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A REVIEW ON THE ROL OF NEUTRACEUTICAL TREATMENT OF ARTHRITIS

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ABSTRACTS

Osteoarthritis (OA) is a disease caused by joint degeneration with massive cartilage loss, and obesity is among the risk factors for its onset, though the pathophysiological mechanisms underlying the disease and better therapeutic approach still remain to be assessed. In recent years, several nutraceutical interventions have been investigated in order to define better solutions for preventing and treating OA. Among them, polyunsaturated fatty acids (n-3 PUFAs) appear to represent potential candidates in counteracting OA and its consequences, due to their anti-inflammatory, antioxidant, and chondroinductive effects. PUFAs have been found to counteract the onset and progression of OA by reducing bone and cartilage destruction, inhibiting proinflammatory cytokine release, reactive oxygen species (ROS) generation, and the NF-κB pathway's activation. Moreover, a diet rich in n-3 PUFAs and their derivatives (maresins and resolvins) demonstrates beneficial effects on associated pain reduction. Finally, it has been shown that together with the anti-inflammatory and antioxidant properties of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, their antiapoptotic and antiangiogenic effects contribute in reducing OA development. The present review is aimed at assessing evidence suggesting the potential benefit of nutraceutical supplementation with PUFAs in OA management according to their efficacy in targeting relevant pathophysiological mechanisms responsible for inflammation and joint destruction processes, and this may represent a novel and potentially useful approach in OA prevention and

treatment. For that purpose, a PubMed literature survey was conducted with a focus on some in vitro and in vivo studies and clinical trials from 2015 to 2020.

KEYWORDS: In recent years, several nutraceutical interventions have been investigated in order to define better solutions for preventing and treating OA.

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease associated with massive cartilage loss, affecting approximately 15% of the total population, and 60% of the elderly population. Normal articular cartilage is made up of connective tissue and covers the load-bearing surfaces at the ends of long bones. The only cells in cartilage are chondrocytes, which constitute the cartilage extracellular matrix (ECM) through a balance between synthesis and degradation. The ECM is basically made up of collagen type II (COL2A1) and proteoglycans, such as aggrecan. This composition guarantees structural integrity and the absence of friction during joint movement. Below the cartilage in the joint is a dense formation: the subchondral bone plate and trabecular bone in the epiphysis, the function of which is to support the loads applied to the joint. There are numerous vessels in the trabecular portion that provide nourishment to the cartilage. Bone formation is attributable to osteoblasts, while osteoclasts' function is bone resorption. In order to perform their functions, these cells need a continuous supply of adenosine triphosphate (ATP); therefore, they are metabolically very active. Articular joints also contain synovial tissue, which is subdivided into intima (the inner layer) and subintima. The synovial intimal cells are fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS); the former is responsible for synovial fluid viscosity, while the latter is tissue-resident macrophages. Moreover, menisci, ligaments, tendons, and adipose depots are all responsible for biomechanical stability and joint function.[5] Hands, knees, and hips are particularly affected by OA, and more specifically, the articular bodies, capsules, bursae, cartilage menisci, ligaments, and muscles. The osteochondral unit consists of cartilage, subchondral bone, and calcified cartilage. This unit, essential for load distribution and joint movement, is modified as OA progresses. In the early stages of disease onset, the cortical plate and subchondral bone undergo rapid bone remodeling, with concomitant bone loss and increased porosity. Changes in calcified cartilage and tidemark destruction are related to the improper passage of substances and vessel generation. Modification of the osteochondral unit leads to unbalanced load distribution with consequent cartilage destruction, which, over time, determines OA onset

and progression. Furthermore, alterations in subchondral bone are responsible for the different crosstalks between chondrocytes and bone cells, which contribute to cartilage destruction. Chondrocytes, responsible for bone formation, are damaged by proinflammatory action of interleukins and metalloproteinases. Furthermore, chondrocytes express molecules such as VEGF (vascular endothelial growth factor), MMP-13 (matrix metallopeptidase 13), and RUNX2 (runt-related transcription factor 2), implicated in hypertrophy and differentiation. Hypertrophy and the surrounding calcified extracellular matrix alter the tidemark on the osteochondral interface, causing microcracks and thinning of the cartilage. OA onset is characterized by greater bone remodeling, with simultaneous bone reduction under articular cartilage. Decreased remodeling and subchondral densification occur during disease progression, together with synovial inflammation and increased inflammatory and catabolic responses. In light of this, intervening on subchondral bone remodeling and maintaining osteochondral unit structural integrity could represent a therapeutic strategy in preventing the onset and progression of OA.

