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Nutraceutical Supplements in the Management & Prevention of Osteoarthritis

Manish Bhagvan Ingle, Miss.Pallavi S. Kandalkar, Dr.Kawade Rajendra M,

Harshwardhan Parasaram Moin

Student, Assistant Professor, Principal, Student

Nandkumar Shinde College Of Pharmacy

Abstract-

Dietary substances known as nutraceuticals play a part in the equilibrium of anabolic and catabolic signals in joints. Nutraceuticals are increasingly being studied for the treatment and, more importantly, prevention of osteoarthritis (OA) due to their regulatory role on the homeostasis of cartilage metabolism. Inflammation of the cartilage and synovium is a hallmark of osteoarthritis (OA), a degenerative disease that can lead to joint stiffness, swelling, discomfort, and loss of motion. OA is a complex illness that is regarded as one of the leading causes of disability worldwide because of its high prevalence and overall rise in life expectancy.

The integration of nutraceutical compounds into the diet expands the treatment options for patients with established OA beyond conventional rehabilitation, medication, and surgical strategies because OA impairs the structural integrity of articular cartilage, which heavily depends on a balance between the anabolic and catabolic processes that occur in chondrocytes and synovial fluid of the joints. In our assessment of the current literature, we highlight a few of the numerous nutraceutical components that are readily available and might be utilized as integrators in a daily diet. Examples of these include fish oil, olive oil, and plant extracts used as non-pharmacologic treatments.

Keywords: nutraceuticals; osteoarthritis; prevention; diet

INTRODUCTION

The degenerative condition known as osteoarthritis (OA) is typified by inflammation of the synovium and cartilage, which can result in joint stiffness, swelling, discomfort, and decreased mobility. OA is a multifactorial, extremely complex illness. Owing to the high prevalence of the disease—women are more likely than men to have it after menopause (18%)—and the extended life expectancy, OA is regarded as one of the leading causes of disability worldwide. Even though OA mostly affects the knees, hands, and hips, it also causes changes in the ligaments, synovium, and subchondral bone, among other joint structures. The structural integrity of articular cartilage, which is largely dependent on the equilibrium between

anabolic and catabolic processes in chondrocytes and joint synovial fluid, is compromised by OA. Nutraceuticals are dietary substances that appear to be involved in certain articular cartilage processes based on data from the literature.

The purpose of our descriptive review is to emphasize the significance of non-invasive approaches in the treatment of OA by utilizing the most widely used and accessible nutraceuticals, such as olive oil, fish oil, and botanical extracts, despite the fact that there are numerous studies in the scientific literature regarding the use of a wide range of nutraceuticals as an alternative treatment of OA.

