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Potential Role of Nutraceuticals in the Management of Knee and Hip Joint Osteoarthritis

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Abstract Nutraceuticals is a broad umbrella term that is used to describe any product derived from food sources with extra health benefits in addition to the basic nutritional value of that food. Over the years nutraceuticals have attracted considerable interest due to their potential nutritional, safe and therapeutic effects in a variety of chronic and life style related diseases like coronary blockage, diabetes and osteoarthritis. Osteoarthritis, better considered as a wear and tear of joint is a result of gradual deterioration of underlying cartilage tissue. The disease results in joint pain, stiffness and its long term effect leads to functional impairment. The current treatment modalities of OA include physical, pharmacological and surgical interventions. Use of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and hyaluronic injections have proved significantly effective in pain relief and symptomatic management of this disease however their prolonged use have proven side effects on kidney, heart and liver functioning. The surgical methods like total joint arthroscopy, joint debridement, joint irrigation etc. are employed in severe disease state however recovery and post surgical complications are inevitable. In this view focus is being shifted on the use of alternative therapies and nutritional supplements as pain relieving and cartilage protective agents. In the past 3-4 decades significant research has been conducted on the clinical and *in vitro* testings of nutraceuticals like Glucosamine, Chondroitin sulfate, Hyaluronic acid and others on osteoarthritic subjects and tissues. A large number of dietary supplements are used for a long time for pain relief like cod liver oil for arthritic patients and nowadays as many as one third of suffering populations is using them to improve their clinical condition. The common food sources of these compounds are spinach like leafy vegetables, shark shell, skinned meat etc. Some of the studies have suggested that the efficacy of these nutritional compounds in joint pain relief is equal to non steroidal antiinflammmatory drugs however their onset action is slow. One of the most important limitations associated with their use in treatment of joint related disease is that their clinical efficacy and trials are still lacking. Since nutraceuticals are marketed in a variety of forms like food supplements, injections and powders which have made their effect nonspecific and uncontrollable. In this paper we have covered the results of studies on three well established nutraceuticals (Glucsamine, Chondroitin and Hyaluronic acid) as joint protectors especially in two large weight bearing joints of the body i.e. knee and hip. The results of the studies have indicated that nutraceuticals could represent good alternative means of management of OA however further controlled clinical studies are required for differentiating the effect of purified compound and dose with that of whole food source.

Keywords: *Nutraceuticals, Osteoarthritis, Chondroitin, Glucosamine, Hyaluronic acid*

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1. Introduction

Nutraceuticals are the products isolated or purified from foods and have beneficial role in promotion of health by prevention and treatment of a disease. The term was first coined by Dr. Stephen. Word Nutraceutical is a combination of 'Nutrition' and 'Pharmaceutical'. The advantages of nutraceuticals are their vast availability, no side effects and possibility of self medication [1]. Two major categories of nutraceuticals are phytochemicals and antioxidants. There are a wide variety of phytochemicals like carotenoids from carrot which provide protection from diseases such as cancer, diabetes, heart disease, and hypertension. Antioxidants are present in many organic acids and minerals obtained from plants. Other than these two, many nutraceuticals are animal products like cod liver oil, fishes and others. All these are useful in supplying building blocks of extracellular matrix products of many tissues and prevent cellular damage due to free radicals accumulation. Thus helpful in preventing chronic diseases like osteoarthritis, liver cirrohsis and others [2].

Osteoarthritis (OA) is one of the most prevalent joint disabling disease affecting mainly the elderly (nearly 50% population above 50 years of age and 85% of above 65 years of age worldwide) [3]. The disease is an outcome of gradual deterioration of the articular cartilage tissue due to

wear and tear of it. It results in impaired joint motion, severe pain and stiffness and ultimately leads to joint disability (Figure 1). Its high prevalence and its moderate-to-severe impact on daily life pose a significant public health problem [4].