Micro and Macroscopic Features in Early and Severe Osteoarthritis (OA)

OA is characterized by impairments in the structure and functionality of joint cartilage in consequence of an imbalance between anabolic and catabolic processes in the cartilage tissue that could cause its degradation; if cartilage degradation exceeds reparative processes, the OA goes on and advances. This degenerative disease is characterized by several changes (narrowed joint space, thickening, formation of osteophytes, and cysts in the subchondral bone) that are radiographically visible, even if radiographs do not indicate the degree of cartilage degeneration. It is possible to detect osteophytes also through magnetic resonance imaging (MRI), that allow us also to detect geodes or subchondral cysts in advanced stages of OA. Microscopic alterations in joint cartilage are evaluated by the Mankin score or a modified version by Sakakibara et al, that consider several factors such as cell morphology, extracellular matrix staining, and appearance of the tidemark. The highest scores highlighting the most severe damage of joint tissues are 14 for the Mankin score and 32 for the modified Mankin score. Alterations to healthy joint cartilage usually do not exceed grades of 1–3. Histological grading criteria of Kraus′ modified Mankin score and histopathology OARSI system are used as semi-quantitative methods.

Cartilage is mainly composed of collagen type II and the proteoglycan aggrecan and it is characterized by viscoelastic and compressive properties thanks to the extracellular matrix.

Healthy joint cartilage has a smooth surface and it is white, shiny, and elastic. In OA, cartilage instead shows a dull and irregular surface with discoloration and softening and more synovial fluid may be produced, with newly invaded blood vessels. In particular, at the early stage of degeneration, minimal changes are detected in the cartilage surface in which glycosaminoglycans remain homogenously distributed; as the disease progresses, there is a loss of proteoglycans, and in severe OA the cartilage surface is rough and broken by fissures and cracks.

In healthy joint cartilage, four layers are recognizable: superficial zone, middle zone, deep zone, and calcified zone. In the superficial zone, cells are flat and spindle-shaped, parallel to the joint surface. The superficial zone contains the majority of collagen fibers, parallel to the surface, which results in high tensile modulus to resist shear stress at the joint surface. In early OA, mild fibrillations are found in the superficial zone and cartilage presents thickening, a consequence of hypertrophy. As the disease advances, cells of the intermediate and radial zone show mild to moderate hypercellularity; necrotic chondrocytes with pyknotic nuclei in the intermediate and radial zone are found; the synovial membrane includes hyperplasia of synovial lining cells, thickening of the synovial membrane, infiltration of inflammatory cells, and fibrosis. In severe OA, the cartilage shows extensive degeneration: hypertrophic villi and full-thickness defect areas can be seen where the cartilage is missing completely and the subchondral bone is exposed; the subchondral plate itself is thicker and more dense; cells are arranged in clusters especially around fissures or disappear completely as the disease progresses; the cartilage is replaced by fibrocartilaginous, scar-like tissue with fibroblast-like cells. In other cases, full-thickness defects develop, where the bone lacks the cartilage completely; the loss of proteoglycan content reaches the deep zones; the tidemark becomes unclear and finally is invaded by blood vessels from the subchondral bone, which penetrate into the calcified zone. Osteophytes are found in early stages of the diseases, but become more pronounced in advanced stages of OA. The rate of OA progression depends on species and joint localization, and the extent of damage could be dependent on the joint area, which can be explained by different loading conditions in distinct regions.

Articular cartilage is not vascularized nor innervated, so nutrients and cellular repair molecules are transported to the chondrocytes by diffusion from the synovial fluid. Thus, articular cartilage has limited capacities for self-regeneration and, in OA, shows reduced mechanical capacities compared to healthy cartilage. Chondrocytes are very active cells but

they normally do not divide, so only small defects associated with minimal loss of matrix components can be repaired by regeneration; if more wide defects exceed the repair capacity, the damage can become permanent. Because OA involves progressive loss of the structure and functionality of articular cartilage due to an imbalance between anabolic and catabolic processes in the cartilage tissue, preventive and therapeutic interventions are necessary to prevent OA and/or improve the regeneration capacities of joint cartilage.

