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**Recently highlighted nutraceuticals for preventive management of osteoarthritis**

Ravalli S *et al*. Nutraceuticals for preventive management of osteoarthritis

Silvia Ravalli, Marta Anna Szychlinska, Rosalia Maria Leonardi, Giuseppe Musumeci

**Silvia Ravalli, Marta Anna Szychlinska, Giuseppe Musumeci,** Department of Biomedical and Biotechnological Sciences, Human Anatomy and Histology Section, School of Medicine, University of Catania, Catania 95123, Italy

**Rosalia Maria Leonardi,** Department of Orthodontics, Policlinico Universitario "Vittorio Emanuele", University of Catania, Catania 95124, Italy

**ORCID number:** Silvia Ravalli (0000-0003-3358-1086); Marta Anna Szychlinska (0000-0001-5281-1516); Rosalia Maria Leonardi (0000-0002-9433-9528); Giuseppe Musumeci (0000-0002-8260-8890).

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**Correspondence to: Giuseppe Musumeci,** **BSc, MSc, PhD, Associate Professor,** Department of Biomedical and Biotechnological Sciences, Human Anatomy and Histology section, School of Medicine, University of Catania, Via S. Sofia 87, Catania 95123, Italy. g.musumeci@unict.it

**Telephone:** +39-95-3782043

**Fax:** +39-95-3782034

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**Abstract**

Osteoarthritis (OA) is a chronic degenerative disease of articular cartilage with limited options of treatment. This reality encourages clinicians to suggest preventive measures to delay and contain the outbreak of the pathological conditions. Articular cartilage and synovium suffering from OA, are characterised by an inflammatory state and by significant oxidative stress phenomenon, responsible for pain, swelling and loss of mobility in the advanced stages. This review will focus on olive oil for its ability to exert positive effects on the entire joint, reducing pro-inflammatory cytokines release and increasing lubricin synthesis, olive leaf extract, since it maintains lubrication by stimulating the synthesis of high molecular weight hyaluronan in synovial cells, curcumin which delays the start of the pathological process of cartilage breakdown, sanguinarine (SA), as downregulatory of catabolic proteases, vitamin D, for its capacity to influence the oxidative and pro-inflammatory environment and carnosic acid (CA), as inducer of heme oxygenase-1 (HO-1), preserving cartilage degeneration. These molecules, considered as natural dietary supplements, appear like a cutting-edge answer to this tough context, playing a major role in controlling homeostatic balance loss and slowing down the pathology progression. Natural or food-derived molecules able to exert a potential therapeutic effect are known as “nutraceutical”, resulting from the combination of the words “nutrition” and “pharmaceutical”. These compounds have gained popularity thanks to their easy availability, which represents a huge advantage for food and pharmaceutical industries. In addition, the chronic nature of this pathology implies the use of pharmacological compounds with a proved safety in the long term, especially because current treatments, like nonsteroidal anti-inflammatory drugs and analgesics, improve pain relief but they have no effect on degenerative progression and can also cause serious side effects.

**Key words:** Osteoarthritis; Nutraceuticals; Prevention; Diet; Inflammation; Oxidative stress

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**Core tip:**In osteoarthritis (OA), significative expression of inflammatory cytokines, matrix proteins and proteolytic enzymes are noticed. For this reason, anti-inflammatory molecules play a major role in controlling the adverse effects of the cartilage homeostatic balance loss. Olive oil, olive leaf extract, curcumin and sanguinarine (SA) have been studied as supplements with these properties. Moreover, chondrocytes undergo more significant phenomenon of senescence and cell death when in presence of oxidative stress. Potential targets involved in this mechanism are counteract by anti-oxidant molecules like vitamin D and carnosic acid (CA).

