Nutritional Interventions to Prevent and Treat Osteoarthritis. Part II: Focus on Micronutrients and Supportive Nutraceuticals

Hector L. Lopez, MD

Abstract: Osteoarthritis (OA) is the most common cause of musculoskeletal disability in the elderly, and it places an enormous economic burden on society, which will remain a major health care challenge with an aging population. Management of OA is primarily focused on palliative relief using agents such as nonsteroidal anti-inflammatory drugs (NSAID) and analgesics. However, such an approach is limited by a narrow therapeutic focus that fails to address the progressive and multimodal nature of OA. Given the favorable safety profile of most nutritional interventions, identifying disease-modifying pharmaconutrients capable of improving symptoms and also preventing, slowing, or even reversing the degenerative process in OA should remain an important paradigm in translational and clinical research. The goals of pharmaconutrition for metabolic optimization are to drive biochemical reactions in a desired direction and to meet health condition–specific metabolic demands. Applying advances in nutritional science to musculoskeletal medicine remains challenging, given the fluid and dynamic nature of the field, along with a rapidly developing regulatory climate over manufacturing and commerce requirements. The purpose of this article is to review the available literature on effectiveness and potential mechanism for OA of micronutrient vitamins; minerals; glycosaminoglycans; avocado-soybean unsaponifiable fractions; methylsulfonylmethane; s-adenosylmethionine; undenatured and hydrolyzed collagen preparations; phytoflavonoid compounds found in fruits, vegetables, spices, teas, and nuts; and other nutrients on the horizon. There also is a discussion on the concept of rational polysupplementation via the strategic integration of multiple nutraceuticals with potential complementary mechanisms for improving outcomes in OA. As applied nutritional science evolves, it will be important to stay on the forefront of proteomics, metabolomics, epigenetics, and nutrigenomics, because they hold enormous potential for developing novel therapeutic and prognostic breakthroughs in many areas of medicine, including OA.

PM R 2012;4:S155-S168

INTRODUCTION

The growing incidence of osteoarthritis (OA) creates an enormous economic burden, with direct and indirect costs related to medical management, rehabilitation, arthroplasty, and lost occupational productivity as a result of functional disability [1]. Nutritional interventions and nutraceutical applications for medical conditions, including OA, are currently riding the crest of public enthusiasm. The medical community must be familiar with the current state of the science to evaluate the potential benefits of nutritional methods for preventing and treating OA. The integration of complementary and/or nutraceutical methods expands treatment options for patients with established OA beyond the traditional rehabilitation, bracing, medications, interventional, and surgical strategies [2]. The progression of OA is multifocal, with biomechanical, metabolic, epigenetic, and genetic risk factors; therefore, the most effective outcomes may stem from integrating a comprehensive multimodal treatment program early in the disease process [3]. The increasing incidence and high prevalence of OA creates an opportunity to develop and use relatively low-cost nutraceutical alternatives, with the potential for additional health benefits for other conditions and organ systems. Evidence from higher-quality scientific studies is beginning to emerge, which
documents both the usefulness and limitations associated with various nutritional strategies for OA [4].

In part I of this 2-part review on nutritional interventions in OA, the role of fatty acids in OA was explored. It involves a complex interplay between inflammatory mediators, redox balance, anabolic and catabolic signaling within the synovium, synovial fluid, and the articular cartilage matrix [3,5]. Nutritional strategies have been used effectively in the management of rheumatoid arthritis (RA) to improve clinical outcomes and biomarkers of disease [6]. Given the overlap in the molecular and cellular pathomechanisms between RA and OA [7], it is clear that nutrition may also play a vital role as an adjunctive therapeutic tool in the prevention and ongoing management of OA.

There are more than 40 dietary micronutrient vitamin compounds and mineral elements considered essential in the human diet [8]. These compounds and elements control enzymatic reactions for energy metabolism and biosynthesis of nucleic acids, proteins, and fats essential for cellular and tissue structural integrity and turnover [9]. Among their diverse roles, it is their function in tissue turnover and regulation of oxidative stress that are most critical for maintaining joint structure and health [4]. There also are other dietary compounds, known as nutraceuticals, which have emerged as playing a supportive role in the balance of anabolic and catabolic signals within articular cartilage [4]. This review focuses on micronutrients and nutraceutical compounds that may play a role in metabolic optimization for the preventive or therapeutic management of OA (Figure 1). As the evidence base that supports the use of nutritional and metabolic optimization in musculoskeletal medicine continues to develop, physicians will be better able to serve their patients by judiciously integrating nutritional intervention into their treatment armamentarium.

VITAMINS AND MINERALS IN OA

Micronutrient Vitamins in OA

Vitamins play a vital role in normal enzyme function to regulate oxidative stress and to support chondrocyte metabolism and extracellular matrix (ECM) integrity [10]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important cell signaling molecules under physiologic conditions, which are neutralized to maintain redox balance by the endogenous antioxidant system. The endogenous antioxidant system consists of water and lipid soluble vitamins and enzymes, such as glutathione peroxidase, superoxide dismutase, and catalase. Certain disease states, such as OA and RA, are characterized by oxidative stress from ROS that overwhelm the endogenous defense system and have been shown to contribute to decrements in collagen synthesis and chondrocyte metabolism in vitro [11,12]. Analysis of clinical data by Altindag et al [13] suggested a strong negative correlation between oxidative stress and collagen metabolism, while showing a positive association between total antioxidant capacity and collagen synthesis in patients with OA relative to matched subjects without OA. Kotani et al [14] also

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**Figure 1.** Theoretical mechanisms of nutraceuticals for arthroprotection.
recently confirmed the strong link between increased presence of ROS and knee OA in age-, gender-, and body mass index–matched subjects without OA.