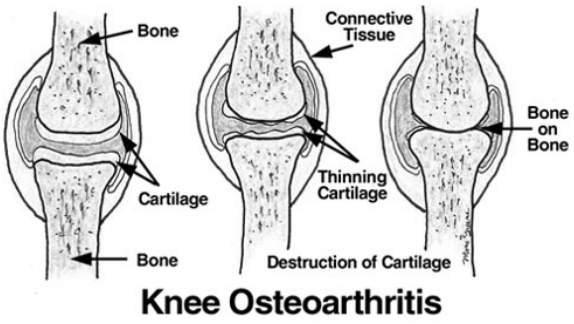

Figure 1. Progression of osteoarthritis in a healthy knee joint

OA has no cure and currently focus is on treatment modalities which relieve the symptoms like joint pain and stiffness. For example, analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly prescribed to OA patients, generally decrease pain and improve function, but have no demonstrated beneficial effect on chondroprotection or OA disease prevention and modification [5]. A prolonged use of these pharmacological agents to relieve OA symptoms is associated with substantial gastrointestinal, renal, and cardiovascular side effects [5,6]. In the current scenario interest has been generated in utilizing nutraceuticals as chondroprotecvive agents due to their safety profile and potential in disease modification. The role of proteins and amino acids, fatty acids (e.g., omega-3), vitamins, and certain minerals in providing building blocks for biological processes and support the structure and function of joints is long established [7,8,9,10].

Various natural compounds present in fruits, teas, spices, wine, and vegetables have shown remarkable potential in modifying OA disease and symptoms. The molecular mechanism is though not clearly known, the effect is believed to be due to their anti-inflammatory, anti-catabolic and antioxidative effects [11,12]. A study has suggested that about 47% of adults in America and Japan consume non-prescribed alternative medications (including food supplements and nutraceuticals) for OA management and it has industry worth 86 billion$ annually in USA [13]. However there are various limitations associated with the use of nutraceuticals in management of osteoarthritis and other diseases like their clinical testings and regulations are not as stringent as pharmaceuticals, majority of them are not regulated by FDA, their bioavailability is lower and effect may be attributed to that of a placebo as their molecular action is not very clear.

Consequently, there is a timely and urgent need for OA therapy which can improve disease symptoms, prevent its progression and is safe for clinical use over long periods of time. This review has provided an imminent view on the efficacy and mechanism of action of commonly used nutraceuticals like Chondroitin sulfate, Glucosamine sulfate and Hyaluronic acid and has discussed recent experimental and clinical data on their effects in management of osteoarthritis with special reference to knee and hip joint.

2. Current Modalities for Management of Osteoarthritis

The primary management of OA is largely based on the alleviation of symptoms and to provide relief to the patient. However the goals of OA therapy are gradually being expanded beyond the current concept of only “pain relief/ joint preservation” to:

- interfere with the induction of cartilage degrading mechanisms due to injury,
- restore normal cartilage and joint homeostasis,
- arrest disease progression in osteoarthritic and post osteoarthritic states,
- revert cartilage damage and restore its normal structure and function.

Current recommendations for the management of OA include a combination of nonpharmacological interventions (weight loss, education programs, exercise etc) and pharmacological treatments (paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs]) [14,15]. In this context, there is a need for safe and effective alternative treatments while the absence of any cure reinforces the importance of prevention. Some of the promising avenues in achieving progress towards cartilage regeneration include viscosupplementation (using hyaluronic acid), disease modifying drugs, and use of NUTRACEUTICALS (like chondroitin sulfate hyaluronic acid and glucosamine) [3,16,17].

Nutraceuticals are broadly classified into three categories:

1. Dietary Supplements including botanicals Vitamins, co-enzymes, minerals
2. Functional Foods Oats, bran, Psyllium, lignin's, Prebiotics, Omega-3 milk, Canola oil,
3. Medicinal Foods: Transgenic cows and lactoferrin for immune enhancement, Transgenic plants for oral vaccination against infectious diseases.

Among these vitamins, co enzymes and some animal and plant products have been studied for pain relief in osteoarthritis for last three decades. The efficacy of fish oils (e.g. cod liver oil) in the diet has been demonstrated in several clinical trials, animal feeding experiments and *in vitro* models that mimic cartilage destruction in arthritic disease [18,19,20]. Other than this, there is some evidence of use of other nutraceuticals, such as green tea, herbal extracts, chondroitin sulphate and glucosamine preparations in arthritic joint [13,16].

2.1. Glucosamine

Glucosamine is a naturally occurring substance found in the synovial fluid around our joints. It is naturally present in animal bones, bone marrow, shellfish and fungi (Figure 2). Glucosamine plays a vital role in building cartilage and is commonly consumed as a supplement by people with arthritis, especially osteoarthritis. Glucosamine is vital for building cartilage because it is a precursor for glycosaminoglycans which is a major component of joint cartilage. With aging, glucosamine levels go down, which can lead to eventual joint deterioration.