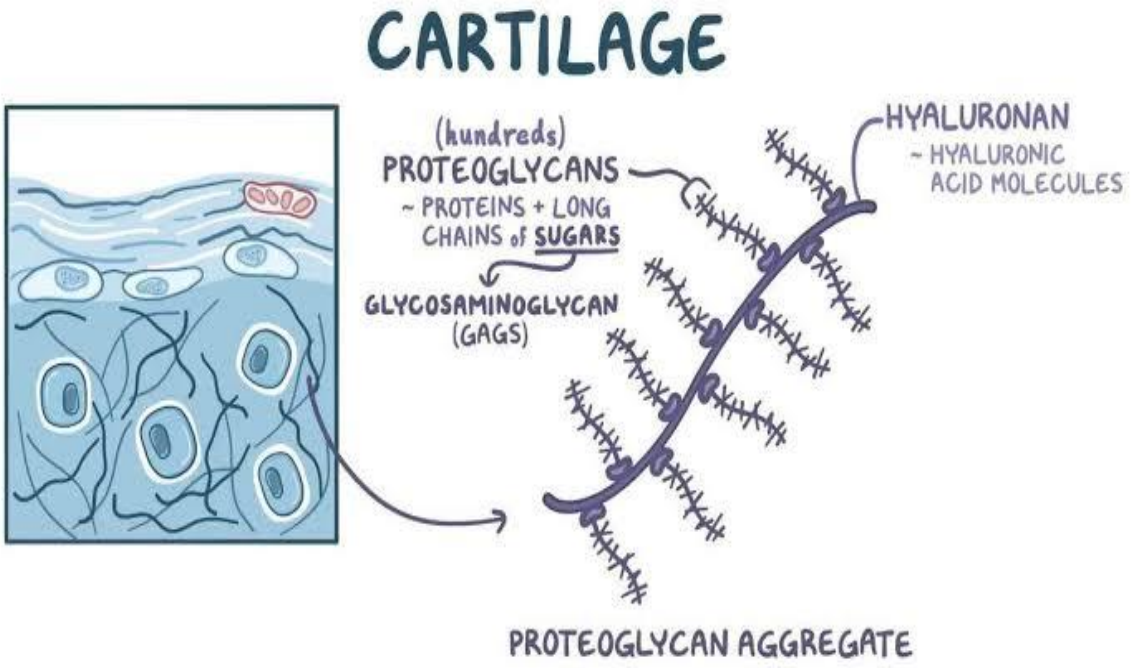
Patients with established OA now have more therapy options thanks to the incorporation of nutraceutical compounds into their diet, which go beyond non-pharmacologic treatment, medicine, and surgery.

CARTILAGE COMPOSITION-

All joints contain hyaline (articular) cartilage, which serves as a low-friction, wear-resistant tissue that distributes and bears weight. It lacks innervation, which makes it insensitive to pain. Additionally, it lacks a blood supply, which results in low metabolic activity and limited capacity for regeneration.

Water, type II collagen, big aggregating proteoglycans, and chondrocytes are the main constituents of cartilage. Around 60% to 80% of the cartilage's weight is made up of water, most of which is found in the interstitial intrafibrillar area. About 10% to 20% of cartilage's wet weight is made up of type II collagen, which also gives the tissue its tensile and shear characteristics.
The two forms of glycosaminoglycans, chondroitin sulfate and keratin sulfate, which are attached to protein cores and connected to hyaluronic acid, make up the big molecules known as proteoglycans. The collagen's entangled proteoglycan arrangement contributes to the cartilage's continued permeability.

An integral component of cartilage connective tissue, chondrocytes are dispersed throughout a dense, biphasic extracellular matrix that is made up of a fluid phase made up of water and ions and a solid phase made up of collagen and proteoglycans. In the bone marrow, chondrocyte cells first develop as stem cells before differentiating into the required cell types.



Initially chondroblasts, the stem cells generate chondrin, which actively constructs and repairs cartilage. As the chondroblasts develop, they become round chondro-cytes instead of flat ones. Chondrocytes start to repair when cartilage is damaged, and they may even be able to replace the destroyed tissue. The only cells in cartilage are chondrocytes, which are in charge of maintaining and secreting this matrix.

More than 90% of the load transmission function is attributed to the stiffness and viscoelastic qualities of the cartilage, which are established by high pressurization and low permeability. Collagen fibers and proteoglycans combine to form a fiber-reinforced composite solid matrix. Chondro-cytes facilitate the fluid exchange between the cartilage's gelatinous layers, which nourishes the tissue and allows waste products to be eliminated. Viscoelastic and mechanical qualities for load distribution are provided by the matrix and fluid combination. Within this extracellular matrix, both anabolic and catabolic activities take place, and their equilibrium is essential for maintaining the homeostasis of articular cartilage.

Nutraceuticals-

Glucosamine-

The production of glycosylated proteins and lipids is preceded by the water-soluble amino monosaccharide glutacamine. One of the most prevalent monosaccharides in the body, glucosamine has an oral bioavailability of about 20% and can be purchased as a dietary supplement. According to the authors of some research, glucosamine influences the cytokine-mediated pathways that control immunological responses, inflammation, and cartilage breakdown. By inhibiting interleukin 1-~ (IL-1}), glucosamine appears to have immunomodulatory effect. This may lessen inflammation and cartilage degradation while promoting the synthesis of pro-teoglycans. Glycosaminoglycans, which have been shown to constitute the main constituent of cartilage, are also precursors of glucosamine.

