function of OA patient [70]. *In vitro* and *in vivo* clinical evidence encourages the use of Boswellia still existing data suggest further investigation.

Ginger

Ginger possess anti-inflammatory activity which helps in treatment of OA by reducing inflammatory markers such as nitric oxide and C-reactive protein [71]. Ginger supplementation along with diclofenac found efficient than individual treatment in OA patient [72]. In another study, Amorndoljai *et al* evaluated topical application of ginger and showed efficacy in relieving joint pain and improves quality

of life in patient [73]. Furthermore, ginger also improves pain relief in patient who demonstrated poor response to NSAIDs. [74] Current data suggest that ginger extract have limited efficacy, but results obtained from them are strong enough to encourage & support further evaluation in OA treatment.

Clinical evidence: Ginger is an ancient medicinal plant native to Asia & used in the treatment of different disease. Mozaffari-Khosravi *et al.*, 2016 investigated effect of ginger powder on proinflammatory factors of OA patient in 3 months randomized double blind placebo-controlled trial. Serum levels of proinflammatory cytokines such as TNF- α & interleukin-1 β found to be reduced at the end of the study. However, further investigation was recommended for evaluation of ginger in OA [72].

Harpagophytum procumbens (Devils Claw)

A South African plant Harpagophytum procumbens known as devils claw contains harpagosides-triterpene glycoside which found to be effective in reduction of IL-1 β induced production of metalloproteinases (MMP-1, MMP-3 and MMP-9) in chondrocytes also down regulate TNF-alpha and COS-2 gene expression [75, 76]. Devils claw extract when used as dietary supplement in the treatment of hip & knee OA patient found to be effective with low adverse effects such as diarrhea and flatulence [77, 78]. For further use, high quality clinical trials are required to determine the efficacy and safety of devils claw.

Table 1: Clinical trials of nutraceuticals in Osteoarthritis patient

Nutraceutical	Dose & comparator	Design & duration	Results	Reference
Fish oil	high-dose fish oil (4.5 g omega-3 fatty acids) 15 mL/day or low-dose fish oil (blend of fish oil and sunola oil; ratio of 1:9, 0.45 g omega-3 fatty acids) 15 mL/day	DB 24 months	Greater improvement WOMAC score & function score in OA patient with low dose	Hill C.L. <i>et al.</i> , [14]
Olive oil	400 mg of olive oil	DB 8 weeks	decreased pain and improvement in activities of daily living	Bitler C. M. <i>et al.</i> , [16]
	Topical olive oil & piroxicam gel	DB 4 weeks	WOMAC score improved in olive oil group after 2 weeks compared to piroxicam	Bohlooli <i>et al.</i> , [17]
Methionine	Methionine 200 mg & celecoxib 200 mg	DB 16 weeks	Pain reduction, improvement from baseline	Naim <i>et al.</i> , [22]
	Methionine (200 +400 mg)	MC 24 months	Well tolerated & good clinical efficacy	Konig, 1987. [24]
Glycosaminoglycans	chondroitin sulfate (400mg) plus glucosamine hydrochloride (500mg) & 200 mg celecoxib	DB; MC 6 months	Reduces pain, stiffness, joint swelling	Hochbers <i>et al.</i> [52]
	glucosamine sulfate & chondroitin sulfate	DB 2 years	reduced joint space narrowing (JSN) and pain	Fransen <i>et al.</i> , [53]
Curcumin	Curcumin 500 mg& diclofenac 50 mg	DB 28 days	Similar efficacy & better tolerance	Shep <i>et al.</i> , [34]
Curcumin & Boswellic acid	350 mg curcuminoids and 150 mg boswellic acid	Phase II 12 weeks	Improved WOMAC joint pain index	Haryon <i>et al.</i> , [35]
Green tea	Green tea tablet 1500 mg & diclofenac 100 mg/day	R; open-label 4 weeks	reduction in VAS pain, total WOMAC & WOMAC physical function score	Hashempur <i>et al.</i> , [64]
Ginger	Ginger 500mg/day	Double blind; 3 months	Reduced pro-inflammatory markers	Niempoog <i>et al</i> 2012

Table 2: Pharmacological actions of nutraceutical in Osteoarthritis (Action: none “-”, Low “+”, Moderate “++”, High “+++”)

Nutraceuticals	Potential role					References
	Anti-inflammatory	Anti-Oxidant	Anabolic	Anti-catabolic	Structural substrate	
Fish oil	+++	-	-	+++	++	[13, 19]
CAGs	+	+	++	+++	+++	[42, 44]
Olive oil	+++	++	+	-	+	[15, 19]
Methionine	-	+++	+	+	++	[18, 20]
Undenatured collagen	+	-	+	+++	+++	[25, 26]
Curcumin	++	+++	+	+	+	[40]
Quercetin	+	+++	-	-	+	[39,40]
Wogonin	++	+++	-	-	++	[56, 57]
Botanical Extracts						
Avocado/soy unsaponifiables (ASU)	+++	+	-	-	++	[59, 60]
Green Tea	++	+++	-	-	+	[62, 63]
Boswellia	+++	++	-	-	++	[67, 68]
Ginger	++	+	-	-	+	[71, 74]
Devils Claw	++	++	+	+	++	[76, 78]

Conclusion

The efficacy of nutraceuticals in OA is attributed to their anti-inflammatory, antioxidant, immunomodulatory and chondroprotective action. Nutraceuticals discussed in this current review are beneficial for relieving joint pain and improving quality of life. Scientific validation from different studies demonstrate that nutraceuticals not only improve clinical symptoms but also slowdown progression of disease. Healthcare professionals must be made aware about the evidence-based efficacy and safety of certain nutraceuticals for OA. Due to their good efficacy and safety profile, nutraceuticals may be used in combination with conventional therapy for the management of OA.

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