Glucosamine can come in different forms, including like glucosamine sulfate, glucosamine hydrochloride and N-acetyl-glucosamine. Although similar, the three forms

may not have the same effect when used as dietary supplements.

Most studies that have examined the potential health benefits of glucosamine have focused on glucosamine sulfate (GS).

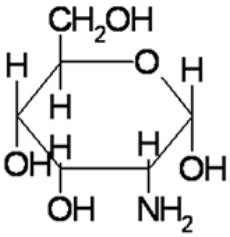

Figure 2. Structure of Glucosamine

Glucosamine has also been used as skin cream for pain relief in arthritis however its effect is not very clear as there is no evidence that glucosamine is absorbed by the skin [21].

According to the National Center for Complementary and Alternative Therapy, a 2007 National Health Interview survey found that 17.7% of adults in the USA regularly took some type of dietary supplement. Of those people, 19.9% took glucosamine, the second most popular dietary supplement after fish oil/omega (37.4%) [22].

Several scientific studies have shown that glucosamine supplements may help patients with osteoarthritis (OA), especially of the hip or knee [23,24,25,26,27]. The effects of glucosamine are manifested by:

- Reduction in osteoarthritis-related pain
- Improved function in patients with knee or hip osteoarthritis
- Reduced stiffness and swelling in the joints
- Continued to provide relief of symptoms up to 3 months after patients stopped treatment.

2.1.1. Molecular Mechanism for Action of Glucosamine Sulfate in OA

The mechanism of action of glucosamine in humans is largely unknown. However being a part of the cartilage matrix in joint tissues; its administration is believed to cause symptomatic relief for OA sufferers by supplying the components for cartilage repair and thus improving pain and disability.

In some recent studies it has been demonstrated in animal models that glucosamine has an anti-inflammatory effect via the reduction of nuclear factor kappa beta induced by interleukin-1 (IL-1) [28,29]. A few studies in humans also have revealed that glucosamine HCl reduces IL-1 stimulated production of catabolic enzymes and inflammatory markers such as prostaglandin E2 by chondrocyte and synovial cells harvested from surgical specimens removed from patients with OA [30,31].

In another recent study on a model of spontaneous osteoarthritis in Harley guinea pigs shows that long-term oral administration of glucosamine sulfate reduces the destruction of cartilage and upregulation of MMP-3 mRNA [32]. Another study suggested that glucosamine can prevent cytokine-induced demethylation of a specific CpG site in the IL1β promoter and cause decreased expression of IL1β [33]. It was suggested that since glucosamine inhibits both anabolic and catabolic genes, the therapeutic effects of glucosamine might be due to anticatabolic activities, rather than due to anabolic activities. In some clinical studies effect of a long term dose of oral GS is monitored and found to have a more decreased Lequesne's index to those receiving a placebo and in comparison to chondotin sulfate and manganese ascorbate [34,35,36].

2.2. Chondrotin Sulfate (CS)

Chondroitin sulfate (CS) is a major component of the extracellular matrix of many connective tissues including articular cartilage. Chondroitin sulfate (CS) is one of the natural glycosaminglycans (GAG) composed of the alternating sugars D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc) (Figure 3). CS is widely distributed in matrix where it forms an essential component of proteoglycans by covalent links with proteins [37]. Commonly referred as a "symptomatic slow-acting drug in OA" (SySADOA), CS is widely used in the management of OA patients [38]. It is often used in combination with other products, including manganese ascorbate, glucosamine sulfate, glucosamine hydrochloride, or N-acetyl glucosamine.

