Application of Some Herbal Medicine Used for the Treatment of Osteoarthritis and Chondrogenesis

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Received: 19 Apr 2020 Revised: 4 May 2020 Accepted: 11 May 2020

Abstract

Rheumatic diseases such as osteoarthritis (OA), rheumatoid arthritis (RA), and low back pain are very popular. The drugs available to treat these diseases are almost ineffective and have significant side effects. There are several approaches used to replace conventional drugs to treat these diseases. One of these methods is the use of herbal medicines. In this study, the effects of herbal medicines and medicinal plants used in the treatment of these diseases include. Searching for articles published in English from 1985 to 2020 using keywords include scientific and traditional names of plants reviewing Scopus and PubMed databases. There is limited research on the anti-rheumatic effects of these plants and the active ingredients. Therefore, further research is needed to determine the mechanism of action, the interaction of effects, the efficacy and safety of medicinal plants, and the potentially beneficial plant nutrients in treatment of these diseases seems necessary. The aim of this review was to update information on OA and chondrogenesis, also importance of herbal drugs for the management of arthritis.

Keywords: Herbal medicines; Articular cartilage; Osteoarthritis; Chondrogenesis

Citation: Anvari M, Dortaj H, Hashemibeni B, Pourentezari M. Application of Some Herbal Medicine Used for the Treatment of Osteoarthritis and Chondrogenesis. Trad Integr Med 2020; 5(3): 126-149.

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Introduction

Articular Cartilage

Articular cartilage is mainly composed of hyaline cartilage, which is found on the surfaces of the bone joint in the diarthrodial joints. Joint cartilage is a specialized connective tissue that authorize for the unimaginable movement of dissenting bones in the joint. Hyaline cartilage is found in the rib cage at the sternum and is distinguished from other cartilaginous forms by its high content of type II collagen and the rich proteoglycans matrix made by cartilage cells. Synovial fluid provides pain-free movement with endurance during life [1].

Articular cartilage forms a thin layer of tissue, depending on the circumstances and position in the body, its thickness varies. However, it is perfectly compatible with compressive strength. In humans, depending on the joint, the thickness of the articular cartilage can range from 1 to 4 mm [2]. This tissue is capable to deform to increase the total surface area of the contiguity surface to decrease throughout stress. The relaxation of articular cartilage stress, stating its viscoelasticity properties, demonstrates its unparalleled efficiency in resistance to damage against applied practical loads [3]. Furthermore, this tissue is also capable of neutralizing the compression by pressurization of the interstitial fluid with more than 95% of the load carried by fluid [4]. The function of articular cartilage in producing resistance versus shear forces and compression is associated with the particular adjustment of its extracellular matrix macromolecules. In particular, the collagen fiber orientation and arrangement greatly dictate the extent and orientation of deformation caused by applied stress [5].

Articular cartilage is organized into four areas: superficial, intermediate, deep, and calcified cartilage. In the superficial region, the cartilage cells are in the form of flat cells in close proximity to each other, and collagen fibers are placed parallel to the joint surface. In the middle area, the cartilage cells are oblique and the collagen fibers are randomly arranged in different directions. Deep area cartilage is characterized by spherical cartilage cells arranged in columns, and collagen fibers in this area are perpendicular to the surface of the joint. Collagen fibers penetrate deep into the water inside the calcified cartilage and provide structural stability for the articular cartilage [6].

Chondrogenesis is affected by a variety of mechanisms, including growth factors secreted by the surrounding matrix, cytokines, oxygen supply, and mechanical force. Hypoxia is characteristic of the growth and regeneration of articular cartilage and acts as a stimulant to initiate the expression of the gene that regulates cartilage cells, causing the cells to proliferate, differentiate, and metabolize. Mesenchymal stem cells (MSCs) and cartilage cells are in a hypoxic microstructure and respond to changes in oxygen through the hypoxia-inducible factor (HIF-α) induced during the growth and repair of cartilage. HIF-α is a primary mediator for oxygen measurement in mammalian cells [7].

Various signaling pathways have been identified to regulate the differentiation of cartilaginous cells, including WNT/β and catenin pathways, bone morphogenetic protein (BMP) and
conversion in tissue growth factor-β (TGF-β) pathways, as well as Parathyroid hormone-related protein (PTHrP) [8]. Among these signaling pathways, Bone morphogenetic protein (BMP)/TGFβ plays a regulative role in the differentiation of cartilage cells and osteoblasts, and its expression increases in hypertrophic chondrocytes [8].

