



REVIEW ARTICLE

A Review of Non-pharmacological Oral Supplements Containing Nutrients and Micronutrients in the Treatment of Osteoarthritis

Nastaran Tabari Shahandasht¹, Marzieh Bolandi^{*1}, Majid Rahmati², Moslem Jafaristani³

¹Department of Food Science and Technology, Damghan Branch, Islamic Azad University, Damghan, Iran

²Department of Medical Biotechnology, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran

³Clinical Biochemistry, Shahroud University of Medical Sciences, Shahroud, Iran

Received: 28 January 2021

Accepted: 4 December 2021

KEYWORDS

Inflammation;
Nutritional
supplements;
Non-pharmacological
methods;
Osteoarthritis

ABSTRACT: Since osteoarthritis is the most common musculoskeletal inflammation that causes people to be unable to move with age, a proper diet can be effective in treating it. Therefore, understanding the impact of non-pharmacological nutritional supplements may provide guidelines for the prevention of this disease thereby reducing the costs of medical care. The purpose of this study was to review the effect of various non-pharmacological dietary supplements containing nutrients and micronutrients in the prevention and treatment of osteoarthritis. Taking these non-pharmacological nutritional supplements over a short to medium term reduced pain and inflammation, and improved patients' quality of life. However, their impact was low to moderate. To achieve the best treatment results in patients with osteoarthritis, it is recommended that these dietary supplements be taken along with medication and adopt a healthier lifestyle.

INTRODUCTION

Today, osteoarthritis or arthrose is one of the most common inflammatory diseases of the joints, which progressively destroys articular cartilage, leading to inflammation and swelling of the joints through aging. The disease typically affects the knees, pelvis, fingers or lower back, leading to pain, limited movement of the joints involved, and decreased physical activity. In fact, osteoarthritis is a modern disease that is growing rapidly and has become one of the ten debilitating diseases in developed countries [1]. It is estimated that its social costs account for between 1 and 2.5% of the GDP of these countries. The prevalence of osteoarthritis in Iran is estimated at 26% in rural areas and 25% in urban areas. These statistics confirm the high prevalence of osteoarthritis of the knee, the most common joint involved in patients in the country (1 in 6.5 people), which can be justified by the increasing average age,

improper lifestyle and pernicious habits. This necessitates research on effective treatments which can create healthier life with a lower economic burden on the citizens. Although the cause of osteoarthritis is still unknown, its contributing factors include age, obesity, and joint damage such as trauma, gender-related components, genetics background, and metabolic and endocrine diseases such as diabetes [2, 3].

Common methods in the treatment of osteoarthritis and its related challenges

Numerous studies have shown that 80% of people with osteoarthritis have limited mobility, while in about 20% of patients; the severity of the disease is so high that it prevents them from performing basic daily activities. Although the nature and symptoms of osteoarthritis are well defined and the risk factors associated with it have

been carefully studied, there is currently no effective treatment available for osteoarthritis given the limited capacity of cartilage to repair and regenerate [3]. Therefore, pharmacological and non-pharmacological methods can be employed to treat osteoarthritis. Chemical drugs i.e. painkillers and lifestyle modifications such as weight loss and exercise are the strategies available to reduce pain and inflammation and improve patients' life. On the other hand, due to the chronic nature of the disease, pharmacological approaches should be adopted with caution for long-term use. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as acetaminophen, ibuprofen, naproxen, gels, and creams containing topical analgesics are the mainstay of osteoarthritis pain treatment recommended by physicians, but these have serious side effects such as cardiac, vascular and gastrointestinal tract conditions, and have debilitating effects on the structure of joints. In addition, they have short-term effects and need to be used frequently to relieve clinical manifestations. Among the treatments with long-term effectiveness are injections of hyaluronan and finally joint replacement with surgery. However, although acute osteoarthritis can be effectively treated with joint replacement, functional improvements in this area as well as the longevity of the prosthesis appear to be limited [4]. Therefore, in order to prevent the spread of osteoarthritis due to the increase in the middle-aged to elderly population and the greater prevalence of overweight, effective treatment strategies are needed.