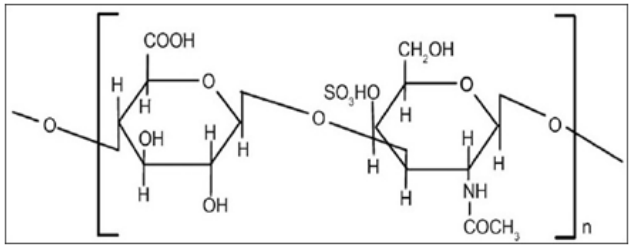

Figure 3. Structure of Chondroitin Sulfate

2.2.1. Molecular Mechanism for Action of Chondroitin Sulfate in OA

Chondroitin Sulfate is part of a protein molecule that helps give cartilage its elastic properties and is thought to have an anti-inflammatory effect, which can help to reduce the painful swelling in the joints that occurs when the exposed bones in the joint rub together. In addition, chondroitin sulfate may also help slow the breakdown of cartilage and help restore cartilage growth to better cushion the joints [39]. Clinical trials have shown that CS reduces pain and improves articular function, reduces joint swelling and effusion, and prevents joint space narrowing of the knee more effectively than Placebo [38,40,41].

CS has a complex role in reducing pain and swelling in joints which may be explained by an anti-inflammatory effect of it, mediated by diminishing the expression of phospholipase A2 (PLA2) [42], of cyclooxy genase-2 (COX-2), and the concentrations of prostaglandin E2 (PGE2) [43,44]. CS is also known to reduce the concentrations of pro-inflammatory cytokines, such as TNF-a [45] and IL-1b [46] and systemic and joint concentrations of NO [47] and of reactive oxygen species (ROS) [45].

Various studies in animal models and in humans have supported that CS has beneficial effect on both articular cartilage and synovial membrane [24,48,49,50]. However the mechanism of action underlying the reduction of synovitis by CS and other glycosaminoglycans remains incompletely characterized.

CS also has *in-vitro* anti-inflammatory properties and its addition to synoviocytes culture during the stationary phase of growth stimulates hyaluronate synthesis which is suggested to reduce inflammation in articular tissues [51,52,53].

In a significant GAIT study (Glucosamine/ chondroitin arthritis Intervention trial) conducted by Sawitzke et al 2008, the individual and combined effects of CS and GS were monitored in a large no of human subjects [54]. The results showed potential effect of these compounds only in higher grade of disease. In some cell culture studies, CS has been shown to have anti-inflammatory and anti-catabolic properties on chondrocytes [55].

In a previous study conducted by one of the authors of this paper, CS supplementation has shown an improved chondrocytes morphology and collagen synthesis along with cyclic pressurization protocol in alginate seeded culture of goat chondrocytes [56].

Another study has shown downregulation of m-RNA of inflammatory mediators and matrix degrading enzymes on bovine cartilage explants with glucosamine and chondroitin sulfate treatment [57].

2.3. Hyaluronic Acid

Hyaluronic acid (HA) is a nonsulfated glycosaminoglycan distributed widely in connective tissues like cartilage (Figure 4). It is a naturally occurring substance found in the synovial fluid which acts as a lubricant to enable bones to move smoothly over each other and as a shock absorber for joint loads.

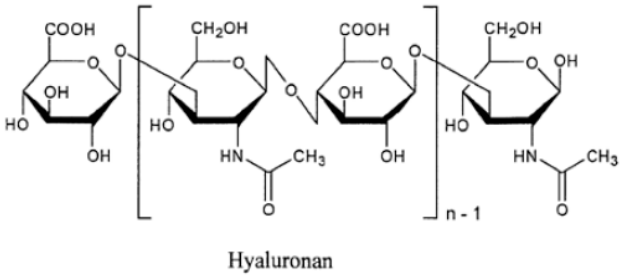

Figure 4. Structure of Hyaluronic Acid

HA is responsible for the viscoelastic quality of synovial fluid that acts as both a lubricant and shock absorber [58]. In synovial fluid, HA coats the surface of the articular cartilage and shares space deeper in the cartilage among collagen fibrils and sulfated proteoglycans (PGs). In this respect, HA probably protects the cartilage and blocks the loss of PGs from the cartilage matrix into the synovial space, maintaining the normal cartilage matrix [58].

Injection of hyaluronic acid into arthritic knee joint with aim of pain relief is known as 'viscosupplementation'.

Viscosupplementation has been shown to relieve pain in many patients who have not responded to other nonsurgical methods [59,60]. The technique was first used in Europe and Asia, and was approved by the U.S. Food and Drug Administration in 1997. Several preparations of hyaluronic acid are now commercially available.

In a significant study intraarticular hyaluronic acid injections were highly effective in improving resting and walking pain in patients with osteoarthritis of the knee [61]. These data support the potential role of intraarticular hyaluronic acid as an effective long-term therapeutic option for patients with osteoarthritis of the knee.