**Articular Disease**

Illness, trauma or constant mechanical loading can cause degradation of articular cartilage. The main types of cartilage damage include: superficial matrix disorder, regional thickness defect, and complete thickness defect [9]. Superficial matrix damage occurs from straight trauma whereby the extracellular matrix (ECM) is disturbed. However viable chondrocytes aggregate into clusters and can polymerize new matrix. Regional and partial thickness defects disrupt the external surface of cartilage but do not expand into the subchondral bone. The complete thickness defects arise from damage that penetrates profound into the subchondral bone [10]. These defects can induce a repair response due to accessibility to the marrow cells; as regards, they are typically filled with fibrocartilage. This type of maintenance tissue is much weaker than hyaline cartilage and demonstrate poor long-term proficiency due to poor compressive strength and continuity and may cause degeneration [10,11].

**Osteoarthritis (OA)**

The pathologic feature of OA include articular cartilage degradation with subchondral bone thickening, osteophyte organization, ligament degeneration, synovial inflammation, and capsule hypertrophy [12]. With the extension of molecular biology, disease reclaiming osteoarthritis drugs have become a considerable matter of interest for researchers. OA is an ordinary chronic joint disease distinguished by affliction, deformity, instability, and diminution of function and movement [13]. Unlike focal defects which, in common, queer a younger population who endure an acute trauma and implicate localized cure, OA affects elderly patients and frequently the entire joint surface [14]. OA is certainly one of the basic reasons of incapacitation in older adults over the age of sixty. The communal increase in lifetime expectancy makes OA one of the most significant reason of disability [14]. The pathology mostly includes knees, hips, cervical and lumbosacral spine, and ankle. The distal, proximal inter-phalangeal, and carpometacarpal joints may be affected, as well. Signs and symptoms include affliction which is exacerbated or happened by physical activity, stiffness on walking and after inactivity, and edema in joint [13-15]. Cartilage alterations in OA mostly concern an inconsistency in tissue remodeling due to changes in chondrocyte bearing action [16]. OA articular surface displays swelling which progresses with fibrillation and finally to full-thickness erosions that expose the subchondral bone [13]. Chondrocytes become activated by producing ECM-degrading enzymes such as matrix metalloproteinases (MMPs) and MMPs with thrombospondin-like motifs (ADAMTS). In particular, MMP-13 plays an important role in the degradation of
Coll II; while ADAMTS-4 and -5 both act on Aggrecan (AGG) [17,18]. For this aim, such enzymes contribute to regulate the expression of multiple cytokines, chemokines, inflammatory mediators and matrix degrading enzymes by activating several signaling pathways including Notch and nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB) [18], and deregulating the expression levels of some MicroRNAs (miRNAs) (endogenous small non-coding RNAs that suppresses gene expression by binding to complementary segments of messenger RNA and interfering with the formation of proteins by translation) [17,19,20]. The progressive detriment of cartilage structural architecture, together with an increased osteoclast function in the subchondral bone, causes the presence of bony channels carrying inflammatory cells and blood vessels. In this way, the resistance of natural articular cartilage to neo-vascularization is dominate by the production of proangiogenic factors such as Vascular Endothelial growth factors (VEGF) [21]. Another key feature of OA is the presence of clonally clusters due to the increased proliferation activity by chondrocytes that produce inflammatory mediators, such as cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), reactive oxygen species (ROS) and nitric oxide (NO), all contributing and accelerating the degradation and triggering apoptosis processes (presence of empty lacunae and positivity for caspases mediators) [22]. Ultimately, chondrocytes tend to differentiate towards a hypertrophy-like phenotype (enlarged cytoplasm mostly positive for Coll X and MMP-13) and begin to deposit calcium in the ECM as occurs in the endochondral ossification procedure in the epiphyseal plate [22,23]. Generally, osteochondral alterations frequently lead to an elevated aggregation of important biochemical markers of tissue malfunction and inflammation, which include procollagen pro-peptide of Coll I and Coll II (PINP; PIINP), carboxy-terminal procollagen propeptide of type I and II collagen (PICP; PIICP), C-terminal cross-linking telopeptides (CTX-II), osteocalcin (OC), total pyridinoline (PYD) in urine, and bone sialoprotein (BSP) [24,25].

**Articular Cartilage Repair**

Contemporary curative procedure for articular cartilage repair have two principal focuses: marrow stimulation and cell/tissue-based transplantation [26]. The marrow stimulating surgeries such as transcortical Pridie drilling, abrasion arthroplasty and microfracture induce blood supply and recruit local stem/progenitor cells into the affected lesion from bone marrow through the subchondral bone [27,28]. The cell/tissue-based transplantations fill the cartilage defects and promote regeneration with autologous chondrocytes, osteochondral allografts, cartilage allografts, or MSCs [29,30]. Both strategies often include biomaterials as scaffolds combined with biomechanical or biochemical signals to better fill the defect areas, enhance marrow stimulation, maintain chondrogenic phenotype, or promote chondrogenesis in-vivo or ex-vivo [26]. The biochemical signals widely studied are growth factors such as TGF-β family members (e.g. TGF-β1, 2, 3, and BMPs),
IGF-1 and FGF-2 that are identified as functional stimuli to promote chondrogenic differentiation and cartilage growth [31,32]. However, the exogenous growth factors are costly and subject to quick degradation, and their clinical efficacy and safety remain to be established, raising the demand for novel, effective, safe, bio-stable and low cost alternatives [7].