Pathogenesis of osteoarthritis

Numerous studies have shown that increased oxidative stress contributes to the progression of osteoarthritis [5]. In osteoarthritis, exposure to inflammatory cytokines such as interleukin beta elevates oxidative stress by stimulating the production of reactive oxygen species and nitric oxide in cartilage cells and sinusocytes. Therefore, cartilage is destroyed as a result of an imbalance between the synthesis of anabolic and catabolic breakdown of cartilage matrix. Thus, strategies that reduce inflammatory cytokines and oxidative stress slow the rate of osteoarthritis, indicating the potential to increase dietary antioxidant intake to manage osteoarthritis. Laboratory and clinical studies have provided a rationale for consuming natural products [6] and antioxidants to manage osteoarthritis [7].

New approaches in the treatment of osteoarthritis

Today, new evidence of the role of nutritional factors in improving (decelerating or reversing) symptoms and treating osteoarthritis has been published in clinical trials. Dietary supplements are compounds that have antioxidant, anti-inflammatory, or protective effects, and can alleviate chronic pain and the course of the disease. In addition, the health features, affordability and availability of the nutrients have made them suitable for preventing disorders such as osteoarthritis, and slowing the progression of chronic inflammatory diseases. In this article, we review the effectiveness and health of various non-pharmaceutical oral supplements in this area, which will be mentioned below (Table 1).

Table 1. The oral supplements containing different types of nutrients studied in the current research

Type of nutrients	Active components
Micronutrients	Antioxidant vitamins (C, E, and Beta-carotene)
	Non-antioxidant vitamins (D, B, and K)
	Salts and minerals (magnesium, selenium, zinc and copper)
Macronutrients	Essential amino acids
	Carbohydrates (hyaluronic acid, glucosamine and chondroitin sulfate)
	Fats (soybean oil, avocado oil and omega 3 fatty acids)
Other ingredients	Collagen hydrolysates
	Polyphenols
	Turmeric
	Gum (e.g., <i>Boswellia serrata</i>)
	Root extracts (e.g., ginger root extract, the devil's claw, cat paw)

The effect of oral supplements containing micronutrients

These supplements contain three groups of vitamins and minerals. These substances are not energizing, but they play a key role in the body's biochemical reactions. We will mention the effect of micronutrients in the treatment of osteoarthritis.

Antioxidant vitamins

Ascorbic acid (vitamin C)

Not only does ascorbate completely protect lipids from oxidative damage, but it also protects oxidative damage from alpha-tocopherol, urate (salt or uric acid ester) and bilirubin. The data showed that a higher intake of vitamin C was associated with a reduced risk of knee pain but was not effective on pain intensity [2]. Other studies have reported that a higher intake of vitamin C in the form of calcium ascorbate was associated with a reduction in osteoarthritis of the knee [8], reduced joint space degradation, and pain relief [9].

Alpha-tocopherol (Vitamin E)

Alpha-tocopherol is the only fat-soluble antioxidant and chain breaker in plasma red blood cells. The results of several studies showed that osteoarthritis patients received less vitamin E than the recommended daily allowance. In short-term clinical trials, researchers reported that vitamin E intake was effective in relieving pain and had a similar effect to diclofenac. Longer-term clinical studies have confirmed the effects of vitamin E supplementation on improving pain, stiffness, or physical function in patients with knee osteoarthritis over 6 months. In two other studies, it was found that higher dietary vitamin E intake was associated with a reduced risk of knee osteoarthritis in men and reduced osteoporosis in women [9].

Beta-carotene and other carotenoids

Beta-carotene can act as a free radical scavenger antioxidant at low oxygen pressures (less than Torr 150). However, at high oxygen pressures, it loses its antioxidant activity and shows a peroxidant effect. Studies showed that volunteers with the highest serum levels of lutein or beta-cryptoxanthin were less likely to

develop osteoarthritis, while participants with the highest levels of trans-beta-carotene were more likely to develop osteoarthritis [7]. Although more beta-carotene reduces the risk of osteoarthritis, there is no evidence that carotene supplementation is associated with reduced pain and improved knee function in patients with osteoarthritis of the knee [1].