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**INTRODUCTION**

Osteoarthritis (OA) is a very complex and multifactorial disease of articular cartilage, which represents a leading cause of joint pain and disability worldwide[1]. The entire synovial joint is affected by the progression of this pathology, including the underlying bone, synovium, meniscus, ligaments/tendons, and cartilage[2,3]. OA is characterized by the degradation of the articular cartilage, which can be used as hallmark of pathological advancement, beyond changes in subchondral bone, osteophyte formation, joint space narrowing and synovial chronic inflammation[4]. In normal joints, cartilage covers and cushions the ends of bones, reducing friction and absorbing shocks. Its destruction progress leads to stiffness, pain, mobility limitations and compromised overall quality of life[5,6]. Some of the most important risk factors include aging, inflammatory state, muscle atrophy, injury and metabolic disorders[7].

 The management of this pathology focuses on alleviating its secondary effects since, currently, there is no resolutive cure. Nonsteroidal anti-inflammatory drugs and analgesics, generally prescribed to patients, are only able to reduce pain and improve joint function, but fail in modifying the progression of the disease in term of prevention and chondroprotection[8]. The chronic nature of OA forces to choose pharmacological approaches which can be considered safe for long term use and, at the same time, might be able to slow its progression. The bases of articular damage rely on impaired balance of anabolic and catabolic mechanism which can be influenced by dietary compounds, like nutraceuticals[9]. In virtue of their minimum side effects, especially in long terms, their easily extraction and their low costs of production, they can represent a valid support to preventive management of OA.

 Forty-seven percent of people who suffer from the disease use complementary medications, including nutraceuticals, thanks to their ability to show anti-inflammatory and antioxidant activity[10]. Herbal and natural products have been used since ancient times. A 5000 years old Sumerian clay tablet is the first proof of plant use as medicament, especially to treat pain and inflammation[11].

 Improvement of chemical technologies, during the 19th century, allowed the extraction of active substances from medicinal plants such as alkaloids, tannins, saponosides, etheric oils, vitamins and glycosides, isolated in pure form[12]. The term “nutraceutical”, resulting from the combination of the words “nutrition” and “pharmaceutical”, is used to define any natural or food-derived molecule able to exert a potential therapeutic effect that could be used as integrators in a daily diet[13].

 Statutory law of these type of medicaments changes in different countries. In the United States, for instance, they are considered as dietary supplements by the Dietary Supplement Health and Education Act of 1994[14]. Food and Drug Administration is in charge to review and approve any health claims of these products. In some countries of the European Union, nutraceuticals may require registration procedure whereas in others, they could be easily sold as food preparations[15].

 This review will overview natural-based approaches for chondroprotection, highlighting the peculiarity of some molecules whose positive effect, in preserving cartilage health, has recently been discovered. This approach may be useful both to prevent OA onset and also to slow down its progression.

**ANTI-INFLAMMATORY APPROACH**

The involvement of an inflammatory component, marked by joint pain, swelling and stiffness, is now well recognized in the pathogenesis of OA. Indeed, chondrocytes undergo a loss of homeostatic balance which includes expression of inflammatory cytokines, matrix proteins such as collagen and lubricin and proteolytic enzymes[16]. The most important pro-inflammatory cytokines involved are interleukin (IL)-1β and tumor necrosis factor (TNF)-α[17]. Some of the consequences of the development of an inflammatory scenario are: downregulation of structural components, including type II collagen and proteoglycans[18-21], upregulation of proteolytic enzymes, such as matrix metalloproteinases (MMPs)-1, -3, -13, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)[22-24] and stimulation of inflammatory mediators like prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2), Reactive oxygen species (ROS)[25,26].

 Recently, our lab carried out studies to determine the chondroprotective role of phytoactive molecules [*e.g.* polyphenols and monounsaturated fatty acids naturally present in olive tree-derived products, olive oil (-OO-) and olive leaf extract (-OLE-)] able to preserve the articular cartilage and skeletal muscle condition, in the context of early development of OA, because of their antioxidant and anti-inflammatory properties[7]. In addition, the study questioned about the differences between three types of oils in term of origin and polyphenols contents: Sicilian extra virgin olive oil (S-EVOO), Tunisian extra virgin olive oil (T-EVOO) and Tunisian extra virgin olive oil and leaves extract (T-enriched-EVOO), concluding that the first variety of oil (S-EVOO) is the best in exerting positive effects on the entire joint, reducing remarkably IL-6 release and increasing lubricin synthesis, compared to the others diet protocols (Figure 1). The effects of physical activity where analysed too in combination with the diet[27]. The studies demonstrate that an olive oil supplemented diet and physical activity improve cartilage recovery, after anterior cruciate ligament transection (ACLT), by lowering the expression of IL-6 and IL-1 and by increasing the expression of lubricin suggesting the chondroprotective activity. Lubricin is a glycoprotein released to synoviocytes type B and chondrocytes from the superficial layer of articular cartilage, its functions are to lubricate and nourish articular cartilage[28].