Remedies with herbal medicines are one of the main categories of complementary and alternative medicine with an increasing public interest. Most complementary and alternative therapies have not been well studied, and there is no centralized source of information about many of the widely used herbal remedies. Currently, in spite of the accessibility of traditional medicine provenance and the clinical experiment of traditional medicine drugs, the essential evidence of its effectiveness, term of use, and the area of their effects, as well as information on how to select a drug and its advantages over a drug with an equivalent effect are not available. Traditional, complementary and integrative system of medicine is generally believed as one of the natural sources to discover novel therapies and have been applied in both prevention and treatment, especially for chronic disorders. This study reviewed the pharmacological treatments of OA and chondrogenesis with herbal medicine.

Methods

Electronic databases including ISI Web of Knowledge, PubMed, and Scopus, were searched from 2010 to 2020. The search strategy included a combination of the following Medical Subjects Headings (MeSH) terms: herbal medicines, osteoarthritis, chondrogenesis, and articular cartilage. Additionally, we searched the references of retrieved articles to find additional, potentially related studies. We have considered herbal therapies which were applied orally or topically. A total of 103 studies were found via the electronic search. Finally, 36 studies fulfilled the eligibility criteria and were included in this review (Figure 1).

![Figure 1. Schematic diagram of applied studies for accomplishment of this review](http://jitim.tums.ac.ir)
## Results

### Table 1: List of some herbs used in osteoarthritis and chondrogenesis

| No | Name of the Herb                | Family      | Part Used          | Active Ingredient                                                                 | Pathway Effect                                                                 |
|----|---------------------------------|-------------|--------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| 1  | Avocado/soybean                 | Lauraceae   | Leaves             | Phytosterols, beta-sitosterol, stigmasterol, campesterol                          | Suppression of IL-6, IL-8, MIP-1β, PGE2, the inhibition of NF-κB, producing TGF-β |
| 2  | Epimedium granuliflorum         | Berberidaceae| Rhizome and Root   | Icariin, epimedin A, and epimedin C                                               | Inhibition of MMP-1, MMP-3, and MMP-13, inhibiting NF-κB                         |
| 3  | Pomegranate                     | Punicaceae  | Fruiting bodies and seeds | Punicalagins, hydrolysable tannins, anthocyanin, and ellagic acid                 | Inhibited IL-1β-induced expression of MMP-1, MMP-3, and MMP-13, activation of MKK3, p38α-MAPK |
| 4  | Oliban Oil                      | Burseraceae | Leaf, Root extract, gum tragacanth | 1, 8-cineole, α-pinene, limonene, globule                                         | Inhibition of lipoxygenase5, TNF-α •IL1- |
| 5  | Cinnamomum Cassia              | Lauraceae   | Fruiting bodies, leaves | Cinnamaldehyde, benzyl benzoate                                                   | Enriched by KEGG, including osteoclast differentiation, arachidonic acid metabolism, hypoxia-inducible factor (HIF)-1, nuclear factor κB (NF-κB), Toll-like receptors (TLRs), and tumor necrosis factor (TNF). |
| 6  | Ginger Rhizomes                 | Zingiberaceae| Root               | 6-gingerol, 6-shogaol, and 6-paradol                                               | Inhibition of Cox-2 and lipoxygenase5 and TNF-α                               |
| 7  | Huangqi (Astragalus Propinquus) | Leguminosae | Root               | Flavonoids, isoflavones, lactic polysaccharides, saponins                         | Reducing the expression of iNOS, COX-2, IL-6, IL-1β and TNF-α, inactivation of p38 and Erk1/2 and inhibition of NF κappaB |
| 8  | Grape Seeds                     | Vitaceae    | Seeds, fruit body  | Proanthocyanidins                                                                 | inhibition of NO, PGE2 and IL-1β, TNF-α and IL-17                             |
| 9  | Harpagophytum procumbens        | Pedaliaceae | Extract            | Harpagoside, glycoside Iridous                                                    | inhibit the production of IL-1β, IL-6, and TNF-α by RAW 264.7                |
|   | Plant Name                  | Family   | Part       | Active Components                                                                 | Action                                                                 |
|---|----------------------------|----------|------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| 10| Urtica Dioica              | Urticaceae | Leaves    | Neophytadiene, Phthalic acid, Dibutyl phthalate, Bis (2-ethyl hexyls') maleate, 1,2-benzenocarbonyl carboxylic acid | Suppresses the expression of MMP-9 and MMP-3, inhibiting NF-κB pathway activation |
| 11| Danshen (Salvia Miltiorrhiza) | Lamiaceae | Root       | Salvianolic acid B                                                                 | Activation of JAK2/STAT3 and AKT pathways, inhibition of the NF-κB, PTEN, AMPK, and ERK signaling pathway. |
| 12| Centella asiatica          | Apiaceae  | Leaves    | Madecassoside, asiaticoside, madecassic acid and Asiatic acid                       | Production of pro-inflammatory cytokines, NO, and oxidative stress     |