Therefore, it's also plausible that taking glucosamine supplements could encourage the creation of glycosaminoglycans or lessen their breakdown. Lastly, it has been shown that glucosamine serves as a substrate for the manufacture of new chondroitin sulfate.

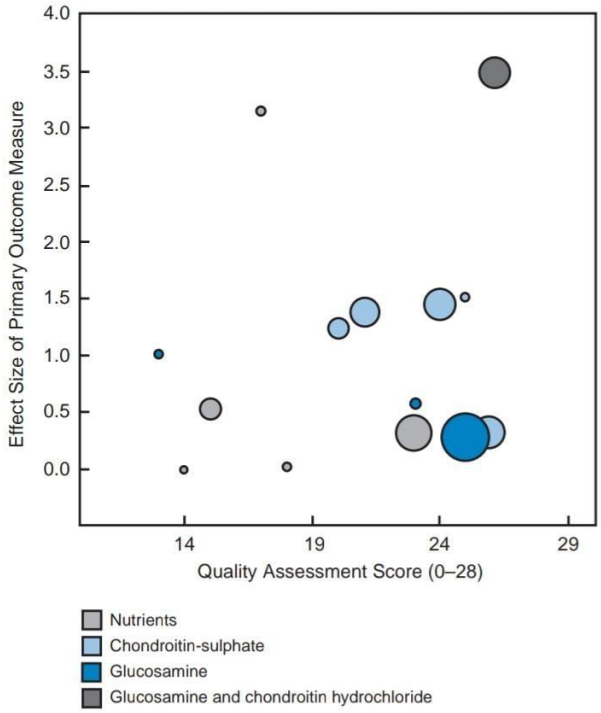


Figure 1. Bubble graph demonstrating the single studies with quality assessment scores on the x-axis and effect sizes of the primary outcome measured on the y-axis; the size of the bubble varies according to the number of patients included in the study. The dark blue bubbles denote studies with glucosamine; the light grey bubbles indicate studies with diverse nutrients, the dark grey one a study with a combination of glucosamine and chondroitin hydrochloride, and the light blue bubbles refer to studies with chondroitin-sulphate.

Chondroitin

The most prevalent glycosaminoglycan in cartilage is chondroitin 4- and/or 6-sulphate, which is made up of glucuronic acid and galactosamine. Along with collagen and non-collagenous glycoproteins, it is a component of the proteoglycan macromolecule (Figure 1), which gives cartilage its resilience. About two million Daltons make up its molecular mass. The amount that reaches the synovial fluid, cartilage, and bone, as well as whether and how this substance is reabsorbed from the gastrointestinal tract into the blood, are still unknown. Federal drug agencies in Europe, but not in the USA, control this product, which is made from the cartilage of sharks and cows.

In vitro and in rabbits, chondroitin sulphate has demonstrated cartilage-preserving qualities. It reduces the amount of collagenolytic activity generated by human articular chondrocytes in culture in a dose-dependent manner and prevents cartilage loss in rabbits with chymopapain-induced articular artilage damage. Only monosubstances—not combinations of compounds—were taken into consideration in order to produce trustworthy proof. The quality assessment scores of the placebo-controlled or comparative studies are summarized in Table 1, together with the median effect sizes of pain as the main outcome measure.

