Interventions with polyphenols in osteoarthritis

Subjects: Nutrition & Dietetics

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Polyphenols are plant-derived molecules with established anti-inflammatory and antioxidant properties that have been extensively evaluated in clinical settings and preclinical models in OA. As more knowledge is gained in the research field, an interesting approach in the management of OA is the additive and/or synergistic effects that polyphenols may have in an optimized supplement.

anti-inflammatory antioxidant polyphenols osteoarthritis synergy

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive destruction of the articular cartilage. It affects joints of the body with a greater range of motion, referred to as the diarthrodial joints. Structurally, a diarthrosis comprises, from the inside out, of (a) articular cartilage, which lines the end of the bones; (b) synovial fluid, a lubricating media between two bones; and (c) the joint capsule, which consists of the outer fibrous capsule and the synovial membrane. OA is the most common arthritic malady globally. As expected, the burden of this disease on the health care system is increasing due to the aging of the population [1].

According to Osteoarthritis Research Society International (OARSI), OA “manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function)” [2]. These three domains—molecular, anatomic, and physiologic disease elements—culminate to illustrate the multifaceted pathophysiology of the disease.

Structural alterations are manifested clinically as cardinal symptoms of OA such as pain, crepitus, stiffness, loss of function, erythema and edema. However, the complexity of OA pathophysiology translates to heterogeneous phenotypes that call for different approaches [3]. Delineation of the related phenotypes is challenging and difficult to address and incorporate in the study design of clinical interventions, albeit a meaningful proposition given the poor trial outcomes and limited effective treatment options for OA [4].

Revised recommendations by the American College of Rheumatology (ACR) for the current treatment approach in knee OA comprise of exercise, weight loss, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), and intraarticular glucocorticoid injections [5]. Hyaluronic acid injections are also applied as lubricating agents, while

autologous mesenchymal stem cell (MSC) treatment constitutes a rather recent and effective alternative for the treatment of knee OA [6].

In view of the urgent need for more effective treatments for OA with fewer side effects, several dietary compounds have been examined for their therapeutic potential. OA is a noninfectious civilization disease, and various dietary interventions may predict or slow its progression. Among different nutrients, non-nutrient components, e.g., polyphenols (which are important constituents of a human diet), may be beneficial in the prevention of OA due to their antioxidant and anti-inflammatory properties [7]. As their mechanisms of action in OA are being elucidated, an opportunity arises for their combined use in clinical trials. With that in mind, a review was conducted with the aim of recording recent literature that has evaluated the additive and/or synergistic effects of polyphenols in preclinical models or clinical trials in the management of OA.

2. Polyphenols

Polyphenols are a class of phytochemicals and secondary metabolites of plants with high antioxidant properties. Their structure comprises of at least two phenyl rings and one or more hydroxyl substituents. There are four classes of polyphenols, namely flavonoids, phenolic acids, stilbenes, and lignans. Flavonoids can be further categorized into flavanols, flavanones, flavones, flavonols, isoflavones, and anthocyanins. A well-established body of literature confirms their potent contribution in OA treatment [8][9][10].

Preclinical evaluation of the chondroprotective effects of polyphenols, such as epigallocatechin gallate (EGCG), curcumin, carnosol, hydroxytyrosol (HT), and resveratrol, has shown that these constituents can improve clinical indices and decrease catabolic enzymes, inflammatory cytokines, and oxidative markers [11][12].

At the clinical level, dietary polyphenols have been evaluated in randomized controlled trials (RCTs) such as freeze-dried strawberry powder [13], freeze-dried blueberry powder [14], pomegranate juice [15], tea rich in rosmarinic acid (RosA) [16], and tart cherry juice [17]. Whereas these interventions have reported several beneficial effects, the fact that serum and plasma biomarkers do not always correlate with statistically significant improvement of pain and quality of life highlights the complexity of OA manifestation. Furthermore, lack of uniformity in the primary endpoints set, variation in study duration, and heterogeneity of the administered mixtures do not allow for the definition of their therapeutic attributes.