**Avocado/soybean Unsaponifiables (ASU)**

Avocado/soybean Unsaponifiables (ASU) are natural vegetable extracts made from avocado and soybean oils, consisting of the leftover fraction (approximately 1%) that cannot be made into soap after saponification. ASU is composed of one third avocado and two thirds soybean Unsaponifiables [33]. The major components of ASU are phytosterols, β-sitosterol, campesterol, and stigmasterol, which are rapidly incorporated into cells. ASU is a complex mixture of many compounds including fat-soluble vitamins, sterols, triterpene alcohols, and possibly furan fatty acids [33,34]. The identity of the active components remains unknown. The sterol contents of ASU preparations are the primary contributors to biological activity in articular chondrocytes [35]. Some studies have suggested that the phytosterols (i.e., β-sitosterol, campesterol, and stigmasterol) and isoflavones (i.e., daidzein, genistin, and glycitin) present in ASU extract play an important role in inhibiting the development of OA and RA [36].

The biological attributes of ASU function can be characterized by proliferating the value of collagen in tissues, increasing tissue lipids, and the proportion of extractable components in respect to insoluble substances, with considerable enhancement in tissue proteases and significant increases and activation of collagenase leucine peptidase serum [33,37,38]. With regards to unsaponifiable extracts, they contain substances characteristic of soybean and avocado seed extracts, which rectify the metabolism of connective tissue. Avocado extract stimulates stromal related enzymes; while soybean extract alone sensitively stimulates lysosomal enzymes with an acidic pH and, to a lesser extent, some neutral lysosomal proteases [39]. Consequently, the association of both extracts which constitute ASU exerts more powerful synergistic effects [40]. The function of both indistinguishable in the composition of granuloma has also been confirmed. Increasing the ratio of macromolecules (collagen, glycoproteins) in both soluble and insoluble parts of granuloma extract can be explained as a symptom of increased destruction of these tissue compounds [41].
able effects observed after ASU administration and can be attributed to an reduce effect on collagenolysis [42].

ASU has been used in numerous experimental studies to test its possible biological effects. A recent experimental evidence has recommended the use of ASU extract as a potent therapeutic agent for various arthritic diseases [43]. So, ASU has been studied for its anti-inflammatory, anti-catabolic, and anabolic effects on cartilage metabolism, principally on chondrocytes [44]. Some studies have explored the action of ASU that seems to act on different molecular mediators implicated in various target tissues/ organs [34]. The molecular mechanism of ASU involves the inhibition of NF-κB activation. NF-κB is a transcription factor that regulates the inflammatory response in chondrocytes. It normally resides in the cytoplasm; however, once activated, it moves towards the nucleus to induce the expression of pro-inflammatory genes, including enzymes degrading the cartilage matrix [45]. Likewise, ASU reversed the catabolic effect of IL-1β in human fibroblasts by inducing a significant decrease in MMP-2, MMP-3, and tissue inhibitors of MMP-1 in the presence of IL-1β [46]. The mechanism of action of ASU in OA is not well elucidated, but there is some evidence of its inhibitory effects on MMPs and stimulating TGF-β synthesis, which has a significant participation in cartilage tissue homeostasis. ASU has an inhibitory effect on inflammatory and catabolic mediators, thus preventing the destruction of cartilage. Prevents the production of cytokines, chemokines, PGE2, NO, and MMP. In human articular cartilage cells stimulated in cultures with IL-1β, ASU suppresses IL-6, IL-8, MIP-1β, PGE2, and NO [44].

For instance, some in-vitro studies reported that ASU extract is capable of stimulating matrix production and reducing the deleterious effect of IL-1, possibly by producing TGF-β [34]. ASU is also known to stimulate and restore the AGG production, even after IL-1β treatment, decrease the MMP-3 production and stimulate the tissue inhibitor of metalloproteinase's-1 (TIMP-1) production [34]. Hashemibeni et al. compared the efficacy of ASU and TGF-β3 on chondrogenic differentiation of human adipose-derived stem cells (hADSCs) on PLGA/fibrin hybrid scaffold, stated that hADSCs containing the ASU are an effective way to potentially enhance cartilage specific genes (Sox9, Coll II, AGG) with less hypertrophy and fibrosis in-vitro. Also, enhanced cellular viability was observed in the ASU group compared to the TGF-β3 group [38]. They compared the efficacy of ASU and TGF-β1 on chondrogenic differentiation of hADSCs. The study reported that ASU improved proliferation and increased the survival of differentiating chondrocytes in fibrin scaffolds more effectively than TGF-β1 [47]. Ownby et al. made a mixture from ASU and epigallocatechin gallate extract and studied the responsiveness of articular chondrocytes of the carpal joints of mature horses and tested its ability to inhibit joint inflammation [48]. Another study included 60 patients with knee OA. The patients were given either ASU (300 mg daily) or diclofenac (25 mg, 3 times/day) for 8 weeks and results were estimated using WOMAC in
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The study suggested that ASU can be a promising substitute to NSAIDs due to its better patient compliance and WOMAC score [49].