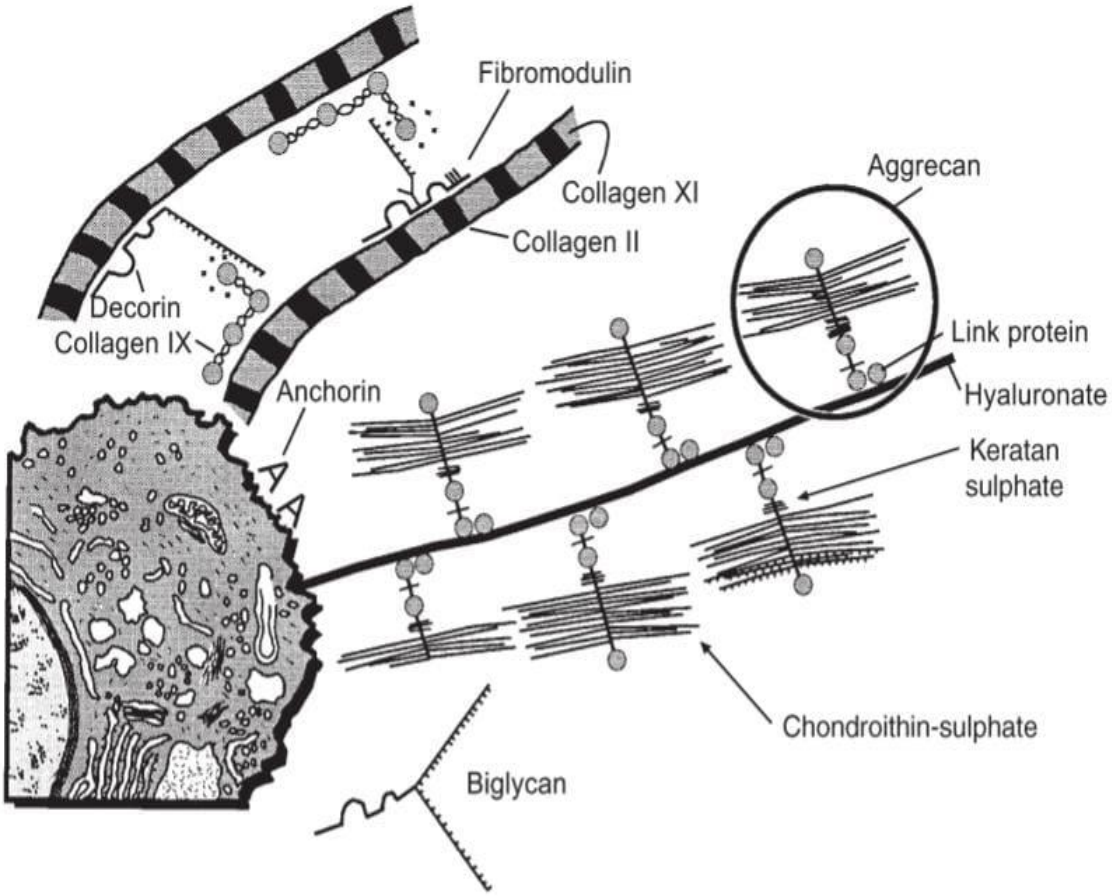


Figure 2. Schematic representation of several proteoglycan molecules attached to a central linear hyaluronan molecule. Each proteoglycan has a central protein core to which are covalently bound keratan sulphate (small side-chains) and chondroitin-sulphate (long side-chains).

The median effect size for pain, the main outcome measure, was 1.37 (range 0.32±1.5), which is comparable to a previously published meta-analysis by McAlindon et al. According to Cohen, this has a significant impact. It's noteworthy that the effect size of MazieÁ et al.'s methodologically most conservative trial showed a value of 0.32 in the intention-to-treat population, similar to the largest study employing glucosamine-sulphate11. Compared to previous trials that lacked intention-to-treat analysis and properly defined outcome measures, this effect magnitude is significantly smaller.Compared to the studies employing glucosamine-sulphate, the median value of the effect size and the effect size of the study with the best methodology were higher (Table 1). Furthermore, compared to glucosamine-sulphate and nutrients, the data are more consistent in terms of effect size and quality assessment score, as seen in Figure 2. When comparing the most recent and largest studies of MazieÁ lva et al. and Reginster et al. with the earlier ones, we could only see a negative association between quality assessment score and effect size since our review's inclusion criteria were more stringent than those of other meta-analyses.