 Another recent study that confirms the healthy effect of OLE was presented by Maruyama *et al*[29], which addressed the main activity to hydroxytyrosol (4-(2-hydroxyethyl)-1, 2-benzenediol) (HT), one of the polyphenols of OLE. STR/ort mice were used as model for knee OA and OLE was administrated, orally, every day, for 8 wk with a dosage of 100 mg/kg. The chondroprotective effect of the extract was proven by the results of the Mankin scores of the non-OA control group, OA control group and OLE-treated group which were 3.50, 11.13 and 7.20, respectively. Moreover, the study suggests that these natural molecules were able to impair cartilage damage and, consequently, the pathology progression, since they stimulate the synthesis of high molecular weight hyaluronan in synovial cells, in vitro. High molecular weight hyaluronan is renowned to maintain the moisture and lubrication of the joints[30]. The authors suggest, finally, that OLE administration can effectively help suppressing OA progression.

 Traditionally used as anti-inflammatory treatment in Chinese and Ayurvedic medicine, *Curcuma longa* is a plant rich in phytochemicals responsible for its most impressive and wide-ranging health benefits. Some of its active components, curcumin and tetrahydrocurcumin (THC), a major metabolite of curcumin, has been studied because of their anti-inflammatory, anti-oxidant, chemopreventive, anti-aging and anti-bacterial activities[31,32]. Park *et al*[33] analysed the effects of the long-term administration of THC and curcumin in the overview of OA progression in rats with estrogen deficiency. Ovariectomized obese rats undercame monoiodoacetate injections into the knee to simulate OA conditions and then, curcumin and THC were feed to preventing postmenopausal and OA symptoms. One of the best finding of the study is the analysis of the differences between the two molecules investigated. The chemical structures of curcumin involved in exerting the main activities are methoxy, hydroxyl, α,β-unsaturated carbonyl, and diketone groups; whereas its metabolite lacks of the presence of the α,β-unsaturated carbonyl group, so its functionality and efficacy change (Figure 2). Park *et al*[33] found that both natural products show similar ability to decrease expression of TNF-α, IL1β, IL6 and MMP3 and MMP13, but only THC can enhance glucose tolerance and, therefore, it is able to decrease advanced glycation end products in articular cartilage, delaying the start of the pathological process of cartilage breakdown.

 Furthermore, Ma *et al*[34] demonstrated, for the first time, the anti-inflammatory effect of sanguinarine (SA), a benzophenanthridine alkaloid isolated from the roots of *Sanguinaria canadensis*, on the pathogenesis of OA, *in vitro*, *ex vivo* and *in vivo*. Evaluation of the potential cytotoxicity of SA reveals that this compound does not affect cell viability at lower concentration that 1.25 μmol/L. As stimulation of IL-1β increased the mRNA expression of MMP1a, MMP3, MMP13, and ADAMTS-5, SA demonstrated to downregulate these catabolic proteases trough dose-dependent manner interdiction of IL-1β. More specifically, the anti-inflammatory molecule acts as suppressor of the mechanisms of phosphorylation of the c-Jun N-terminal kinases (JNK) and nuclear factor kappa B (NF-κB) (Figure 3). These analyses, *in vitro*, were followed by *ex vivo* evaluation of SA effect on cartilage matrix degradation, finding correspondence with the previous results. Intra-articular administrations of different concentrations of SA were used to determine whether the molecule could slow down the progression of the pathology in mice with ACLT-induced OA. The hypothesis was, finally and positively, confirmed by immunochemistry results, evaluation of mRNA levels of proteases and Osteoarthritis Research Society International scoring.