**Herb Epimedium (HEP)**

Herb Epimedium (HEP) is a widely used traditional Chinese herbal medicine in arthritis [50,51]. Icariin (ICA) is the major active constituent of HEP [47,51,52]. ICA could regulate the anabolism of osteoblasts through the upregulation of BMP-4, BMP-2 and SMAD4 expression [53-55]. Some reports proved that ICA was a safe and strong chondrocyte anabolic agent which could affect the proliferation of chondrocytes and reduce the degradation of ECM, suggesting ICA-loaded biomaterials to be a potential candidate for cartilage tissue engineering [56]. In addition, ICA could promote the expression of chondrogenesis genes of chondrocytes like AGG, Coll II and Sox9 genes [57]. Recent study has identified that ICA stimulated cartilage repair through the activation of HIF-1α in chondrocytes [7].

Hashemibeni et al. compared the efficacy of ICA and TGF-β3 on chondrogenic differentiation of hADSCs on a fibrin scaffold. The results indicated ICA to be a potential stimulator for chondrogenesis and in cooperation with TGF-β3 could reduce its hypertrophic effects [47]. In another study, natal rabbit chondrocytes were embedded by ICA/Coll I hydrogels to construct engineered grafts, ICA upregulated the expression of cartilage specific genes of seeded chondrocytes. Furthermore, ICA can increase the synthesis of cartilage matrix, accelerates and maintains the formation of chondroid tissue. Finally, ICA improves the efficiency of the restoration of supercritical sized osteochondral defects by engineered cartilage. Even, ICA can enhance the integration of new formed cartilage with subchondral bone. These indicate that ICA may be a potential promoting compound for cartilage tissue engineering [55].

Zhan j and colleagues in a study aimed to develop ICA conditioned serum (ICS) together with hyaluronic acid (HA) and determine their ability in repairing osteochondral tissue in a critical sized defect in rabbit knees. ICA at a low dose of 0.94 g/kg has significantly promoted the proliferation of chondrocytes and enhances the secretion of Glycosaminoglycan (GAG). Femoral condyle from rabbits treated by ICS together with HA was observed to be integrated with native cartilage and more subchondral bone regeneration. ICS together with HA could promote the repair and increase the neoformation of cartilage [58].

A study by Sun and colleagues reported that ICA suppressed bone and cartilage deteriorations in mice with collagen induced arthritis [59]. Yuan Luo et al, in a mouse model of OA, showed that ICA treatment decreased the destruction of cartilage, inhibited chondrocyte hypertrophy, promoted chondrocyte differentiation, upregulated the expression of parathyroid hormone related protein (PTHrP) and down-regulated the expression of Ihh. According to these findings ICA may have an effective role in OA by its effects on Ihh and PTHrP signaling to adjust chondrocyte differentiation[8]. Studies revealed that ICA prevented OA inflammation and chondrocytes apoptosis though activation of autophagy via inhibiting NF-κB signaling pathway [60]. Furthermore, ICA exerted a chondroprotective effect.
through the inhibition of MMP-1, MMP-3, and MMP-13 or the suppression of osteoprotegerin (OPG), receptor activator of nuclear factor kappa-B ligand (RANKL), and receptor activator of nuclear factor kappa-B (RANK) system via MAPK pathway in IL-1β stimulated chondrosarcoma cells [61,62]. However, the molecular mechanisms of ICA alleviating OA and its relationship with NLRP3 inflammasome are not fully understood. Yan Zu et al. studied the effects of ICA on OA which showed inflammasome NLRP3 to play a key role in the pathogenesis of OA. ICA could alleviate pyroptosis by inhibiting NLRP3 signaling-mediated caspase-1 pathway, thereby attenuating the damage of chondrocytes and the occurrence of OA in rats. ICA may be a promising target drug for the treatment of OA [63].