Vitamin C (ascorbate) is an antioxidant organic acid that also functions as a coenzyme for proline and lysine hydroxylation–dependent cross-linking of collagen fibrils in cartilage and connective tissue extracellular matrix. Although clinical evidence in humans is limited, there are in vitro data that demonstrate that vitamin C stimulates chondrocyte metabolism, collagen, and proteoglycan synthesis, in addition to chondroprotection of the knee in an animal model [15]. Similar metabolic effects have been reported for vitamin E (tocopherols), which is known for its potent fat-soluble free radical scavenging effects. Vitamin E also has shown improvement in pain and stiffness in small human clinical trials, in addition to enhanced chondrocyte growth for cells in culture [10]. Surapaneni and Venkataramana [16] demonstrated elevated oxidative stress via malondialdehyde as a biomarker of lipid peroxidation, along with reduced levels of antioxidant vitamins C and E. McAlindon et al [17] reported a reduced risk of cartilage loss, knee pain, and OA progression, with the middle and highest tertile intake of vitamin C, equivalent to more than 75 mg daily, in the Framingham Osteoarthritis Cohort Study. This also was seen to a lesser extent with other antioxidant vitamins, β-carotene and vitamin E [17].

Vitamin D has been at the forefront of nutritional medicine recently amidst a litany of emerging scientific evidence that suggests its role in calcium homeostasis and bone health, as well as autoimmune, neurodegenerative, cardiovascular, neoplastic, and metabolic disorders [18]. The prevalence of vitamin D insufficiency or deficiency, as assessed by serum 25-hydroxyvitamin D (25-OH-D), is greater than initially suspected [19]. Furthermore, there are vitamin D receptors on chondrocytes and synoviocytes, which suggests at least a permissive role in the maintenance of articular cartilage structure and function [20]. Recently, Laragione et al [21] identified an effect of calcitriol (an active form of vitamin D) on inhibiting interleukin (IL) 1–induced matrix metalloproteinase (MMP)-1 expression, and reduced synoviocyte invasion in cells from patients with RA. Some longitudinal data about 25-OH-D showed no association with cartilage loss and joint-space narrowing in OA [22]. Analysis of other data suggests a negative association with progression of knee OA [23] and with knee pain in OA, when individuals with the highest tertile of 25-OH-D had the least pain [24]. The relationship between low 25-OH-D levels and the incidence and/or progression of OA may be more important in patients younger than 60 years of age, with stronger statistical significance in even younger patients [25]. Analysis of these data suggests that assessing 25-OH-D status is important at the onset or initial stages of OA. The varied and diverse immunomodulatory, cell-cycle regulating, and calcium homeostatic actions of vitamin D, coupled with the potential for optimizing outcomes in other pathologic states, suggest that correcting vitamin D deficiency should be a priority in patients with joint disease [26].

Vitamin K (phyloquinone) insufficiency is widespread in the United States and the United Kingdom. Its major source is green leafy vegetables, with some endogenous synthesis that takes place in the gut [27]. It is an essential cofactor in the enzymatic γ carboxylation of glutamic acid residues, which are found in a family of proteins (Gla proteins) that affect chondrocyte differentiation and mineralization [28,29]. Although vitamin K is typically not associated with OA, there is emerging preliminary evidence that suggests that low vitamin K levels may be a predisposing risk factor for radiographic features of hand and knee OA [30]. In another study that supports the potential association between vitamin K and OA, the prevalence of radiographic knee OA and joint space narrowing was inversely related to vitamin K intake in a rural Japanese cohort [31]. With each increasing quartile of vitamin K intake, there was a subsequent decreased prevalence of OA based on Kellgren-Lawrence radiographic grading [31].

Niacinamide (vitamin B3) is one of the 2 principal forms of the water-soluble B-complex vitamins. Some very limited, yet intriguing evidence from a randomized double-blind pilot trial that used 3000 mg/d of niacinamide for 12 weeks exhibited improved joint mobility, anti-inflammatory effects, and decreased nonsteroidal anti-inflammatory drug (NSAID) requirements for patients with OA [32]. Kaufman [33], in a prospective, parallel group study that compared high-dose niacinamide (1500-4000 mg daily) in patients with OA with age-matched controls, described enhanced joint range of motion, erythrocyte sedimentation rate, and overall arthritis severity within 2 months in those who took vitamin B3. The putative mechanism of action involves antioxidative and anti-inflammatory effects via poly-adenosine diphosphate (ADP)-ribosyl polymerase inhibition of ADP-ribosylation, thereby causing a suppression of IL-1 induced nitric oxide (NO) synthesis expression by chondrocytes [34,35].

**Micronutrient Minerals in OA**

Selenium, zinc, and copper are all essential elemental cofactors for important endogenous antioxidant enzymes to maintain redox balance. A recent animal model revealed decreased neutrophil infiltration and reduced proinflammatory mediators, tumor necrosis factor (TNF)–α, and IL-1β, in response to a selenium-enriched diet, which added support to continue further study in human patients of arthritis [36]. Selenium and manganese are both cofactors for enzymes involved in the biosynthetic pathway for glycosaminoglycans and proteoglycans [37]. Manganese and copper are both essential for collagen and elastin cross-linking in cartilage and bone tissue [38]. In a double-blind, placebo-controlled study by Hill and Bird [39], the multinutrient antioxidant combination of selenium and vitamins A, C, and E, showed a
trend toward improved pain and stiffness in patients with OA compared with placebo. The improvement was not statistically significant due to sample size and magnitude of the effect of the intervention [39].