Non-antioxidant vitamins

Vitamin D

Since the normal metabolism of bone and cartilage depends on the presence of vitamin D, its deficiency has a negative effect on calcium metabolism, osteoporosis, bone density, and articular cartilage circulation. Vitamin D has a direct effect on articular cartilage by stimulating proteoglycan synthesis. Studies have shown that adequate vitamin D has beneficial effects on maintaining knee cartilage, reducing pain and improving physical function in people with knee osteoarthritis, while low intake of this vitamin was associated with higher risk of developing osteoarthritis of the knee [8].

B vitamins

High-dose niacin (B3) supplementation was associated with reduced osteoporosis and improved osteoarthritis symptoms in women but had no effect in men. Similar results were reported with higher levels of other B family vitamins, such as vitamins B1, B2, B6, and B12 in men and women, which were associated with lower bone density and osteoporosis in women but not in men [9].

Vitamin K

Vitamin K is one of the fat-soluble vitamins that the human body needs to synthesize proteins essential for blood clotting and skeletal maintenance. Clinical studies have shown that reduced plasma vitamin K levels were associated with higher incidence and progression of knee osteoarthritis [9, 10] and increased prevalence of hand osteoarthritis [9]. More vitamin K intake was associated with lower incidence of knee osteoarthritis and reduced joint space and osteoporosis [10].

Salts and minerals

Magnesium acts as a calcium channel antagonist. Studies have shown that higher serum magnesium concentrations were associated with lower prevalence of knee osteoarthritis and less destruction of joint space on radiographic observations [11]. The rate of arthritis degeneration was higher in areas of the world where the daily boron intake was 1 mg/day or as compared with areas of the world where boron daily intake was 3-10 mg/day [11]. Selenium is a component of glutathione oxidase that protects macromolecules against oxidative stress. Taking selenium for several months may help reduce joint pain and inflammation. Low levels of zinc and copper have also been reported in osteoarthritis patients. There is evidence that zinc may play a role in the treatment of osteoarthritis due to its anti-inflammatory and antioxidant activity [12].

The effect of oral supplements containing macronutrients

These supplements contain three groups, including protein as a source of essential amino acids, carbohydrates and fats that are sources of energy, which are discussed below in the role of macronutrients for the treatment of osteoarthritis.

Dairy products fortified with hyaluronic acid

Hyaluronic acid (HA) is a polysaccharide of high molecular weight formed of 1.4- D-glucuronic acid and 1.3-N-acetyl-D-glucosamine [12]. Its molecular weight is between 10^4 - 10^7 daltons. Today, hyaluronan injection is a new analgesic treatment for the osteoarthritis of the knee joint. It is used in patients with no response to simple treatment programs and mild analgesics. It is particularly used for patients who do not tolerate or do not respond well to nonsteroidal anti-inflammatory drugs, although not a definitive treatment. On the other hand, using HA supplements or enriching dairy products with it while increasing the nutritional value of these products can be effective to prevent and treat osteoarthritis. HA is commercially extracted from rooster comb. It is also produced during the fermentation of lactic acid bacteria, especially *streptococci*, including *Streptococcus thermophilus* and *Streptococcus zeopidermicus* [13]. In a

cross-sectional study, the symptoms of osteoarthritis of the knee were significantly lower in milk and dairy consumers than in those who rarely consumed milk. In a study that lasted for more than 4 years, a significant relationship was observed between greater milk consumption and decreased destruction of joint space in women with osteoarthritis of the knee, but the results was not significant in men. Gender seems a key factor in the emergence of the symptoms of this disease [14].

