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Nutraceuticals in joint health: animal models as instrumental tools

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Osteoarthritis (OA) is a degenerative joint disease with no curative treatments. Many studies have begun to demonstrate the efficacy of nutraceuticals for slowing down OA. Animal models are utilized as a compulsory step in demonstrating the protective potential of these compounds on joint health. Nevertheless, there exist a wide variety of available OA models and selecting a suitable system for evaluating the effects of a specific compound remains difficult. Here, we discuss animal studies that have investigated nutraceutical effects on OA. In particular, we highlight the large spectrum of animal models that are currently accepted for examining the OA-related effects of nutraceuticals, giving recommendations for their use.

Introduction

OA is a chronically evolving degenerative disease that affects a growing number of individuals within our aging population, and is associated with both a higher risk of comorbidity [1] and a strong socio-economic burden [2]. The World Health Organization (WHO) reported in 2003 that approximately 10% of humans over 60-years old displayed significant clinical symptoms of OA, with >50% of humans over the age of 65 showing radiological evidence of OA. Moreover, it is predicted that the prevalence of OA will continue to increase in coming years as the population ages, especially if preventive measures are not taken.

From a physiopathological viewpoint, OA is a heterogeneous disease that induces whole-joint damage [3]. It is characterized by progressive cartilage loss, subchondral bone remodeling, osteophyte formation and a low-grade inflammation that affects all joint tissues, including the synovium and the infrapatellar fat pad (IFP) (Fig. 1).

OA begins with re-entry of articular chondrocytes into a proliferative program, leading to the formation of clusters with increased anabolic activity and upregulated extracellular matrix synthesis [4]. Eventually, these cells acquire pathological features, becoming hypertrophic repair-like chondrocytes that display augmented catabolic activity. These hypertrophic chondrocytes, along with synovial and immune cells, secrete prostaglandins and interleukin 1beta (IL1β), which contribute to increased cartilage catabolism. Ultimately, metabolic homeostasis is then broken and the degradation of matrix products overwhelms biosynthesis. This phenomenon primarily results from the synthesis of matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), which is associated with a decrease in the tissue inhibitor of metalloproteinases (TIMPs) [4]. In addition, overexpressed cytokines lead to an increased production of nitric oxide (NO), prostaglandin E2 (PGE2) and leukotrienes, which eventually promote chondrocyte

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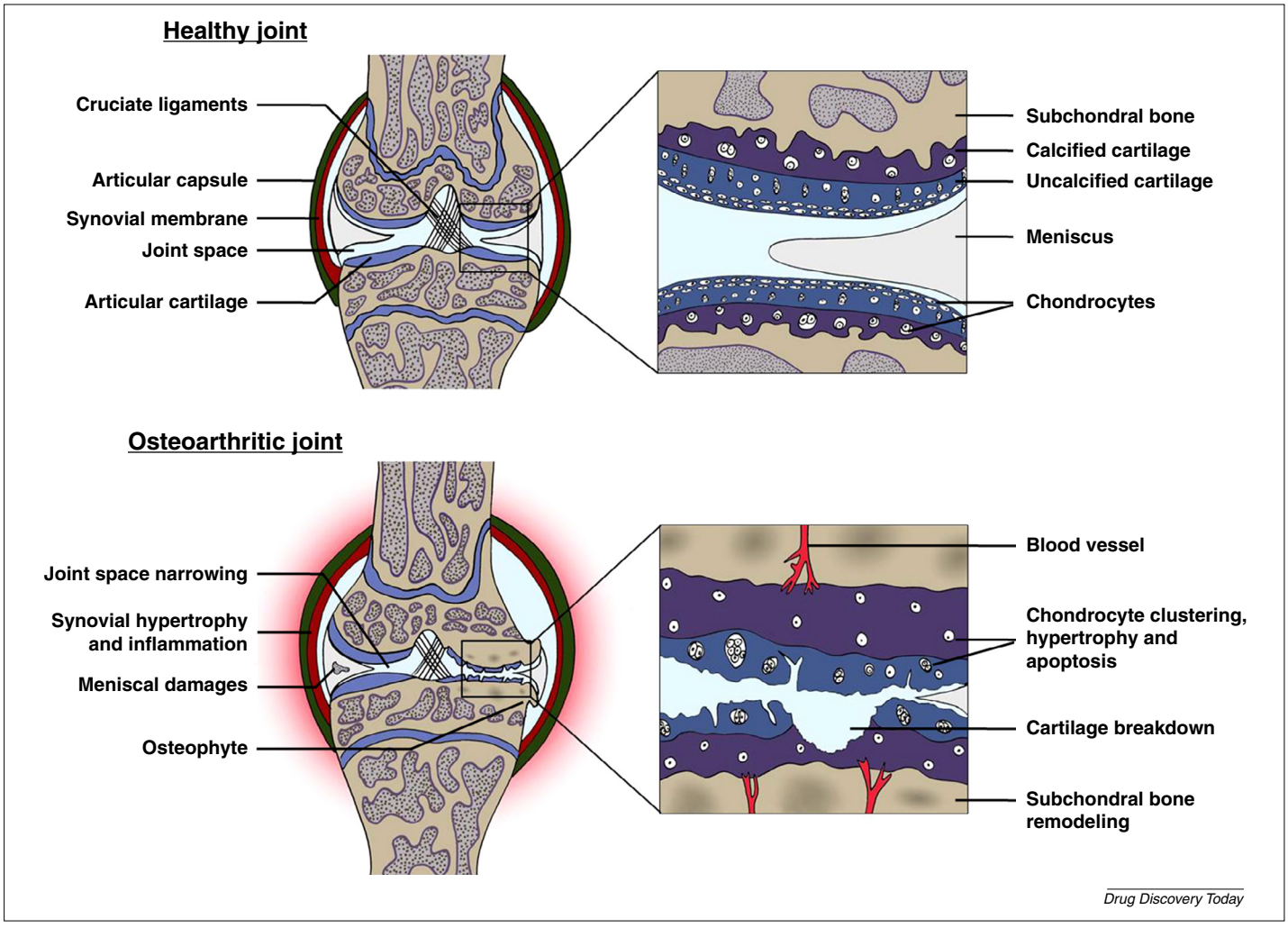