Boron is a nonmetallic trivalent element that may play a role in OA by supporting and maintaining the structural and functional integrity of subchondral bone. Newnham [40] demonstrated that 6 mg/d of boron taken for 8 weeks in a small placebo-controlled randomized trial improved patients’ assessment of pain and function on a multicomponent OA symptom scale [40]. Epidemiologic evidence revealed that, in areas of the world where boron intakes are 3-10 mg daily, the estimated incidence of arthritis ranged from 0% to 10%, as opposed to an incidence of 20% to 70% in areas of the world with boron intakes of ≤1 mg [40]. In addition, Hellwell et al [41] found a strong negative association between the concentration of boron in femoral bone and hip OA, which suggests that boron may have a beneficial effect on osteochondral bone. Given the relative low toxicity of an elemental boron intake of 4-8 mg daily, patients are encouraged to consume a diet rich in fruits, vegetables, and nuts in which boron is found chelated to fructose or mannose. The data for using boron as an intervention in OA or osteoporosis are scarce, and further large-scale, well-designed clinical trials are needed. The tolerable upper intake level for boron in adults is 20 mg daily, so a low-dose supplement that provides 6 mg of boron daily for individuals with OA and concurrent osteoporosis may be reasonable.

Supplementation Dosing and Dietary Considerations

Similar to other water-soluble antioxidants, vitamin C has rapid rates of excretion and plasma clearance; thus an attempt should be made to consume vitamin C in low-to-moderate doses with more frequency. The Recommended Daily Allowance for vitamin C is 90 mg/d for males and 75 mg/d for females, with the tolerable upper level at 2000 mg daily. Typically, for the benefits discussed above, physicians would be prudent to use a range of 250-500 mg up to 3 times a day to attain lymphocyte, tissue, and body pool saturation levels [42].

There are all-cause mortality and cardiovascular disease data that suggest that there is no benefit, and possibly a detriment, to supplementing with more than 400 IU of vitamin E (in the dl-α-tocopherol form) [43,44]. There, however, are 8 structural isomers of vitamin E (4 tocopherols and 4 tocotrienols with α, β, γ, and δ homologues of each group), and there is emerging evidence that supports the use of mixed tocopherols and tocotrienols (particularly γ isomers) [45,46]. Because only approximately 1% of the literature published on vitamin E addresses the non-α isomers, coupled with the more recent promising benefits of supplementing with the other tocopherol and tocotrienol isomers, the disappointing clinical outcomes attributed to the dl-α-tocopherol homologue should be taken with caution [47]. Therefore, depending on patients’ OA progression, comorbidities, and concomitant medications, clinicians may consider recommending 100-300 IU of d-α-tocopherol, which should contain 150-300 mg of the mixed tocopherols with a bias toward the γ stereoisomers.

Vitamin D is a unique lipid-soluble vitamin in that it is more of a secosteroid or prohormone, which typically is supplemented as vitamin D3 (cholecalciferol [animal origin]) or vitamin D2 (ergocalciferol [plant origin]) [48]. Although, both molecular forms of vitamin D have been shown to elevate serum 25-OH-D stores, there are convincing data that demonstrated that vitamin D3 is more potent and bioavailable than vitamin D2 [49]. An oral dose of 4000 IU of vitamin D3 has been set as the tolerable upper limit for healthy adults. The serum 25-OH levels should be checked in 6-10 weeks after initiating supplementation, with a target level of more than 45 ng/mL [50].

OTHER NUTRACEUTICAL OPTIONS IN OA

Glucosamine, Chondroitin, Avocado-Soybean Unsaponifiable Fractions, and Methylsulfonylmethane

A full review of the glycosaminoglycans (GAG) glucosamine, chondroitin, and avocado-soybean unsaponifiable fractions (ASU), along with methylsulfonylmethane (MSM) is beyond the scope of this article. The health and integrity of articular cartilage is dependent on a tightly regulated coupling of anabolic and catabolic processes of chondrocytes and the synovial tissue that surrounds joints. Glucosamine, chondroitin, and hyaluronic acid are basic components of the cartilage ECM, and viscous synovial fluid. Although glucosamine, chondroitin, and hyaluronic acid can be synthesized by chondrocytes and synoviocytes, they may also be consumed via diet, which has fueled interest in nutritional supplementation of the GAGs [11]. Aside from collagen fibers, GAGs are the most important components of the articular cartilage and synovial fluid ECM, of which glucosamine appears to be the rate-limiting substrate that anchors chondroprotection [51]. Although some of the literature has failed to show significant benefits of glucosamine supplementation over placebo or NSAIDs, the totality of the available preclinical and clinical evidence suggests that glucosamine can improve joint pain and function, reduce risk of total joint replacement, and encourage chondroregeneration by decreasing and stabilizing cartilage degradation consistent with reversing the pathology of OA [52-57]. Glucosamine may have roles on both sides of the homeostatic equation by regulating the anabolic processes of cartilage and synovial fluid synthesis, in addition to mitigating degenerative or catabolic process with anti-inflammatory and even antioxidant

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properties. Several clinical trials and a meta-analysis by Uebelhart et al [58], Kahan et al, and Mitchell et al, concluded that chondroitin sulfate can slow progressive joint-space narrowing and decrease pain and inflammation associated with OA [58-60].