Pomegranate

Pomegranate (Punica granatum L., Punicaceae) is an eatable fruit native to Iran which nowadays is grown and consumed all over the world. It has been revered through the ages for its medicinal attributes. This fruit has already been used in traditional medicines for the treatment of patients with hypertension, high glucose and cholesterol, oxidative stress, and inflammatory diseases. Studies have revealed that pomegranate fruit is rich in bioactive compounds like polyphenols, flavonoids, and anthocyanin [64]. The use of pomegranate juice is increasing in popularity because of its high antioxidant content which has a preventive effect on oxidative stress-related diseases [64,65]. Over the past decades, researchers working on pomegranate fruit have explored the therapeutic potential and how they function in cartilaginous degenerative mechanisms to mimic the molecular mechanism of inflammation and joint damage [66-69]. They have shown that a standardized pomegranate fruit extract (PFE) is highly effective in exerting cartilage sparing effects and is non-toxic to human cartilage cells. Pre-treatment of human OA chondrocytes with PFE inhibited IL-1β-induced expression of MMP-1, MMP-3, and MMP-13, which are the classical markers of inflammation and cartilage degradation in arthritic joints [70]. PFE selectively inhibited the IL-1β induced activation of MKK3, p38α-MAPK isoform and DNA binding activity of runt-related transcription factor 2 (Runx2). Runx2-deficient mice with OA showed reduced cartilage destruction and MMP-13 expression [71]. Moreover, Runx2 regulates the induction of genes of major cartilage degrading enzymes MMP-13 and ADAMTS-5 (A disintegrin and metalloproteinase with thrombospondin motifs 5) whose inhibition by PFE could potentially reduce cartilage degradation [72]. In another study, PFE significantly inhibited the excessive production of IL-6 and IL-8 via suppression of the JNK-, extracellular signal regulated kinases (ERK)- MAPKs and NF-κB-signaling events [73]. Studies have also shown that oil extracted from pomegranate seeds is rich in punicic acid and has anti-arthritic activity [74,75]. Experiments on arthritic animals demonstrated that consumption of pomegranate seed oil in diet increases the bone mineral density and inhibits the pro-inflammatory activities [75]. Bioavailable constituents and/or metabolites of PFE
exert an anti-inflammatory effect by inhibiting the activity of eicosanoid generating enzyme COX-2 and the production of NO [68], which are key mediators for inflammation in OA. This further suggests that consumption of pomegranate may be of value in inhibiting inflammatory stimuli-induced cartilage breakdown and production of inflammatory mediators in arthritis. The cartilage protective effects by PFE were reconfirmed by another study in the monoiodoactate induced OA animal model [76]. Shukla et al. demonstrated that oral administration of commercially prepared PFE (POMx) in inflammatory arthritis mouse model protects joints from inflammatory arthritis. They have shown that consumption of POMx potentially delayed the onset and reduced the incidence of inflammatory arthritis in mice. They also showed that in mouse macrophages, POMx abrogated multiple signal transduction pathways and downstream mediators implicated in the pathogenesis of arthritis [67]. A study by Garbacki et al., using human chondrocytes showed that anthocyanin had a positive regulatory effect on proteoglycans and Coll II synthesis [77]. Katani et al. investigated the effect pomegranate extract on chondrogenic differentiation of hADSCs on fibrin scaffold, stated that hADSCs containing pomegranate are an effective way to potentially enhance Coll II genes [78].

Oliban Oil (Frankincense)
Frankincense is a type of aromatic resin obtained from the species Boswellia [79], belonging to the family Burseraceae [80]. Several clinical studies have shown their biological activity and confirmed their anti-inflammatory and antitumor activities [81]. Boswellic acids are the main active component of Frankincense and responsible for its therapeutic effects [82]. The chemical structure of boswellic acids bears a striking resemblance to steroids, and their mechanism of action differs from that of non-steroidal anti-inflammatory drugs, and is part of the immune system and inhibition of lipoxygenase [83]. Boswellic acids, especially acetyl-11-keto-β-boswellic acid are potent inhibitors of 5-lipoxygenase (5-LO), an enzyme that catalyzes the generation of leukotrienes including LTB4 [84], a molecule strongly implicated in OA-associated inflammation [85]. Additionally, Boswellic acid can inhibit toll-like receptor (TLR)-mediated activation of monocytes, suppressing LPS-induced production of NO, IL-1β, and TNF-α [86,87]. Finally, derivatives of Boswellic acid have been demonstrated to suppress IL-β-induced apoptosis of chondrocytes as well as TNF-α induced production of MMP-3 by synovial fibroblasts [88]; thus, demonstrating clear therapeutic potential for the treatment of OA.

Oliban used to keep the eyes moist, and for the treatment of moisture in wounds and toothache, and with olive oil and honey for the treatment of osteoarthritic and bone pain. Oliban oil with olive oil and honey are used to treat joint affliction and chronic cold-emerging pains [89]. Oleogam extract from Indian olibanum and olibanum resin have long been used to treat knee inflammation. Because of its warm and dry nature, Olibanum is impressive in drying and at
taining the preparation and elimination of knee sputum. According to clinical trial studies, Oliban oil has been shown to have useful efficiency in detracting joint pain and stiffness, reducing mobility limitations, and enhancing mobility [90].