ADVERSE EFFECTS

Despite being thought to be safe, glucosamine and chondroitin supplements have occasionally been linked to mild side effects. In a multicenter open study, Tapadinhas et al. found that the most frequent side effects of taking 1500 mg of oral glucosamine sulfate daily were heartburn (2.7%), diarrhea (2.5%), nausea (1%), and epigastric pain or tenderness (3.5%). Furthermore, glucosamine sulfate appeared to enhance the anticoagulant effects of warfarin in an older patient when added to a stable-dose regimen of the medication, according to a single case report. According to one case report, a patient with chronic intermittent asthma experienced occasional shortness of breath due to a glucosamine-chondroitin sulfate complex, to the point that the patient was unable to ascend stairs effectively.

Pavelká et al.'s three-year study found that glucosamine frequently causes negative side effects. The number of adverse effect episodes did not differ between the treatment and placebo groups. The most commonly reported complaints, which were primarily composed of brief episodes of stomach discomfort and dyspeptic symptoms in 25% of patients, were related to the gastrointestinal tract and liver systems.
Thirty percent of the patients reported having more OA-related symptoms rather than less. It was impossible to determine whether the deterioration was brought on by the supplement or the aging-predicted progression of OA. In 23% of patients, cardiovascular events were primarily episodes of elevated blood pressure or recurrent signs of pre-existing ischemic heart disease. Only one patient in the glucosamine group acquired diabetes during the research, compared to four other patients. According to a review by Stumpf and Lin, glucosamine may be administered to patients without impairing glycemic regulation. In a recent review, Dostrovsky et al. came to the conclusion that there is still uncertainty regarding the connection between glucosamine and glucose regulation. 300 participants in a different published trial comparing chondroitin to a placebo had headaches, gastrointestinal pain, and upper respiratory tract infections. These conditions were nearly identical in type and quantity to those in the placebo control group. There is currently no proof that glucosamine may be used safely during pregnancy. discomfort, an allergic reaction, a heart issue, and an infection of the urinary tract.

Methionine-

Because it cannot be synthesized by the human body, methionine is an essential amino acid that must be obtained from diet. S-adenosylmethionine (SAMe), a precursor of glutathione, is the active form of methionine. Glutathione peroxidase, an antioxidant enzyme, is present in the joints and has antioxidant qualities because to SAMe. Furthermore, SAMe protects the cartilage's proteins and proteoglycans by blocking the enzymes that break it down. According to certain studies, SAMe has a regulatory role in cartilage regeneration because it stimulates the anabolic processes of cartilage. It was also demonstrated that, in patients with OA, SAMe treatment has a longer-lasting positive impact than nonsteroidal anti-inflammatory drug (NSAID) treatment, even though in certain clinical trials SAMe was found to be more effective than a placebo for pain and function and as effective as the NSAID.

In individuals with OA and liver or kidney illnesses that are characterized by a challenge in the metabolic activation of methionine, SAMe has been shown to be an even more beneficial supplement. The typical dosage for SAMe is 800–1600 mg daily, along with proof of adequate folate and vitamin B intake.

Olive oil-

One of the main fats and a staple of the Mediterranean diet is olive oil. Olive oil's phytochemicals, including monounsaturated fatty acids (MUFAs) and phenolic compounds, are thought to be responsible for its anti-inflammatory qualities. An olive oil-supplemented diet has been shown to enhance cartilage healing following anterior cruciate ligament transection in rats.
The effectiveness of the traditional techniques employed in some rural areas of Iran was confirmed by the one double blinded, randomized clinical experiment that showed topical application of olive oil improved pain and physical function in individuals with osteoarthritis in the knee. In this instance as well, the advice of this chemical is limited by the absence of scientific trials proving the impact of dietary supplements containing olive oil.