Although glucosamine and chondroitin have a longer onset of action, of 2-8 weeks, they also have persistent or sustained duration of benefit after ceasing supplementation relative to most analgesic medications [53,61]. Analysis of the data from Jackson et al [61] suggests a lack of synergistic effects from co-ingesting glucosamine and chondroitin simultaneously, possibly due to intestinal competition and/or hepatic metabolism; because plasma levels of the individual GAGs were reduced with co-ingestion. However, both agents have been shown, together and independently, to decrease OA progression and to improve clinical outcomes of joint pain and function, which raises the possibility that glucosamine and chondroitin may both be used in a nutritional protocol for OA; however, to derive optimal direct and indirect benefits for OA, glucosamine and chondroitin may need to be dosed independently. For example, daily dosing may be staggered as 1500 mg glucosamine at one time of the day and 1200 mg chondroitin at a different time to avoid the potential interference or competition for intestinal uptake. Further research is needed to investigate the effects of staggered dosing relative to coadministration on pharmacokinetics, bioequivalence, and/or efficacy. Furthermore, most of the earlier preclinical research and pharmacokinetic data from animal models used a glucosamine dose of 20 mg per kg of body weight per day [62]. As such, it is possible that patients who are obese or those individuals who weigh more than 75 kg may require a higher dose than the standard 1500 mg of glucosamine typically used in most clinical trials or commercial dietary supplement preparations to optimize efficacy.

The work of Gruenwald et al [63] provides clinical evidence that supports the concept of rational polysupplementation by using glucosamine sulfate (GAG) along with the n-3 fatty acids eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) from fish oil in an effort to optimize clinical outcomes via a complementary mechanism of action. Glucosamine sulfate with n-3-rich fish oil was shown to be more effective than placebo at improving pain and stiffness assessed via Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in a cohort of patients with moderate to severe hip and knee OA [63]. The totality of available evidence of efficacy and safety supports the use of the following regimen as an aggressive first-line nutritional intervention for OA (depending on specific patient history, needs, comorbidities, and concomitant medications): 20 mg per kg of body weight per day of glucosamine, 1200 mg chondroitin sulfate, 2-4 g of EPA plus DHA from fish oil, 450-2000 mg of γ-linolenic acid from borage oil or evening primrose, in addition to 300 mg of krill oil.

Hyaluronan

Hyaluronan (HA), or hyaluronic acid, is another GAG, composed of repeating units of D-glucuronic acid and N-acetylglucosamine synthesized by synoviocytes and chondrocytes, which form the backbone of proteoglycan polysaccharide polymers within the synovial fluid and ECM of cartilage. In addition to providing viscoelastic biomechanical properties of synovial fluid, HA has been shown to exert biochemical and cell-regulatory roles within joint tissues [64,65]. HA is widely recognized by clinicians as an injectable intra-articular viscosupplement for patients with knee OA, which has demonstrated improvement in pain and function [66]. The use of orally administered HA has been shown to be absorbed, used, and taken up by joint tissue in preclinical pharmacokinetic studies by Balogh et al [67]. Kalman et al [68] contributed important preliminary clinical research on an oral HA-rich product with a randomized placebo-controlled pilot trial in patients with knee OA and with Kellgren-Lawrence grade ≥2. The active HA-rich product resulted in improvements on the WOMAC score for physical function at 4 weeks of treatment and bodily pain on Short Form 36 version 2 at 8 weeks versus placebo, with a nonstatistically significant trend toward decreased pain medication use [68]. Provided that a patient does not have an allergy to chicken byproducts, an oral HA dietary supplement at a dose of 50-100 mg would be considered a lower-tier option, given the scarcity of published clinical data relative to other nutritional agents for OA. Because the rationale is strong and the early proof-of-concept data are compelling, further research is necessary to answer important questions about long-term clinical safety and efficacy of HA.

ASU

ASU is a sterol-rich hydrolyzed lipid fraction from avocado and soybean, which has been shown to possess anabolic, anticatabolic, and anti-inflammatory properties in vitro on chondrocytes [69]. Results of a number of studies revealed that ASU inhibits multiple inflammatory cytokines such as, IL-1, IL-6, IL-8, and prostaglandin E2 and stimulates transforming growth factor β production, collagen, and aggrecan synthesis [70,71]. Two 3-month studies of subjects with knee and hip OA who consumed 300 mg/d of ASU yielded significant improvements over placebo in regard to pain and the need for NSAIDs, and a 6-month study also resulted in an improved Lequesne Functional Index over placebo [72-74]. Although further research may help to clarify the role of ASU in managing OA symptoms and disease progression in the long term, its exceptional safety profile, along with the functional improvements, benefit regarding pain, and NSAID-sparing benefits make it a promising pharmaconutrient for rational polysupplementation, at 300 mg daily.
MSM

Results of animal studies showed that joints affected by OA have lower sulfur content, and undergo decreased joint degeneration when supplemented with MSM (an organic sulfur donor nutrient) [75,76]. MSM, alone or in combination with glucosamine, at doses that ranged from 1500 to 3000 mg daily reduces OA pain, swelling index score, and improved function, while demonstrating a safety profile comparable with that of placebo [77-79].