Soy and avocado oil

In recent years, the use of supplements containing avocado oil and soy extract has greatly expanded in the treatment of osteoarthritis. It seems that the combination of one third of avocado oil and two thirds of aqueous extract of soybean has an effective role in reducing the symptoms of this disease by balancing the catabolic and anabolic processes in cartilage. Recent review studies have shown positive effects of daily intake of 300 to 600 mg of avocado oil and soy extract supplements in the short-term treatment of osteoarthritis, but there is no strong evidence for the effectiveness of this supplement in the long-term treatment of osteoarthritis [15]. In this study, the use of NSAIDs in patients with osteoarthritis of the knee and pelvis was reduced during 6 weeks while using supplements of avocado oil and soy extract. In a similar study, with longer duration of treatment, no statistically significant difference was observed between the two doses of 300 and 600 mg of supplements containing avocado oil and soybean extract [16]. Consumption of soy-containing compounds such as soy milk, soy protein and soy extract alone was effective in improving the symptoms of the disease. In one study, higher dietary intake of soy milk was associated with a reduced incidence of knee osteoarthritis, but it had no effect on reducing joint damage [16].

Glucosamine and chondroitin sulfate

Glucosamine is an amino monosaccharide used in the biosynthesis of proteoglycans and glycosaminoglycans, as components of cartilage, and is obtained from animal sources such as crabs, lobsters, oysters and shrimp. Laboratory studies have shown that glucosamine affects

inflammatory cytokine mediated pathways and the development of immune responses. In several clinical trials, the results of the effect of glucosamine in the form of sulfated and chlorinated derivatives on pain relief and performance improvement in patients were contradictory. In this regard, some studies showed pain improvement [17, 18] while others showed no effect on quality parameters of life [19]. Side effects of glucosamine use include increased insulin resistance in patients with diabetes. However, the side effects of taking it were less than non-steroidal anti-inflammatory drugs [19].

Chondroitin sulfate is a major component of articular cartilage and belongs to the group of glycosaminoglycans. Studies have shown that chondroitin sulfate helps absorb water and nutrients in cartilage. Other functions include maintaining the viscosity of the joints, reducing the apoptosis of cartilage cells, stimulating the mechanisms of cartilage repair, and inhibiting the enzymes that cause cartilage breakdown. Different clinical results have been reported regarding the effects of chondroitin sulfate on pain relief, which was expected due to its anti-inflammatory activity, but these studies did not indicate the effect of treatment duration or clinical efficacy, despite being safe for long-term use [19]. It is commonly used in commercial chondroitin sulfate products with glucosamine for greater effectiveness. Due to the synergistic effect of chondroitin sulfate and glucosamine, this combination has shown better performance in relieving pain and improving the quality of life of patients. However, the mechanism of their effect is still unclear [19].

Omega 3 fatty acids

Marine oils containing omega-3 fatty acids, especially fish oil, seem to be effective in controlling pain in patients with osteoarthritis by reducing inflammatory markers [20]. Although older clinical studies have shown that polyunsaturated fatty acids have no significant effect on the recovery of patients with osteoarthritis, Liu et al. (2018) in a clinical study found that omega-3 intake plays a role in improving pain in these patients [3]. This study also revealed that higher doses of omega-3 have fewer analgesic effects than the common dose. Other studies suggest that omega-3 fatty acids reduce patients' need for analgesics to reduce pain. Also, the role of

eicosapentaenoic acid fatty acids (EPA; 20: 5 n-3) in relieving pain in these patients is greater than that of docosahexaenoic acid (DHA; 22: 6 n-3), for which the ratio of EPA to DHA should be greater than 1.5 [3]. Further studies are needed to draw definitive conclusions about the effect of omega-3 fatty acids in relieving pain in patients with osteoarthritis. Additionally, Peanpadungrat et al. (2015) found that in patients with osteoarthritis of the knee, consumption of 1000 and 2000 mg of fish oil in doses of 200 mg of DHA and 400 mg of EPA reduced patients' pain and the daily movement speed in these people increased compared to the control sample [21]. In addition, the higher dose (2000 mg) was not more effective than the lower dose (1000 mg) [21]. In another study, low-dose fish oil supplementation (0.45 g omega-3 fatty acid) compared with the higher dose group (4.5 g omega-3 fatty acid) in patients with osteoarthritis of the knee over 2 years showed that the lower dose resulted in more pain relief and better knee function. Also, there was no difference between the two groups in terms of cartilage volume loss, bone marrow lesions, quality of life and use of non-steroidal analgesics during 2 years [22].