Extracts from medicinal plants have been extensively investigated for different morbidities, especially in the context of Ayurvedic medicine. Panahi and colleagues (2016) [18] explored the effects of *Elaeagnus angustifolia* extract, which is rich in kaempferol, ferulic acid, and coumaric acid, in knee OA. Patients were enrolled in a 7-week intervention and randomized to receive either a high dose of the extract or a low dose or ibuprofen. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Visual Analog Scale (VAS), Lequesne's Pain-Function Index (LPFI), and the patient's global assessment (PGA) index decreased significantly in all groups but the effect between groups did not reach statistical significance. Another trial [19] evaluated the extract of *Artemisia annua,* formulated as a dietary supplement, in 42 patients randomized in three groups receiving a low

dose of the extract, a high dose of the extract, or a placebo for 3 months. WOMAC and VAS were significantly reduced only in the low-dose group and the extract was well tolerated.

3. Synergy/Pharmaceuticals

A well-known study by Chou et al. published in the mid 1980s [20] focused on the standardization of a theory for quantifying the synergistic interactions between drugs. Currently, this theory is timely as it regards naturally occurring substances with therapeutic potential and their interactions with other constituents, an everlasting struggle of translating and evaluating the preclinical data in living organisms. As Greco et al. (1996) [21] pointed out in reference to anticancer agents, the therapeutic synergy is present when “the observed effect of the combination is more than what would be predicted from good knowledge of the effects of each agent working alone” and there is a fine lining between therapeutic synergy and in vitro synergy.

A therapeutic scheme of drugs must exhibit favorable outcomes at the lowest possible doses. However, when it comes to phytochemicals, this approach is also meaningful, with efficacy and toxicity being at the forefront of every intervention. The need to take the beneficial possibilities of polyphenol-rich interventions one step further in the management of challenging diseases such as OA is unequivocal. This may be achieved with better defined and standardized proprieties that combine constituents with proven therapeutic properties mediated by thoroughly elucidated molecular interactions.

In agreement with this course of action, a standardized extract from the bark of the French maritime pine (*Pinus pinaster Aiton*) Pycnogenol that consists of a mixture of polyphenols [22] has been extensively examined in different models. Preclinical investigation exhibited chondroprotective effects and inhibition of the transcription nuclear factor κB (NF-κB) [23] with the presence of the active ingredients of Pycnogenol not only in serum and blood cells but also in the synovial fluid of patients with severe OA [24]. Furthermore, a RCT showed that all three subscales of WOMAC —pain, stiffness, and physical function—decreased significantly in patients with mild OA receiving 3 × 50 mg of Pycnogenol daily for 3 months compared to the placebo group [25]. Two other RCTs have corroborated these results [26][27].

Another medical food, Flavocoxid (Limbrel), is a product of two flavonoids, baicalin and catechins, that are derived from the botanicals *Scutellaria baicalensis* and *Acacia catechu*, respectively [28]. In a 1-month pilot study, Flavocoxid was deemed as effective as naproxen in reducing short-form WOMAC, physician’s global assessment of disease activity (PGAD), subject’s global assessment of disease activity (SGAD), and subject’s global assessment of disease related discomfort (SGADc), with similar but high percentages of adverse effects for the two groups. In a larger cohort under the same setting but for a longer period, noninferiority of this propriety was demonstrated through the use of WOMAC [29]. At a molecular level, Flavocoxid exerts positive effects mainly through its implication on arachidonic acid metabolism [30][31][32]. Regarding its toxicity and association with acute liver injury and hypersensitivity pneumonitis, a large cohort recently demonstrated that the rate of such incidents was low and marginally elevated compared to NSAIDs [33].

In another RCT, researchers evaluated Reparagen, a polyherbal mixture of extracts from *Uncaria guianensis* (Amazonian tea) and *Lepidium meyenii* (Andean vegetable) against glucosamine, a conventional alternative to NSAIDs [34]. Whereas both treatments yielded significant results in the primary endpoint with a 20% reduction in WOMAC pain in a 2-month period, Raparagen managed to reduce the use of rescue medication.

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