Based on data collected from a variety of laboratory studies, animal models and clinical trials examining the anti-inflammatory effects of Olibanum, there are promising positive effects in the treatment of inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, asthma and cerebral edema [91].

Wang Q et al. in a study showed significant synovial concentration and therapeutic efficacy can be achieved with topical Boswellic acid treatment. These findings suggest that Boswellic acid has potential as a disease-modifying agent in OA [87].

_Cinnamomum cassia_

_Cinnamomum cassia_ has multi-component characteristics, and its mechanism is relatively complex. Traditional Chinese medicine often used _C. cassia_ to treat OA [92]. The positive effects and relatively low toxicity of _C. cassia_ in treating OA have appealed to the consideration of scientists and researchers. _C. cassia_ can be predicted to have efficiency in treating OA by an anti-inflammatory effect, and intercede cell proliferation, differentiation, and apoptosis, hence enhancing the balance of osteoblasts (OB) and osteoclast (OC) and the antioxidant effects [93,94]. Cinnamaldehyde can enhance the activity of catalase, superoxide dismutase, and glutathione peroxidase, and prohibit the oxidation of chondrocytes. Laboratory studies demonstrated the anti-inflammatory and anti-arthritic function of type-A procyandins polyphenoles from the bark of _C. zeyllanicum_ in rats [93,95].

_Ginger Rhizomes (Zingiber officinale)_

Ginger has been used for thousands of years in Ayurveda and Chinese-Japanese medicine to treat inflammation and rheumatism. Ginger rhizomes have been proposed as a complementary treatment for rheumatoid arthritis, musculoskeletal pain, and throat pain, being moderately effective in patients with hip and knee OA [96,97]. Ginger consists of a complex combination of biologically active constituents, of which the compounds gingerols, shogaols and paradols reportedly account for the majority of its anti-inflammatory properties [98]. It has also been shown to be effective in relieving symptoms of OA, possibly via anti-inflammatory properties by inhibiting the activation of TNF-α and cyclooxygenase expression [99,100]. Ginger also inhibits lipoxygenase, resulting in suppression of inflammatory leukotrienes synthesis [101]. Various ginger compounds and extracts have been tested as anti-inflammatory agents, where the length of the side chains determines the level of effectiveness. However, a combination of ginger extracts is more effective in decreasing inflammatory mediators than an individual compound [102].

Studies showed that ginger is used for debarment because of its antibacterial, antiviral, analgesic, and anti-aging properties [103].
study, 28 patients with rheumatoid arthritis, 18 Patients with OA and 10 patients with muscular complaints, ginger was administered at the dose of 1 to 2 g for 3 months to 2-5 years. 55% of patients with OA reported reduction in pain and 50% reported reduction in articular swelling[104]. Wigler et al. found ginger to be significantly more effective than placebo in reducing pain in patients with OA [105]

_Huangqi (Astragali Radix, (Astragalus Propinquus))_

Astragali radix from _Astragalus membranaceus_ (Fisc.) is one of the mainly administrated medicinal herbs of the traditional Chinese medicine having different medicinal attributes and considerable healthy outline [106]. Astragali radix extracts are reported to have several biological functions including immunomodulatory, antioxidant, anti-inflammatory and an arthritic activity [107,108]. The mixture of the dry root extract of AR was lately successfully examined. It has several components, such as calycosin, saponins, polysaccharides, and some other isoflavonoids and astragalosides. AR has displayed anti-inflammatory activity in zymosan air-pouch mice by reducing the expression of iNOS, COX-2, IL-6, IL-1β and TNF-α, and NO production. The documentation showed that AR had an anti-inflammatory effect that was interceded by the MKP-1 associated with inactivation of p38 and Erk1/2 and inhibition of NF kappaB-mediated transcription [109]. Choi et al. revealed that AR had a high blockage effect on hyaluronidase (HAase) activity in vitro and identified calycosin-7-O-β-d-glucopyranoside (CG) as an active element of AR responsible for the effect [110]. Furthermore, AR extracts or CG treatment was found to significantly inhibit matrix degradation caused by recombinant human IL-1β or HAase in the human articular cartilage explants and chondrocytes [111]. Also, CG could inhibit the degradation of cartilage directly and the release of degraded molecules like GAG from damaged tissues, which occurred in parallel with the reduction in the volume of synovial fluid. Astragalus polysaccharides (APS) inhibited cell growth and proinflammatory responses in IL-1β-stimulated fibroblast-like synoviocytes (FLSs) without any significant toxicity and side effects [112]. Choi et al. demonstrated that intra-articular injections of CG significantly reduced the pathologic changes resembling OA in a rabbit model by the gross and histological observations of the cartilage and the fluid volume, protein content and GAG content in the synovial fluid. Also, they showed that the CG significantly alleviated the pathologic changes in the OA-like rabbit knee joints. This propose that CG from AR could be a promising remedy for OA [108]. Jiang J B demonstrated that polysaccharides isolated from AR lowered plasma levels of TNF and IL-1β and reduced the inflammation of knee synovial tissue in a rat model of Rhamatoid Arthritis [113].