Role of Inflammation and Oxidative Stress in OA

The structural changes characterizing OA are determined by a series of factors, the most important of which is inflammation. From a clinical point of view, joint inflammation in OA is characterized by joint swelling, warmth, and pain. In particular, inflammation of the synovial membrane, known as synovitis, occurs as a result of interaction between degraded cartilage fragments and the immune system, which generates a protective inflammatory response via synoviocytes. synoviocyt The cartilage fragments are identified as foreign bodies, and therefore, trigger a response from both the innate and adaptive immune systems. Consequently, the inflammatory response is generated through the activation of inflammatory signaling pathways, such as the NF-κB (nuclear factor-κB) pathway. This change is closely related to aging and also occurs in the absence of other conditions, such as obesity and metabolic syndrome. The most studied inflammatory mediators of OA are cytokines that amplify low-grade inflammation, further compromising cartilage. However, obesity is one of the most important risk factors in the onset of OA. It has been shown that the onset of posttraumatic OA is more linked to biomechanical factors, while metabolic OA arises following chronic inflammation and an unbalanced diet; conditions characteristic of obesity. In fact, chronic inflammation, characterized by the increased synthesis of proinflammatory cytokines, such as IL- (interleukin-) 1β and TNF- (tumor necrosis factor-) α, determines greater osteoclast activation, which is responsible for bone resorption.[5] Furthermore, hormones such as leptin and visfatin, which are associated with obesity, are also involved in OA onset and progression. It has been shown that knee osteoarthritis is the most common form among obese people and, in particular, among aging adults. Therefore, damage to joints is not only determined by increased body weight but is also mainly due to a greater synthesis of matrix metalloproteinases (MMPs), such as MMP-1, −3, −9, and −13, disintegrin, and metalloproteinase with thrombospondin motifs (ADAMTS), such as ADAMTS-4 and −5, the presence of which is related to ECM degradation, synovitis, and cartilage and bone injuries. IL-1β induces the upregulation of these enzymes in addition to other catabolic factors,

including inflammatory mediators, nitric oxide (NO), prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2), and reactive oxygen species (ROS). Additionally, oxidative stress can trigger joint inflammation and pain in response to cellular senescence or obesity-related systemic inflammation. In fact, ROS production is deeply involved in OA triggering the inflammation cycles and catabolism, leading to a reduction of glycosaminoglycans and collagen modifications, causing chondrocyte homeostasis alteration and irreversible cartilage matrix degradation with OA development. Joint aging and dysfunction are also related to impaired autophagy, which results in chondrocytes losing the ability to maintain homeostasis and survive in pathological conditions. Indeed, in aged cartilage and in mouse joints with surgically induced OA, autophagic protein expression is downregulated. In OA inflammation, NO plays an important pathological role. NO is synthesized in chondrocytes by inducible NO synthase (iNOS), and its high production rate generates an inflammatory state that contributes to cartilage destruction and cell damage. Studies conducted in OA patients have shown greater NO concentration and iNOS expression in chondrocytes compared to the (still high) levels present at the synovial level. Therefore, NO produced at the cartilage level contributes to OA pathogenesis. In particular, a higher iNOS expression has been demonstrated in the superficial area of OA cartilage, which thus pinpoints the commencement of OA damage, i.e., the damaged cartilage is responsible for the greater NO production. The latter causes cartilage destruction, as it increases chondrocyte-mediated matrix degradation, increases MMPs activity and, at the same time, inhibits the synthesis of matrix components, such as COL2A1 and aggrecan. NO contributes to OA pathogenesis by triggering the inflammatory response, along with increased synthesis of PGE2 and inflammatory cytokines. Furthermore, NO can also be involved in mechanisms related to oxidative damage and chondrocyte death by apoptosis. Therefore, iNOS modulation represents a possible target for OA therapy; in fact, the chondroprotective effects of many molecules of plant origin, such as pomegranate extract, have been demonstrated.

Therapies in OA

OA is a disabling joint disease with a multifactorial mechanism, causing major impairment to quality of life, as well as pain, limitation of movement, and disability. To date, there are no effective therapies for OA; just therapies that confer symptomatic relief or a definitive treatment, such as joint arthroplasty. Treatment such as joint arthroplasty still has a high postsurgical chronic pain incidence that ranges between 20% and 40%. Osteoarthritis pain after prosthesis implantation is one of the most severe secondary syndromes, depending not