FIGURE 1

Joint tissue affections in knee osteoarthritis (OA). Osteoarthritic joints are characterized by a loss of articular cartilage, synovitis and synovial hypertrophy, as well as sclerosis of subchondral bone, which is accompanied by formation of osteophytes at the joint margins.

apoptosis [5]. In other joint tissues, histological and cellular disorders can also contribute to altered joint homeostasis [3]. Early changes include hyperplasia of the synovial cells ('synovitis'), muscle weakness [6] and fibrillation of the meniscal tissue, as well as thickening of both subchondral bone plate and epiphyseal spongiosa, which are associated with decreased bone mineral content [7].

Collectively, the aforementioned events lead to advanced OA, in which articular cartilage loss is initiated via fibrillation of the superficial zone followed by cartilage damage. Furthermore, cartilage matrix degradation products that are released into the synovial fluid exacerbate inflammation, which results in infiltration of innate immune cells into joint tissues (synovium and IFP) and secretion of inflammatory mediators. As the calcified cartilage zone thickens, the tidemark (i.e. the boundary between calcified and uncalcified articular cartilage) migrates towards the superficial zone [8]. Subsequently, the calcified cartilage becomes invaded by vascular elements, as seen during the endochondral ossification process [9]. Cartilage vascularization enables the recruitment of stem cells, which initiate repair processes (i.e. formation of fibrous cartilage) and lead to an increase in oxygen pressure.

Severe damage of articular cartilage leads to the eburnation of subchondral bone, which produces an imbalance in the mechanical loading of the joint surface. This is likely to contribute to the formation of osteophytes at the joint margins.

Current OA management

To date, there is no curative treatment for OA in humans. Therefore, clinical management focuses only on OA symptoms (e.g. pain and inflammation), using analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, these approaches do not prevent the progression of cartilage degradation and can be associated with adverse effects [10]. Nonpharmacological management currently represents the first line of therapy for OA and includes approaches such as weight loss, education, physical therapy or thermal treatment. Nevertheless, when nonpharmacological treatments become insufficient, pharmacological therapies are used. In this regard, analgesics (e.g. acetaminophen), NSAIDs (e.g. cyclooxygenase and/or lipooxygenase inhibitors) and steroidal anti-inflammatories (SAI) are prescribed to reduce OA-related pain and improve mobility [11]. Ultimately, failure of nonsurgical strategies can lead to total knee and hip replacement [12]. For this reason, an active field of

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