**ANTIOXIDANT APPROACH**

It is well established that ROS production induced by oxidative stress (common experienced because of post-traumatic events or aging) is a crucial mediator of OA disease progression[35]. As a consequence, chondrocytes experience more significant phenomenon of senescence and cell death[36,37]. In addition, cartilage and joint fluid, affected by OA, are not able to counteract this scenario because superoxide dismutase antioxidant levels lower consistently[38]. This is the reason why an effective preventive approach to this pathology should consider boosting antioxidant shield in order to enhance potency of constitutive defendant such as antioxidants catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase.

 A study about dietary supplementation in OA by Manoy *et al*[39] highlights the role of the commonly renowned antioxidant vitamin D. Even though the correlation between this vitamin and muscle-skeletal diseases is still not very clear, low levels of 25-hydroxyvitamin D (25(OH)D) are registered in OA patient’s serum. In fact, evidence states vitamin D deficiency as a co-factor to OA pathogenesis[40]. The study involved 175 primary knee OA patients who received 40000 IU vitamin D (ergocalciferol) per week. After six months since the first administration, the patients experienced ameliorated grip strength, physical performance and improved quality of life (Figure 4). Moreover, to confirm its anti-oxidant activity, analysis of level of protein carbonyl were performed to obtain information about oxidative damage. The results confirmed that vitamin D supplementation remarkably lowered carbonyl level and, as a consequence, stress and pro-inflammatory environment that could affect protein function and DNA. The underlying mechanism for this vitamin D activity may be explained by evidences of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), IL-6, TNF-α, NF-kB and p38 downregulations[41,42].

 Heme oxygenase-1 (HO-1) is another potential target to be used in an anti-oxidant strategy against OA. Constitutive expression of this enzyme, in chondrocytes and meniscus in mice, has been linked to preserve cartilage degeneration[43]. For this reason, Hiroyuki *et al*[44] explored the effect of carnosic acid (CA) as inducer of HO-1 upregulation in preventing OA progress. This molecule is a natural diterpene commonly found in rosemary and common sage which has demonstrate protective qualities in pathology like cancer, diabetes and neurodegenerative disease[45]. Immunoblotting assay was used to test whether this acid was able to act on the expression of HO-1 in articular chondrocytes then, results showed that CA increases enzyme levels in a dose-dependent manner. More specifically, the best treatment seemed to require 10 to 50 μmol/L of CA. In addition, it was able to restore HO-1 levels under IL-1β treatment which specifically inhibits the anti-oxidant effects of the enzyme. According to this study, the mechanisms by which this natural compound acts rely on: downregulation of MMP-13 and ADAMTS-5, activation of nuclear factor erythroid 2-related factor 2 (Nrf2), regulation of the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 (KEAP1/NRF2) transcriptional pathway and through increase of microRNA 140 (miR-140) binding to 3’UTR of Bach1 (a HO-1 repressor) in articular chondrocytes (Figure 5).

 Furthermore, our lab questioned the relationship between oxidative stress and physical activity or sedentary lifestyle, suggesting therapeutic solutions that involve natural dietary supplements. One study analysed the effects of oleic acid on ROS production induced by exhaustive physical activity in rat skeletal muscle[46]. The results highlight the importance of extra-virgin olive oil as protective agent against the oxidative stress following physical efforts. The group of rats, subjected to exhaustive exercise, but fed with a diet rich in oleic acid, experienced decrement of hydroperoxides and thiobarbituric acid reactive substances and increment of antioxidant defences, rated as non-enzymatic antioxidant capacity and levels of 70 kDa heat shock proteins (Hsp70). OA cannot be completely prevented, but some precautions can help in delaying the outbreak of the pathology and in managing the risk of its progression[47]. Since sarcopenia and sedentary life are possibly associated with knee OA[48], another study is worth citing because it evaluates whether different dietary profiles, containing or not vitamin D, could exert some effects on muscle fibres[49]. The study found out that muscle fibres of rats, fed with high-fat extra-virgin olive oil-based diets, were hypertrophic, comparable to those of the regular diet group and confirming that this natural supplement does not impair muscle fibres metabolism like high-fat butter-based diets do instead. In addition, Vitamin D exerts a trophic action on muscle fibres both in rats fed with regular diet and also in those fed with the diet enriched with extra-virgin olive oil, suggesting also that, insulin-like growth factor-1 (IGF-1) and dickkopf-1 (DKK-1) could be involved in this mechanism.