S-Adenosyl-Methionine

S-adenosylmethionine (SAMe) is the activated form of the amino acid methionine and is a precursor of glutathione. SAMe protects synovial cells by reversing glutathione depletion, thus supporting levels of an important internal antioxidant enzyme known as glutathione peroxidase [80]. In addition to its antioxidant protection, it may protect synovial cells by blocking the enzymes that degrade cartilage. It may also protect the important cartilage proteins and proteoglycans in the joint lining. Results of in vitro studies have demonstrated that SAMe increases the chondroproliferation and proteoglycans synthesis, which suggests that SAMe treatment may play a role in chondroprotection and regeneration by influencing the anabolic side of cartilage homeostatic metabolism [81,82]. In 2 studies that compared SAMe with NSAIDs for OA, the data suggested that SAMe was equal to or more effective and better tolerated than the NSAIDs [83,84]. Moreover, Maccagno et al [85] reported that the clinical improvement achieved by the 12-week treatment with SAMe on 45 patients with knee OA was sustained for a longer period of time than with NSAID treatment. SAMe may be considered in the nutritional armamentarium as a second- or third-line supplement for OA in consideration of its favorable risk:benefit ratio. SAMe is dependent on metabolic activation of the essential amino acid methionine; as such, its efficacy may be more pronounced in patients with OA and with chronic pathologic states that may impair methionine activation, such as hepatic and renal impairment. When supplementing with SAMe, there is a theoretical need to have sufficient methylation B-vitamin status (ie, vitamins B₆, B₁₂, and folate) to handle homocysteinaemia, because homocysteine is a metabolite of SAMe. SAMe has been reported to be activating for patients on psychotropic medications. Typical doses used in clinical trials range from 800 to 1600 mg daily in divided doses.

Collagen Preparations (undenatured type II collagen, hydrolyzed collagen products)

Although undenatured type II collagen supplementation was initially applied to RA, there are accumulating compelling data from animal and human studies that demonstrate how it may improve mobility, reduce pain, and enhance functional status in OA [86-88]. Numerous studies in animal models of OA have shown superiority with undenatured type II collagen over glucosamine and chondroitin in clinical signs and biomarkers of joint disease, in addition to additive benefits when they are all coadministered [86,89,90].

Undenatured type II collagen’s potential mechanism of action is likely mediated via T-cell “re-education” from oral immune tolerance, which results in cellular and humoral immunomodulation [91]. Ingesting intact type II collagen repeatedly creates antigenic interactions with dendritic cells and resident T-regulatory cells within gut-associated lymphoid tissue that line the gastrointestinal tract. The T-regulatory cells secrete immunomodulatory cytokines, such as IL-10 and transforming growth factor-β, that inhibit immune responses to the antigen (type II collagen) [92], which may decrease targeted amplification of the immune response toward exposed type II collagen within the ECM of articular cartilage, thereby preventing the immune system’s proinflammatory overreaction to articular cartilage in arthritic conditions.

Given the different and potentially complementary mechanism of action of undenatured type II collagen, in addition to the available evidence that supports its safety and efficacy, it may be considered as a rational synergistic supplement and may be added at 40 mg daily as a second- or third-tier agent to the fundamental nutritional intervention protocol for OA. Alternatively, if a patient has an intolerance or allergy to other nutritional interventions, then type II collagen may substitute or take on a primary role in the nutritional protocol for OA.

Hydrolyzed type II collagen peptides with or without a low-molecular-weight GAGs, such as HA and chondroitin sulfate from chicken-sternal cartilage, represent alternatives to undenatured, structurally intact collagen preparations. The hydrolyzed collagen differs in putative mechanism of action from the undenatured type II collagen, in that, instead of encouraging oral immunomodulation and tolerance by exposing intact collagen to re-educate T-regulatory cells, the hydrolyzed collagen peptides provide building blocks of the macromolecular components to support the matrix of cartilage. In addition, hydrolyzed chicken-sternal cartilage also contains the GAGs HA and chondroitin sulfate that are structural components of articular cartilage and synovial fluid. Results of in vitro data show a dose-dependent stimulation of collagen by chondrocytes to hydrolyzed type II collagen, whereas intact collagen or noncollagen hydrolysat failed to stimulate anabolism in cultured cells [93]. Oesser et al [94] reported accumulation of radioisotope-labeled hydrolyzed collagen peptide from oral consumption within joint tissue in mice. A post hoc subset analysis suggested 10 g/d of hydrolyzed collagen over 24 weeks was superior to placebo only in patients with severe OA [95]. An additional study, by Adam [96], demonstrated 10 g/d of a hydrolyzed collagen prepara-
tion was superior to egg albumin for improving visual analogue scale pain scores in patients with OA. Most clinical studies with isolated hydrolyzed collagen used 10 g/d dosing; however, there are some hydrolyzed chicken sternal cartilage matrix preparations that may have increased bioavailability due to the lower molecular weight of the collagen peptides and GAG components [97]. Although more data are needed to make firm recommendations on the use of hydrolyzed chicken sternal cartilage or hydrolyzed type II collagen for OA, the safety of these naturally occurring, functional food ingredients make hydrolyzed type II collagen an option as a third-tier ingredient to complement a nutritional intervention program for OA in doses ranging from 2 to 10 g/d.