The effect of other oral supplements in the treatment of osteoarthritis

Methyl sulfonyl methane (MSM)

It is usually found in combination with glucosamine and/or chondroitin supplements. Methyl sulfonyl methane is present naturally and in small amounts in some green plants, fruits and vegetables. MSM has anti-inflammatory and analgesic properties. In two clinical trials, MSM alone was evaluated in combination with glucosamine and chondroitin for the treatment of patients with osteoarthritis. The results showed that MSM reduces swelling on average but does not reduce joint dryness. Also, based on the results of this study, the combined use of glucosamine-chondroitin-MSM significantly reduced pain and increased the ability to move compared to glucosamine-chondroitin [23]. It should be noted that based on limited research, MSM reduces some of the symptoms of osteoarthritis on average, but since these trials are short-lived and there is no reliable evidence of long-term safety of the drug, it is strongly recommended that this combination not be prescribed for long-term use.

S-adenosyl methionine (SAmE)

This compound is produced from methionine in the liver. SAmE is thought to increase chondrocytes and increase cartilage thickness and may also reduce cytokine-mediated chondrocyte destruction. SAmE may reduce inflammation by inhibiting cyclooxygenase-2 (Cox-2) and directly lead to analgesic effects in the center or peripheral surfaces of the joints. Therefore, SAmE has the potential to be used to treat osteoarthritis patients. Studies have shown that the effectiveness of SAmE in reducing osteoarthritis pain is comparable to NSAIDs. Although SAmE reduces pain, therapeutic effects take several weeks to appear [23]. A 16-week study of the efficacy of SAmE with celecoxib in patients with osteoarthritis of the knee showed that the SAmE group was slower in the onset but, like celecoxib, improved the symptoms of osteoarthritis. It was also found that SAmE was very effective in reducing functional limitation but not in reducing pain [24]. Since SAmE is an unstable compound, lower amounts of SAmE or less active compound derived from it in a pharmaceutical product may raise concerns about the reliability of osteoarthritis treatment.

Collagen hydrolysates peptides (Collagen Hydrolysates)

These compounds are made from the breakdown of collagen in the connective tissue of animals. As a major disorder associated with osteoarthritis is the destruction of articular cartilage to varying degrees, the use of collagen supplements that are produced through partial hydrolysis of collagen allows the body to absorb larger amounts of amino acids, which improve the structure of the cartilage matrix. Lightweight peptides from collagen hydrolysis are likely to have a direct effect on pain. Also, a study in patients with mild osteoarthritis of the knee confirmed an increase in the thickness of the tibial cartilage (Tiba) over 24 weeks under the influence of hydrolyzed collagen [24].

Polyphenols

Pycnogel or bark of a pine tree, also known as Pinus pinaster, is a polyphenol concentrate containing phenolic acid, catechins, taxifolin, and proanthocyanidins, which has various clinical effects. This type of plant substance is effective in reducing inflammation by inhibiting metalloproteinases. The most important phenolic

compounds in pomegranate (*Punica granatum L.*) are punicalagin B and flavonoids that are effective in relieving pain and inflammation [25]. Green tea (*Camellia sinensis*) also contains phenolic compounds such as epigallocatechin-3-galate, whose positive effects on reducing pain and inflammation have been confirmed [25]. Hashempur et al. (2018) evaluated the effectiveness of green tea extract in patients with knee osteoarthritis for 4 weeks. The results showed a decrease in pain scores and an increase in physical function in the green tea extract group with diclofenac compared to the diclofenac group alone [26].