only on surgery but also on organic changes before and after joints replacement. Opioid employment could influence postsurgical pain and lead to tolerance or addiction. It is well known that the involvement in hypersensibility of the immune system, the nervous system, and the peptidergic ones is connected due to the opioid receptors on immune cells surface. Recently, it has been shown that the percentage of Mu-positive B cells is statistically lower in OA patients, and this data could be used as a biological marker for an objective diagnosis of chronic pain. Therefore, in order to be effective, OA therapies must be applied either in a preventive manner, or in the initial stages of disease onset. Chronic joint pain is the main symptom of OA, and strategies to relieve it are necessary to improving the quality of life in patients with OA. In fact, the drugs used in OA patients are analgesic and/or nonsteroidal anti-inflammatories (NSAIDs), which only counteract symptoms without acting on OA progression and pathophysiology. Additionally, in long-term therapy, NSAIDs have side effects at the gastrointestinal, renal, and cardiovascular levels; they also manifest liver toxicity, hemorrhaging, and negative effects on chondrocytes and cartilage matrix formation. Consequently, in recent years, alternative solutions with fewer side effects have been sought by the scientific community, such as treatment with natural compounds. In fact, nutritional treatments for the prophylaxis and therapy of other diseases, including heart disease, hepatic steatosis, and metabolic syndrome, are all considered viable therapeutic alternatives. Therefore, such compounds are believed to be important in the prevention and management of articular cartilage structural damage in OA. The data obtained from *in vitro* and *in vivo* preclinical studies confirm the anti-inflammatory and antioxidant effects of the natural compounds used in counteracting both the progression and symptoms in OA. Additionally, human clinical trials have demonstrated the effectiveness of natural compounds for the management and relief of OA pain; this is likely attributable to their anti-inflammatory and antioxidant properties. Thus, although nutraceutical supplementation with natural compounds has been widely used in the past decades to find better solutions to counteract OA development, the benefit of such an approach is not well defined and further studies are required to understand the potential for nutraceutical supplementation in OA treatment. Recently, evidence has been collected showing that polyunsaturated fatty acids (PUFAs) may represent right candidates for nutraceutical supplementation in treating OA, alongside with traditional pharmacological approach. In particular, it has been suggested that their selective anti-inflammatory and antioxidant properties may significantly produce chondroprotective thereby attenuating cartilage loss. In this review, we aim to summarize scientific data demonstrating the effectiveness of PUFAs in OA management and their potential role in

nutraceutical supplementation in OA-related pathophysiological mechanisms. The interest in these nutraceuticals is linked to the fact that they represent important components of the Mediterranean diet.

Polyunsaturated Fatty Acids (PUFAs)

Polyunsaturated fatty acids (PUFAs), and all unsaturated fatty acids (FAs) in general, are lipids consisting of a long hydrocarbon chain with a carboxyl group (-COOH) at the polar hydrophilic end and a nonpolar hydrophobic methyl group (-CH3) at the opposite end. Two classes of PUFAs, n-3 and n-6, are defined as "essential," as they must be taken in via the diet because humans do not have the Δ12- and Δ15-desaturases that catalyze double bond formation in positions n-3 and n-6 of the FA carbon chain. In particular, the n-3 PUFAs have their first double bond between the third and fourth carbon atoms, while n-6 PUFAs have it between the sixth and seventh carbon atoms, counting from the methyl end of the FAs. Linoleic acid and α-linolenic acid, are essential PUFAs as they must be taken in via the diet [36]. The main products of LA metabolism are n-6 PUFA, γ-linolenic, and arachidonic acid, while n-3 PUFAs, such as eicosapentaenoic acid, and docosahexaenoic acid, derive from ALA. The vegetable dietary sources of LA are safflower, soy, and corn oils. ALA, on the other hand, is present in flax seeds, beans, nuts, and the leaves of some green plants. The levels of EPA and DHA obtained by the liver from α-linolenic acid are minimal, and most of their content in the body derives from the diet. In particular, EPA and DHA are abundant in the flesh of both lean and fatty marine fish, as well as in fish oil and algal-derived supplements, although they can also be found in lower quantities in many other foods of animal origin. Therefore, including them in our daily diet in the correct proportions is highly recommended.

CONCLUSIONS

OA, considered by the Osteoarthritis Research Society International (OARSI) a disease characterized by molecular, anatomical, and physiological alterations, needs effective treatment with fewer side effects than current therapies. Therefore, it has been shown that dietary interventions can yield positive results in preventing and slowing the disease. In this context, for example, polyphenols, thanks to their antioxidant and anti-inflammatory properties, are effective. In particular, Valsamidou et al. reported preclinical and clinical studies attesting the positive role of combined polyphenols in the OA treatment.[65] In this review, however, we wanted to focus on the latest research related to the treatment of OA

with other components of the diet, PUFAs. *In vitro* and *in vivo* studies, as well as studies on patients, have shown that nutraceuticals such as n-3 PUFAs can prevent and counteract joint degeneration and cartilage loss in OA. Their efficacy is demonstrated at various molecular levels, but their anti-inflammatory and antioxidant properties seem to have a greater chondroprotective role. In addition, clinical trials have also reported their positive effect on the reduction of pain associated with OA, which is very important as it could improve patients' quality of life.

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