**Phytoflavonoids and Botanicals**

Phytoflavonoids, functional polyphenols, and bioflavonoids are natural compounds found in a wide variety of fruits, berries, teas, spices, nuts, wine, cocoa, and vegetables. As a class of phytochemicals, many flavonoid polyphenols have been characterized to be powerful anti-inflammatory agents with free-radical scavenging antioxidant properties [98-102]. There is ample evidence to suggest that phytoflavonoid can interfere with some of the metabolic and biochemical processes that are associated with the development and progression of OA. More than 5000 of these naturally occurring polyphenolic compounds have been characterized, including epigallocatechin gallate, ellagic acid, curcuminoids, stilbenoids, resveratrol, quercetin, hesperidin, nobiletin, naringenin, oleuropein, hydroxytyrosol, proanthocyanidins, catechins, and baicalins. Results of studies have already shown that green tea, berry, and other botanical phytoflavonoid-rich extracts inhibit the production of proinflammatory cytokines, including IL-1β, TNF-α, IL-6, and prostaglandin E2 in arthritic joints [103-107]. Additional studies found that, as a class, many flavonoids may suppress inducible nitric oxide synthase, which inhibit production of nitric oxide and neutralize other RNS and ROS, such as superoxide [108,109]. These powerful free radicals and oxidative species are involved in promoting inducible, inflammatory gene expression [110].

Bioflavonoid polyphenols derived from maritime pine bark extract have recently been evaluated for their clinical efficacy in OA. Two clinical studies demonstrated improvements in WOMAC OA index scores and joint function, with a low toxicity potential and a good safety profile [111,112]. Peng et al [113] recently reported combined in vitro and in vivo data that show pine bark extract flavonoid-mediated cyclooxygenase (COX) 2 and inducible nitric oxide synthase (iNOS) inhibition and IL-8 suppression within chondrocytes and synoviocytes in urate crystal–induced joint inflammation. In addition, there are emerging data on pine bark extract–derived flavonoids that support other organ systems and mitigate risk factors for chronic diseases, such as chronic venous insufficiency, diabetes and metabolic syndrome, cardiovascular disease, and asthma and/or chronic obstructive pulmonary disease [114-116].

Flavocoxid is a U.S. Food and Drug Administration–regulated prescription medical food composed of a concentrated proprietary mixture of the flavonoid molecules baicalin and catechin extracted from *Scutellaria baicalensis* and *Acacia catechu*, respectively [117]. These flavonoids have been found to inhibit phospholipase A2 (PLA2), peroxidase activity of COX-1, COX-2, and 5-LOX, in addition to selectively downregulating COX-2 gene expression with preferential selectivity [102,118]. PLA2 inhibition prevents arachidonic acid, the n-6 polyunsaturated fatty acid (PUFA), from being liberated from injured cell membrane phospholipids and subsequently entering the COX and/or LOX enzymatic pathways that generate inflammatory eicosanoid metabolites. In addition, flavocoxid exerts broad antioxidant activity for scavenging ROS and RNS to support redox homeostasis and to reduce inducible inflammatory gene expression [110]. In a randomized, double-blinded, controlled, 12-week noninferiority trial, Levy et al [119] demonstrated that flavocoxid at 500 mg twice daily was as effective as naproxen in reducing symptoms of mild-to-moderate knee OA. Further post hoc subset analysis revealed strong trends in favor of the flavonoid-rich flavocoxid product over naproxen for a longer duration of treatment and in patients with milder disease [120]. In addition, an open-label, multicenter, postmarketing study with more than 1000 patients with OA support safety and efficacy of flavocoxid for the dietary management of OA [121]. The available data to date suggest that the dual COX and 5-LOX inhibition of arachidonic acid metabolism may be responsible for its cardiovascular, gastrointestinal, and renal safety, even in patients with concurrent antiplatelet and anticoagulation therapy, relative to NSAIDs [118,122-124]. Overall, the available literature on phytoflavonoid polyphenols demonstrates numerous potential benefits for OA pathobiology and chondroprotection, while being associated with exceedingly low toxicity and an impressive safety profile [124-126]. Their pleiotropic effects in reducing inflammation and oxidative stress, phytoflavonoids may help to protect against a host of other health maladies aside from OA and joint discomfort, including cardiovascular, neurologic, immunologic, and endocrine/metabolic [127,128]. Typical adult diets already include 200-400 mg daily from various food, beverage, and condiment sources; and clinical trials consistently appear to require supplementation with standardized preparations that contain 150-1500 mg daily. In addition, the medical food flavocoxid may provide a viable option to manage clinical symptoms of OA for patients with a contraindication or intolerance to NSAIDs. The phytoflavonoid polyphenols may act predominantly as anticatabolic agents to decrease the uncoupling of synthesis and degradation within articular cartilage in OA. Therefore, they may be included as adjuvants to other chondroprotective agents and
structural building blocks of synovial fluid and cartilage ECM in the nutritional intervention protocol for OA.

Curcumin is a diferuloylmethane aromatic component of the Indian spice turmeric and is an anti-inflammatory compound that inhibits both COX-2 and 5-LOX enzyme activity, along with protecting chondrocytes from the negative effects of IL-1β [129-131]. There are data that support an additive effect of curcumin with capsaicin or resveratrol that support cartilage ECM integrity, chondrocyte differentiation, and survival by modulating IL-1β, nuclear factor-κB (NF-κB) signaling, and the catabolic enzymes collagenase, hyaluronidase, and elastase [132,133]. Kuptniratsukul et al [134] reported non-inferiority data in a randomized controlled clinical trial that compared the effects of 2 g of *Curtuma domestica* extract to 800 mg of ibuprofen over a 6-week period on pain with walking and in performance in 100-m walk and stair-climbing tests. In vitro and animal studies demonstrated curcumin's broad range of therapeutic potential via anticarcinogenic, antioxidant, anti-ischemic, neuroprotective, cardioprotective, and anti-inflammatory properties [135-138]. Results of clinical studies have shown curcumin to be well tolerated and safe at doses of 2-10 g daily, but it should be used with caution in individuals on antiplatelet and anticoagulation therapy. Piperine (a component of black pepper) and other enhanced delivery systems, such as a lecithin-based phospholipid complex, have been shown to enhance the serum concentration, the bioavailability, and the extent of absorption of curcumin in humans without any adverse effects. There are a rationale and in vitro data that show a synergistic effect of the n-3 PUFAs EPA and DHA, along with curcumin, for enhancing eicosanoid, antioxidant, and inflammatory cytokine modulation [139].