**CONCLUSION**

When physical activity and healthy lifestyle are not enough, anti-inflammatory drugs and painkillers are commonly used to get rid of the pain and, sometimes, rehabilitation and surgical intervention are unavoidable. For these reasons, trying to preserve cartilage joint is imperative.

 The use of natural approaches to this scope is a cutting-edge strategy. Nutraceuticals answer to this tendency offering a wide range of molecules able to exert positive effect at different structures of the joints and with several mechanisms of actions. In particular, this review focus on the anti-inflammatory and antioxidant properties of compounds, which show to ameliorate cartilage conditions and suggest taking in consideration the opportunity to integrate them within a framework of prevention.

 The presented studies offer thorough evaluations of olive oil, noticing that it reduces IL-6 release and increases lubricin synthesis, of olive leaf extract, as mighty stimulator of the synthesis of high molecular weight hyaluronan in synovial cells, of curcumin, addressing its benefit to the ability to decrease expression of TNF-α, IL-1β, IL-6 and MMP3 and MMP13, of SA, as downregulatory of catabolic proteases trough interdiction of IL-1β, of vitamin D, since it influences the oxidative and pro-inflammatory environment and of CA, as inducer of HO-1, preserving cartilage degeneration, even under IL-1β treatment.

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 From a general analysis, it is worth noticing that a common positive element of all these molecules is their easily availability in nature, which represents a huge advantage for food and pharmaceutical industries, and their low side effects, that allow to conceive a large and safe use of the derived products.

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**Figure 1 Composition of fatty acids, vitamin E and polyphenols in sicilian extra virgin olive oil supplemented diet.** Palmitic acid (16:0) (mg/kg) 9002; palmitoleic acid (16:1) (mg/kg) 579; stearic acid (18:0) (mg/kg) 1689; oleic acid (18:1) (mg/kg) 24047; linoleic acid (18:2) (mg/kg) 20352; linolenic acid (18:3) (mg/kg) 2018; vitamin E (mg/kg) 72.167; Polyphenols (mg/kg) 5.960.



**Figure 2 Chemical structure of curcumin and tetrahydrocurcumin.** A: Curcumin, C21H20O6; B: Tetrahydrocurcumin, C21H24O6.

**Figure 3 Anti-inflammatory effect of sanguinarine.** Sanguinarine acts as suppressor of IL-1β, targeting the pathways involved in the activation of JNK and the degradation of IκBα, an inhibitory subunit of NF-κB. IL: Interleukin; IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; NF-κB: Nuclear factor kappa B; JNK: c-Jun N-terminal kinases; MKK7: Dual specificity mitogen-activated protein kinase kinase 7.

**Figure 4 Vitamin D levels in osteoarthritis patients at baseline and after vitamin D2 supplementation.** At baseline, 72 participants had vitamin D deficiency (< 20 ng/mL) and 103 patients had vitamin D insufficiency (20-30 ng/mL). After 40000 IU of vitamin D2 supplementation per week for six months 100 knee OA participants achieved concentration above 30 ng/mL, 70 knee OA participants had vitamin D insufficiency, and only 5 patients had vitamin D deficiency. Vit D: Vitamin D; OA: Osteoarthritis.



**Figure 5 Mechanisms of heme oxygenase-1 upregulation by carnosic acid.** CA induces the expression of HO-1 by: Activation of the Nrf2 transcription factor, downregulation of Bach1 *via* miR-140 and downregulation of the IL-1β induced expression of extracellular matrix degrading enzymes such as MMP-13 and ADAMTS-5. CA: Carnosic acid; HO-1: Heme oxygenase-1; Nrf2: Nuclear factor erythroid 2-related factor 2; IL: Interleukin; MMP: Matrix metalloproteinase; ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; miR-140: MicroRNA 140.