Turmeric (Curcuma longa)

Turmeric contains three active compounds, curcumin, demotoxic curcumin, and bis demotoxic curcumin of which curcumin inhibits inflammation, cell growth, and induces programmed cell death. The anti-inflammatory effects of curcumin depend on the inhibition of cyclooxygenase, TNF- α and other inflammatory factors. Recent studies confirm the positive effect of curcumin in reducing pain and inflammation in osteoarthritis. It also showed a reduction in the severity of inflammation and pain in these patients [26]. Another study by Panahi et al. (2014) on 19 patients with osteoarthritis found that patients who took capsules containing 1500 mg of curcuminoid for 6 weeks had less pain and inflammation than the control group [27]. Another study in patients with osteoarthritis of the knee for 6 weeks showed that turmeric reduces pain and the use of painkillers, while this combination has no side effects with a good acceptance among patients [28]. Nevertheless, Pinsornsak et al. (2012) reported that the use of a combination of curcumin and diclofenac in comparison with diclofenac alone did not show any beneficial effect on osteoarthritis patients [29].

Boswellia serrata

Boswellia serrata is a gum extracted from the Frankincense Indian tree native to tropical Africa and Asia that has long been used to treat inflammatory diseases such as rheumatoid arthritis and osteoarthritis. This type of gum contains a chemical compound that inhibits the enzyme

lipoxygenase. In a study in patients with osteoarthritis of the knee that lasted for 8 weeks, a statistically and clinically significant difference was observed between the group consuming *Bosulia cerata* extract and the control group in terms of reducing pain and joint swelling and enhancing the ability of the knee to bend and move [30].

Ginger (Zingiber officinale)

Ginger root extract can be used as a powder, capsule and oil to reduce the clinical manifestations of osteoarthritis patients due to the presence of small amounts of salicylate. Studies show that ginger has an inhibitory effect on Cox-2 and lipoxygenase, which leads to anti-inflammatory effects in the affected person. In a study conducted by Dehghan et al. (2018), it was found that ginger gel was effective in relieving pain, reducing morning dryness and improving the physical function of patients with osteoarthritis of the knee [30]. Also, the effect of topical application of ginger gel was not significantly different from that of piroxicam gel. Besides, they stated that ginger extract with specific phytochemicals is effective in reducing inflammation and relieving pain, so it can be used as a safe supplement for patients with painful osteoarthritis of the knee [30].

The devil's claw (Harpagophytum procumbens)

This plant is native to Africa, which takes its name from the appearance of its fruits, which prevents animals from accessing the seeds of the plant; the underground roots and stems of this plant have therapeutic effects. The active ingredients of this plant are harpagoside, harpagid, flavonoids (luteolin and camphorol), phenolic acids, cinnamic acid, caffeic acid, chlorogenic acid, quinones and phytosterols. In particular, the devil's paw contains iridoid glycosides which have antioxidant and anti-inflammatory effects and prevent the activation of free radicals. This plant has anti-inflammatory and analgesic properties due to its inhibition of Cox-2 and lipoxygenase, thereby having antioxidant effects. Evidence showed improved joint pain and function in both groups, but the harpagophytom group used fewer antipyretics and NSAIDs and had fewer side effects [30]. The Food and Drug Administration estimated the effectiveness and safety of taking an 8-week course of the aqueous extract of Harpagophytum Doloteffin on patients suffering from

back pain or osteoarthritis of the knee or pelvis. Joint pain and function improved between the fourth and eighth weeks. About 10% of patients suffered minor side effects. Overall, studies have shown that the root of the navel plant can reduce osteoarthritis pain in patients at lower doses than NSAIDs, and that its use is less risky than nonsteroidal anti-inflammatory drugs [4].

Cat paw (Uncaria tomentosa)

This plant is a type of climbing plant and is found in the forests of the Amazon and the tropics, South and Central America. It is so named because of the curved thorns on the body of the plant, which resemble a cat's paw. Among the effective compounds in the roots of this plant are tannins, antioxidant compounds and quinoic acid glycosides that are effective in reducing inflammation. The use of cat paw extract in patients with arthritis decreased inflammation by improving the body's immunity. This plant is used as an oral extract or topical creams for use on the sore spot. The American Medicinal Plants Association believes that if not consumed in moderation, this plant may cause abdominal pain or gastrointestinal problems, requiring further studies in the field [7]. The results of research conducted by Liu et al. (2018) on the cat paw plant showed that this plant significantly improved day and night pain, as well as dryness and inflammation of the joints over a period of 8 weeks. The need for conventional analgesics also decreased in these patients [2]. Similar results were found in reducing the symptoms of patients who used cat paw and glucosamine sulfate. In addition, analgesic use was significantly lower in patients who used cat paw and no serious side effects were observed [12, 19].