Fish oil-

There is still much to learn about the precise advantages and efficacy of fish oil consumption in OA patients. Indeed, investigations conducted both in vitro and in vivo demonstrated a dose-dependent reduction in the inflammatory damage to cartilage tissue brought on by fish oil administration. Fish oil contains n-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) that have been shown to have anti-inflammatory properties. These mechanisms include competition with n-6 fatty acids, resolvins, which are anti-inflammatory molecules derived from EPA and DHA, competition for n-3 product receptors with proinflammatory molecules, decreased gene expression of cytokines, cyclo-oxygenase 2, and degrading proteinases, disruption of inflammatory signaling pathways, and decreased lymphocyte proliferation. Probably the biggest obstacle to fish oil being regularly advised is the dearth of human clinical trials demonstrating the effects of supplementation in OA patients. Hill and colleagues' recent clinical experiment, which showed that moderate dosages of fish oil supplementation performed better than high amounts, sparked yet another contentious discussion about the compound's practicality.

Undenatured Type II Collagen

A dietary supplement called undenatured type II collagen (UC-II) is made from the cartilage of the chicken sternum. Research in the literature indicates that treating OA patients with UC-II improves joint mobility and functionality while lowering pain. Through T-regulatory cells that secrete cytokines including transforming growth factor-β and IL-10, which suppress the immune response to collagen type II found in the extracellular matrix of the articular cartilage, UC-II affects the humoral and cellular immune response in an animal model. Therefore, UC-II treatment stops the immune system's proinflammatory overreaction against the articular cartilage in OA patients.

Methylsulfonylmethane (MSM)

The complicated substance and byproduct of dimethyl sulfoxide metabolism in humans is methylsulfonylmethane. It is essential for the body's maintenance and repair of connective tissues. It possesses chemopreventive, anti-inflammatory, and anti-atherosclerotic qualities. It suppresses the formation of prostacyclin (PGI2), according to several studies. It also inhibits peripheral nerve conductance, has antioxidant action, promotes cartilage formation, stabilizes cell membranes, slows down cell loss, and neutralizes free radicals. According to the WOMAC score, forty-nine men and women with knee OA between the ages of 45 and 90 who participated in a 12-week prospective randomized controlled study reported improvements in their physical function and pain. Additionally, studies showed that it has extremely mild negative effects include headache, constipation, bloating, and insomnia. Other nutraceuticals like chondroitin sulfate, glucosamine sulfate, and hyaluronic acid can be combined with MSM.

Curcumin

Due to its numerous therapeutic benefits, turmeric (Curcuma longa) has been utilized for centuries. Turmeric's active component is curcumin. A natural color called curcuma longa has long been used for beauty and therapeutic purposes. It Through the suppression of NF-κB activation through the inhibition of I-κBa phosphorylation, I-κBa degradation, and p65 nuclear translocation, TNF-alpha and matrix metalloproteinase-13 were inhibited. Curcumin may have chondroprotective, antioxidant, and anti-inflammatory properties in OA patients, according to in vitro research. In a 6-week clinical research, OA patients who took 2 grams of curcumin daily reported much less pain than those who took 800 mg of ibuprofen daily. Additionally, there was a noticeable improvement in the pain when walking. In a different study, taking 1500 mg of

turmeric extract daily for 28 days decreased pain in comparison to taking 1200 mg of ibuprofen daily. Curcumin does not cause stomach pain or discomfort like ibuprofen does.

Curcumin's limited systemic bioavailability was also mentioned. Therefore, it should be coupled with Meriva, Theracurmin Flexofytol, and Bioperine to enhance its bioavailability. Additionally, curcumin nanoparticles were created, demonstrating enhanced chondroprotective and analgesic effects. Curcumin-loaded coatings and sustained release curcumin were used to orthopedic implants to guard against gram-positive and gram-negative bacterial infections. Diarrhea, nausea, headache, rash, yellow stool, and elevated serum alkaline phosphatase and lactate dehydrogenase levels were among the adverse effects documented in multiple clinical trials. When breastfeeding, it is not advised. Whole or partial curcumin plants, extracts, powders, tablets, and capsules are all available for purchase.