Ginger is classified as an anti-inflammatory and antirheumatic agent in holistic medicine, and is standardized for bioactive components gingerols and shogaols [140]. In preclinical studies, ginger extract suppressed TNF-α and inhibited COX-2–mediated synthesis of proinflammatory mediators [141]. Altman et al [142] and Srivastava and Marcussen [140] published 6-week and 2.5-year placebo-controlled trials, respectively, which demonstrated improvements in WOMAC index and visual analogue scale pain profiles for OA of the knee.

An in vitro study that investigated the effects of stinging nettle leaf (*Urtica dioica*) extract demonstrated significantly suppressed inflammatory eicosanoids and IL-1(β)–induced expression of matrix metalloproteinase [143], with human whole-blood ex vivo data that show reductions in TNF-α and IL-1 [144]. The clinical data that support stinging nettle extract is still nascent, but a recent 3-month randomized placebo-controlled trial in patients with established knee or hip OA revealed significant improvement in favor of the nutraceutical in WOMAC scores for pain, stiffness, and function with decreased NSAID use. However, the active product contained nettle extract in an admixture with fish oil, vitamin E, and zinc [145]. Doses typically range from 500-1000 mg daily, but, until more data are available, stinging nettle extract is not yet a firmly established component of a multinutrient dietary intervention protocol for OA.

*Harpagophyllum procumbens*, also known as devil’s claw, is a South African plant whose extracts are standardized for harpagosides-triterpene glycoside compounds. Harpagosides from devil’s claw have been reported to reduce the IL-1β–induced production of MMP-1, MMP-3, and MMP-9 ECM catabolic enzymes by chondrocytes, and downregulate TNF-α and COX-2 gene expression [146,147]. There is evidence of efficacy for the use of devil’s claw extract as a dietary supplement, when providing 60 mg of harpagoside daily in the treatment of hip and knee OA [148]. This efficacy, coupled with a favorable safety profile and limited toxicity concerns based on published randomized clinical trials that involved more than 4000 patients, lends credence to the use of devil’s claw standardized for 60 mg of harpagoside as a reasonable third- or fourth-line addition to the nutritional intervention protocol in patients with OA [148,149].

The oleoresin from the tree bark of *Boswellia serrata* has been used in traditional medicine for its anti-inflammatory properties. Animal in vivo data and human pilot clinical trials support the potential of *B. serrata* gum resin extract for the treatment of a variety of inflammatory diseases such as inflammatory bowel disease, RA, OA, and asthma. Analysis of in vitro data indicated the main mechanism of action as 5-LOX inhibition of leukotriene synthesis via the 2 main boswellic acids (keto-boswellic acid and acetyl-keto-boswellic acid) [150]. However, there are conflicting data that suggest that 5-LOX inhibition is a less likely mode of therapeutic action due to low bioavailability and low plasma concentration levels of the boswellic acids. It now is speculated that the higher levels of β-boswellic acids may modulate inflammation via prostaglandin E synthase–1 and the serine protease cathepsin G [151]. One 8-week crossover, double-blinded, randomized clinical trial that used 333 mg *B. serrata* extract 3 times daily in isolation reported improved pain, mobility, and swelling indices for knee OA [152]. Two other clinical trials showed efficacy of a boswellia-containing multinutrient in reducing pain, tenderness, and swelling in OA. However, these were cocktail mixtures, and the true effect of boswellia is difficult to determine [153,154].

**Proteolytic Enzymes**

Bromelain is an aqueous extract of stems and immature fruits of pineapple known to contain a number of proteolytic enzymes. Results of several preclinical studies and small pilot trials have suggested that bromelain and other proteolytic enzymes may have anti-inflammatory, analgesic, antithrombotic, and antifibrinolytic properties [155]. Multiple small trials used bromelain in doses that ranged from 270 mg to more than 1800 mg daily for knee OA, with mixed results...
[155-157]. Most trials exhibited improvements in the functional endpoints of both the active bromelain groups and placebo or diclofenac control groups, which suggests spontaneous resolution as confounding clinical improvements in patients. Moreover, 1 trial with a higher dose of 945 mg daily of bromelain resulted in greater adverse effects relative to 100 mg of diclofenac [158]. Until more rigorous, high-quality randomized clinical trials with appropriate controls in a stable, well-defined, matched OA patient population demonstrate a consistent dose-response with safety and validated clinical outcomes, a categorical recommendation is difficult at this time.