In some of the recent studies attempts are made to repair cartilage defects using injection of a variety of hydrogels like bone marrow concentrate, hyaluronic acid and fibrin and encouraging results are found [62,63].

2.3.1. Molecular Mechanism for Action of Hyaluronic Acid in OA

In acute and chronic inflammatory processes of the joint, the size of HA molecules decreases at the same time as the number of cells in the joint space increases [58]. Administration of exogenous HA in knee cultured cells facilitate the production of new HA synthesis in a dose dependent manner [64].

HA also has a role in nociception i.e. affecting the nerve impulse and nerve sensitivity thus causing a relief in pain as indicated in some of the studies [65,66]. Exogenous HA has noted effects on the extracellular matrix, inflammatory mediators, and immune cells as reported in *in vitro* studies. The influence of HA on these factors may contribute to overall cartilage protection in OA.

In vitro experiments indicate that HA administration can enhance the synthesis of extracellular matrix proteins, including chondroitin and keratin sulfate, and PGs in chondrocytes [67,68].

HA has also been shown to suppress cartilage damage by fibronectin fragments *in vitro* and *in vivo*. These fragments of fibronectin are responsible for increased levels of Matrix metlloproteases and thus suppress PG synthesis [69,70]. Studies have also suggested role of hyaluronan on inflammatory mediators including cytokines, proteases and their inhibitors, and prostaglandins that may translate into cartilage protection. *In vitro* studies showed that HA alters the profile of inflammatory mediators such that the balance between cell matrix synthesis and degradation is shifted away from degradation [71,72,73,74,75].

3. Natural Food Sources of Glucosamine, Chondroitin Sulfate and Hyaluronic Acid

Glucosamine is made in the body from glucose (a sugar) and the amino acid glutamine. Food sources containing high concentrations of glutamine include raw parsley and spinach. Glucosamine sulfate is found in the largest amounts in cartilage-containing products like those harvested from shark and bovine sources. It is widely distributed in the animal world and humans have been ingesting glucosamine in the form of cartilage ("gristle") for thousands of years. It's also a natural component of chitin, a major structural component of the hard shells of clams, oysters, and other shellfish.

The significant source of chondroitin sulfate is also animal cartilage. The major commercially available source is bovine, porcine (pork), chicken and shark cartilage.

Animal products are considered by far to be the best dietary source of hyaluronic acid especially in tissues like meats with large amounts of skin, bones and other connective tissues, beef or pork. Most vegetables are also good sources of hyaluronic acid especially with starchy

roots and tubers like potatoes, sweet potatoes, peas and carrots. Brown rice, soyabean is rich in hyaluronic acid. In addition to meat and vegetables, seeds, nuts, and fruit are all good hyaluronic acid food sources. Foods that is rich in magnesium increases hyaluronic acid absorption like apples, tomatoes, avocados, strawberries, and pineapples. Other foods that may contain or help in the production of hyaluronic acid are pumpkin seeds, yeast, and peanuts.

4. Conclusion

Numerous studies across the world have supported the use of nutraceuticals for relief in clinical symptoms of osteoarthritis and allied diseases. These nutraceuticals not only improve the quality of life in elderly population but also supports the nonsurgical nonpharmacological intervention in osteoarthritis. The strongest data in combating the onset of these symptoms/diseases supports use of supplements of glucosamine, chondroitin sulfate and hyaluronic acid. According to the National Institutes of Health, glucosamine effectively relieves pain, swelling and stiffness in people with this chronic and debilitating condition. Its benefits have been most conclusively demonstrated for people with mild to moderate forms of osteoarthritis affecting the knees. Despite limited availability in natural food sources of glucosamine and chondroitin, some products have been fortified to contain medicinally active quantities of the compound. The potential use of these natural therapies in preventing or minimizing the debilitating effects of osteoarthritis could be worth a try. The clinical effects of glucosamine, chondrotin sulfate and Hyaluronic acid on pain associated with OA of the knee and hip joints are probably mediated by several factors. *In vitro* and *in vivo* studies indicate that these factors can contribute in synthesis of extracellular matrix of cartilage, suppress pain mediators and inflammation and cause relief. However studies related with the efficacy of these compounds in pure form as well as food products, concentration dependent role and their combinatorial effects are still needed.

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Statement of Competing Interest

The authors have no competing interest.

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