Ginger

Around 2500 years ago, ginger (Zingiber officinale) was widely utilized to treat a variety of ailments, including vascular abnormalities, arthritis, and nausea. Gingerol, a volatile oil that gives ginger its fiery flavor, is the primary active ingredient in ginger. Gingerol has anti-inflammatory and antioxidant properties because it inhibits COX-2 and, by activating nuclear factor erythroid derived 2-like 2, inhibits interleukin-1b-induced catabolic and inflammatory mediators such as matrix metalloproteinase-13, prostaglandin E2, and nitric oxide. Gingerol has been shown to suppress the synthesis of nitric oxide and numerous other reactive nitrogen species in animal models. According to studies, individuals who took ginger extract for six weeks experienced a significant reduction in WOMAC stiffness scores, walking pain, and standing discomfort. Consuming 1g of ginger powder daily decreased CRP (C-reactive protein) and the serum levels of nitric oxide. This data implies that it possesses anti-inflammatory qualities.

Vitamin D

Vitamin D is a necessary component for bone health, helping to maintain bone mass as people age. A common strengthening ingredient, vitamin D is a fatsoluble vitamin. It is extremely vulnerable to light, heat, and oxygen, which can cause deterioration and isomerization. Vitamin D deficiency causes rickets in children and osteomalacia and osteoporosis in adults. Children and adults may require at least 800-1000 IU of vitamin D3/day if they do not receive enough sun exposure. Research on vitamin D intake and serum or plasma 25-hydroxy vitamin D status was carried out from 1993 to 2017. There was a positive correlation found between 25-hydroxyvitamin D and milk beverages supplemented with vitamin D.

For the formation of previtamin D3 and vitamin D3 in the skin, the maximum amount of sunlight exposure occurred between 11 a.m. to 2 p.m. throughout the year. reduced physical activity, indoor occupations or sports, reduced sun exposure, etc., are all contributing factors to hypovitaminosis D. Increased levels of vitamin D may improve athletic performance. Vitamin D helps the intestines absorb calcium. One function of vitamin D is to lower inflammation in our bodies. Vitamin D can be found in very few natural foods. The finest sources of vitamin D are fish liver oil and fatty fish, such as mackerel, salmon, and tuna.The finest source of vitamin D is liver oil. Only a few nations are advised to use vitamin D-fortified foods.
There are two types of vitamin D: D2 (ergocalciferol) and D3 (cholecalciferol). Ergosterol (yeast) is used to make vitamin D2, and lanolin and cholesterol are used to make vitamin D3. The American Academy of Pediatrics advises older children and adolescents to take 400 IU of vitamin D each day.

Conclusion-

The use of analgesics and anti-inflammatory drugs, surgery, and rehabilitation to promote a healthy body weight, way of life, and level of physical activity are the cornerstones of the management and treatment of OA. However, in addition to conventional clinical treatment, nutritional intervention is a continuous approach to controlling and preventing OA. By controlling the ratio of anabolic to catabolic processes in joint tissue, nutritional interventions may impact redox balance, immunological response, and free radical scavenging, thereby supplying the structural precursors of synovial fluid and cartilage extracellular matrix. Since several of the nutraceuticals we discuss in this study, such GAGs and botanical extracts, have positive effects on joints, nutraceutical intervention is currently seen as a strategic tool for controlling and preventing OA due to its low cost and favorable risk-benefit ratio. Furthermore, research shows that this type of approach not only helps with functional improvement and clinical symptoms, but it may also be able to detect a disease regression. Our descriptive review aims to emphasize the value of non-invasive approaches to treating OA, such as non-pharmacologic therapy, using the most popular nutraceuticals, especially for less severe forms of the disease, even though there are many papers in the scientific literature that address alternative treatments in the management of OA.

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