OTHER NUTRACEUTICALS POTENTIALLY ON THE HORIZON

Dietary supplementation with probiotics (lactate-producing bacteria of the *Bifidobacterium* and *Lactobacillus* genus), and prebiotics (select nondigested oligosaccharide fibers composed of inulin, fructooligosaccharides, and/or galactooligosaccharides) have been used to support a healthy intestinal microflora. Synbiotics refer to the coadministration of both probiotic bacteria with their selectively fermented prebiotic fiber for providing a synergistic environment to promote the gut microbiota. The data that support probiotic use for supporting joint health are still nascent and continue to emerge, with the majority focused on immunomodulatory mechanisms in RA. However, a recent study, by Mandel et al [159], on the addition of probiotics to a standard medication regimen in patients with RA over a 60-day period demonstrated greater improvements over placebo in pain, C-reactive protein, global patient assessment of function, and 2-mile walking capacity. Results of preliminary studies in collagen-induced animal models of RA revealed improvements in serum proinflammatory cytokines and, when probiotics were coadministered with type II collagen, resulted in enhanced oral tolerance with decreases in edema, joint lymphocyte infiltration and cartilage degeneration [160]. Results of another intriguing study, by So et al [161], suggests that the probiotic *Lactobacilli casei* may hold therapeutic potential for OA by reducing pain, inflammatory cytokines, and biomarkers of cartilage degradation. Given their pleiotropic health benefits in other areas of medicine, along with their favorable safety profile, synbiotics appear to be another nutraceutical intervention on the horizon in the therapeutic armamentarium for OA.

*Cissus quadrangularis* is a vine indigenous to warm climates in Asia and West Africa; it is used extensively in traditional medicine for a variety of symptoms, including bone fractures and joint pain. There are in vitro and animal data that support an osteoprotective effect, subchondral bone ECM synthesis, and the ability to influence mesenchymal stem cell differentiation [162,163]. Organic glucosinolates and isothiocyanates are naturally occurring phytochemicals found predominantly in cruciferous vegetables, such as broccoli, Brussels sprouts, watercress, horseradish, kale, and mustard greens, to name a few. Isothiocyanates are known to possess endogenous antioxidant enzyme induction and anti-inflammatory properties that have resulted in in vivo evidence of IL-6, TNF-α, and nuclear factor-κB signal suppression. A recent investigation on sulforaphane, an isothiocyanate found in broccoli, demonstrated improved clinical in experimental arthritis model, albeit an RA model [164].

**SUMMARY**

Maintenance of a healthy body weight, lifestyle, and physical activity; medical management with anti-inflammatory agents and analgesics; use of minimally invasive and/or surgical procedures; and use of physical medicine and rehabilitation methods remain the most common strategies for treating and preventing OA. However, strategic nutritional intervention is emerging as an additional cost-effective tool in OA, with a favorable safety profile for optimizing outcomes as a complement to traditional clinical treatment strategies. Dietary immunomodulation, redox balance, and free-radical scavenging by influencing the balance of anabolic to catabolic metabolism within joint tissue, and providing structural precursors of synovial fluid and cartilage ECM are the most common factors among the majority of nutritional interventions explored in this 2-part review (Table 1). The goals of pharmacounutrition for metabolic optimization are to drive biochemical reactions in a desired direction and to meet health condition-specific metabolic demands. Certain macronutrients and nutraceuticals, such as the n-3 fatty acids EPA plus DHA, vitamin D, phytoflavonoid polyphenolics, and probiotics provide extra-articular benefits to multiple organ systems for mitigating chronic, degenerative disease, and for supporting optimal health and wellness (Table 1).

There is ample fundamental scientific rationale for the promise of nutraceutical intervention as a frontline intervention early in the disease course of OA, given its risk:benefit ratio, relatively low cost, and pleiotropic potential for improving clinical management of OA. An emerging body of evidence also demonstrates that strategic nutritional intervention supports not only clinical symptom and functional improvement but may also be disease modifying.

An evidence-based foundation is critical for evaluating established and emerging interventions such as nutraceuticals. However, to optimize clinical outcomes for patients, fellow clinicians and scientists must fairly appraise the totality of evidence and appreciate the entire spectrum. When using data from the spectrum of scientific evidence, physicians should use extreme caution with interventions that have only in vitro data; recommendations can be made with greater confidence when consistent human clinical trial evidence is available.
Applying advances in nutritional science to musculoskeletal medicine (or any other discipline in medicine) remains challenging, given the fluid and dynamic nature of the field, along with a rapidly developing regulatory climate over manufacturing and marketing requirements. As applied nutritional science evolves, it will be important to stay on the forefront of proteomics, metabolomics, epigenetics, and nutrigenomics, because they hold enormous potential for developing novel therapeutic and prognostic breakthroughs in many areas of medicine, including OA.

REFERENCES


<table>
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<tr>
<th>Nutraceutical Agent</th>
<th>Anti-inflammatory Cytokines</th>
<th>Anti-inflammatory Eicosanoids</th>
<th>Redox Balance/An antioxidant capacity</th>
<th>Chondro-Synovial Anabolic</th>
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<td>2-4 g daily EPA + DHA; 0.5-2 g GLA</td>
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<td>200-400 mcg; 5-10 mg; 6-8 mg; 25-50 mg daily</td>
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Check marks = relative contribution of the mechanistic category for each nutraceutical agent; PUFA = polyunsaturated fatty acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; GLA = γ-linolenic acid; GAG = glycosaminoglycan; HA = hyaluronic acid; ASU = avocado-soybean unsaponifiable fraction; SAMe = S-adenosylmethionine; MSM = methylsulfonylmethane; Se = selenium; Mn = manganese; Bo = boron; Zn = zinc.
0. 44. Friedrich MJ. To “E” or not to “E,” vitamin E’s role in health and disease is the question. Jama 2004;292:671-673.
0. 52. Kirkham SG, Samarasinghe RK. Review article: Glucosamine. J Orthop Surg (Hong Kong) 2009;17:72-76.