CONCLUSIONS

Osteoarthritis is a major cause of disability and reduced quality of life, especially in older ages. Osteoarthritis is divided into primary and secondary types depending on the presence or absence of predisposing factors. In the primary type, there is the slower process of joint involvement, while in the secondary type which includes single joint involvement; there are predisposing causes such as diabetes, fractures, dislocations and various inflammations. Due to the fact that the use of painkillers

is controversial in the treatment of this disease due to their side effects, nutrients can be consumed to prevent and relieve osteoarthritis symptoms as a non-pharmacological treatment alone or in combination other medications. On the other hand, dietary supplements found in green plants, fruits and vegetables are healthy, safe and cost-effective compounds which can have long-term usage. Therefore, it is recommended to design clinical trials with higher quality using greater variety of contributing factors such as supplements for safer and more effective treatment of osteoarthritis.

REFERENCES

1. Richette P., Latourte A., Frazier A., 2015. Safety and efficacy of paracetamol and NSAIDs in osteoarthritis: which drug to recommend? *Expert Opin Drug Saf.* 14(8), 1259–1268.
2. Liu X., Machado G.C., Eyles J.P., Ravi V., Hunter D.J., 2018. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis, *Br. J Sports Med.* 52(3), 167–175.
3. Wang A., Leong D.J., Cardoso L., Sun H.B., 2018. Nutraceuticals and osteoarthritis pain. *Pharmacol. Ther.* 187, 167–179.
4. G.B.D., 2016. Disease and injury incidence and prevalence collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the global burden of disease study. *Lancet.* 388(10053), 1545–1602.
5. Sanghi D., Mishra A., Sharma A.C., 2015. Elucidation of dietary risk factors in osteoarthritis knee-a casecontrol study. *J Am Coll Nutr.* 34(1), 15–20.
6. Muraki S., Akune T., En-yo Y., 2014. Association of dietary intake with joint space narrowing and osteophytosis at the knee in Japanese men and women: The ROAD. *Study Mod Rheumatol.* 24(2), 236–242.
7. Li H., Zeng C., Wei J., 2016. Associations between dietary antioxidants intake and radiographic knee osteoarthritis. *Clin Rheumatol.* 35(6), 1585–1592.
8. Zheng S., Jin X., Cicuttini F., 2017. Maintaining vitamin D sufficiency is associated with improved structural and symptomatic outcomes in knee osteoarthritis. *Am J Med.* 130(10), 1211–1218.
9. Misra D., Booth S.L., Tolstykh I., 2013. Vitamin K deficiency is associated with incident knee osteoarthritis. *Am J Med.* 126(3), 243–248.
10. Shea M.K., Kritchevsky S.B., Hsu F.C., 2015. The association between vitamin K status and knee osteoarthritis features in older adults: the health, aging and body composition study. *Osteoarthritis Cartil.* 23(3), 370–378.
11. Zeng C., Wei J., Li H., 2015. Relationship between serum magnesium concentration and radiographic knee osteoarthritis. *J Rheumatol.* 42(7), 1231–1236.
12. Hamad G.M., Taha T.H., Elsayed E., Hafez E.H., Sohaimy S.E., 2017. Physicochemical, molecular and functional characteristics of hyaluronic acid as a functional food. *American J of Food Technol.* 12(2), 72–85.
13. Martinez-Puig D., Mo'ller I., Ce' Fern'andez C., Chetrit C., 2013. Efficacy of oral administration of yoghurt supplemented with a preparation containing hyaluronic acid (Mobilee™) in adults with mild joint discomfort: a randomized, double-blind, placebo-controlled intervention study. *Mediterr J Nutr Metab.* 6, 63-68.
14. Lu B., Driban J.B., Duryea J., McAlindon T., Lapane K.L., Eaton C.B., 2014. Milk consumption and progression of medial tibiofemoral knee osteoarthritis: data from the osteoarthritis initiative. *Arthritis Care Res.* 66(6), 802–809.
15. Gluszek P., Stasiak M., 2016. Symptom-modifying effects of oral avocado/soybean unsaponifiables in routine treatment of knee osteoarthritis in Poland. An open, prospective observational study of patients' adherent to a 6-month treatment. *Reumatol J.* 54(5), 217–226.
16. Li H., Zeng C., Wei J., 2016. Relationship between soy milk intake and radiographic knee joint space narrowing and osteophytes. *Reumatol Int.* 36(9), 1215–1222.
17. Harrison-Munoz S., Rojas-Briones V., Irrrazaval S., 2017. Is glucosamine effective for osteoarthritis? *Medwave.* 17(suppl 1), e6867.
18. Kongtharvonskul J., Anothaisintawee T., McEvoy M., Attia J., Woratanarat P., Thakkinstian A., 2015. Efficacy and safety of glucosamine, diacerein, and

NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis. *Eur J Med Res.* 20, 24.

19. Zeng C., Wei J., Li H., 2015. Effectiveness and safety of glucosamine, chondroitin, the two in combination, or celecoxib in the treatment of osteoarthritis of the knee. *Sci Rep.* 5, 16827.

20. Calder P.C., 2015. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta.* 1851(4), 469–484.

21. Peanpadungrat P., 2015. Efficacy and safety of fish oil in treatment of knee osteoarthritis. *J Med Assoc Thai.* 98(suppl 3), S110–S114.

22. Hill C.L., March L.M., Aitken D., 2016. Fish oil in knee osteoarthritis: a randomized clinical trial of low dose versus high dose. *Ann Rheum Dis.* 75(1), 23–29.

23. Lubis A.M.T., Siagian C., Wonggokusuma E., Marsetyo A.F., Setyohadi B., 2017. Comparison of glucose amine chondroitin sulfate with and without Methylsulfonylmethane in grade I-II knee osteoarthritis: a double blind randomized controlled trial. *Acta Med Indones.* 49(2), 105–111.

24. McAlindon T.E., Nuite M., Krishnan N., 2011. Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. *Osteoarthr Cartil.* 19(4), 399–405.

25. Ghoochani N., Karandish M., Mowla K., Haghhighizadeh M.H., Jalali M.T., 2016. The effect of pomegranate juice on clinical signs, matrix metalloproteinases and antioxidant status in patients with knee osteoarthritis. *J Sci Food Agric.* 96(13), 4377–4381.

26. Hashempur M.H., Sadrneshin S., Mosavat S.H., Ashraf A., 2018. Green tea (*Camellia sinensis*) for patients with knee osteoarthritis: a randomized open-label active-controlled clinical trial. *Clin Nutr.* 37(1), 85–90.

27. Panahi Y., Rahimnia A.R., Sharafi M., Alishiri G., Saburi A., Sahebkar A., 2014. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. *Phytother Res.* 28(11), 1625–1631.

28. Madhu K., Chanda K., Saji M.J., 2013. Safety and efficacy of curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. *Inflammo Pharmacol.* 21(2), 129–36.

29. Pinsornsak P., Niempoog S., 2012. The efficacy of Curcuma longa L. extract as an adjuvant therapy in primary knee osteoarthritis: a randomized control trial. *J Med Assoc Thai.* 95(suppl 1), S51–S58.

30. Dehghan M., Abdoli-Tafti A., Ganji F., Ghaedi R., 2018. Comparison the effects of ginger (*Zingiber officinale*) jelly and piroxicam jelly on pain of knee osteoarthritis. *Sci J of Kurdistan Uni Medical Sci.* 23, 8–17.