_Grape Seeds (GS)_

Grape seeds (GS) are rich sources of proanthocyanidins, which include polyhydroxyxylan oligomers or polymers. The beneficial therapeutic properties of grape seed protein proteases are
attributed to their conjugated metabolites. There is a two-way correlation among intestinal microbiota and proanthocyanidins of grape seed. In vitro and in vivo studies have shown that grape proanthocyanidins have pharmacological effects including antioxidant and anti-osteoarthritis properties [114].

Procyanidins (PCy) are active polyphenols found in many plants such as grapes, pine bark, cocoa and raspberries. PCy has numerous health-promoting effects due to their antioxidant activity, as well as their ability to inhibit the synthesis of inflammatory mediators [115]. Previous studies have thus shown that PCy from grape seed extract (GSE) had the ability to alleviate inflammation in-vitro and in-vivo through the inhibition of NO, PGE2 and IL-1β production [115,116]. Interestingly, it has also been suggested that PCy may exert a protective effect on the ECM degradation as observed in OA through their targeted affinity with collagen [117]. A preventive effect of procyanidin B3 isoform on cartilage degradation has been reported recently in a murine model of OA [117]. Researchers reported the anti-arthritic effect of GSE by reducing the production of Coll II specific IgG2a and inflammatory cytokines, such as TNF-α and IL-17 [118]. Suri et al. suggested that vascular cartilage damage causes pain[119]. GSE has been reported to be effective in inhibiting angiogenesis [120]. Therefore, it is possible that GSE relieves pain by inhibiting vascularization after monosodium iodoacetate (MIA)-induced arthritis treatment [121].

GSE may apply its therapeutic effects on the MIA OA mouse not only through its antioxidant activity, but also by its anti-inflammatory function. Damavand et al. showed that progressive gene expression such as IL-1β, iNOS, and COX2 can increase in cartilage cells in the primary stages of MIA-induced OA [122]. Li et al. demonstrated that GSE has anti-inflammatory effects as it inhibited the production of inflammatory cytokines such as IL-1β, TNF-α, and prostaglandin E2, as well as NO [123]. Yun Ju Woo et al. demonstrated that treatment with GSE utilize the MIA-induced pain and histological changes in the knee joint. The antinociceptive and anti-arthritic effects of GSE were interceded by blockage of cartilage disruption, synovitis and subchondral bone fracture, the decrease in secretion of nitro tyrosine and MMP-13 and the suppression of osteoclastogenesis. It is also proposed that the advantageous effects of GSE in MIA-induced arthritis are secondary to its antioxidant effects. They indicate that GSE has great potential as a therapeutic constraint for treating OA [123].

Proanthocyanidins exert chondroprotective effects in human chondrocytes [124]. GS proanthocyanidins decrease perichondrial inflammation and alveolar bone loss by decreasing MMP-13, MMP-8, HIF-1α, TNF-α and IL-17 levels and increasing osteoblastic activity [125]. GS proanthocyanidins extract also reduce the T cell subset levels and upregulate Tregs and Th2 cytokine-producing cell numbers [126]; thus, potentially opening up novel avenues for OA treatment [121].

Harpagophytum procumbens (Devil’s claw)
A perennial plant belonging to the Pedaliaceae
family that grows in southern and eastern Africa. Its tuber is consumed due to its medicinal properties [96]. Devil's Claw is a leafy plant with horny roots and buds. The plant lacks a disgusting odor but contains substances that make it taste bitter. Devil's claw is used in traditional South African medicine for the treatment of arthritis, headaches and for digestion, neuralgia, back pain, nerve pain and fever [97]. Much research has been done on laboratory animals and humans over the past three decades, and the effectiveness of the devil's claw plant has been proven to be due to anti-inflammatory, anti-rheumatic, and analgesic properties. Ingredients of *H. procumbens* include harpagoside, harpagid, flavonoids (luteolin, camfrol), phenol acids, cinnamic acid, caffeic acid, chlorogenic acid, quinolones and phytosterols [99]. The main ingredient, Harpagoside, is a glycosylated iridoid and is responsible for most of its biological effects [103]. This active is converted into another substance, harpagonin, in the body which is also an anti-inflammatory compound [127]. Its anti-inflammatory effects are exerted by preventing the effects of TNF-α [128]. Harpagoside has been shown to inhibit indistinctive-ly both COX-1 and COX-2 (37.2 and 29.5%, respectively) activity and greatly inhibited NO production in vitro [129]. Harpagoside, has also been reported to inhibit the production of IL-1β, IL-6, and TNF-α by RAW 264.7 mouse macrophages [130]. However, the effect of harpagoside on IL-1β-induced inflammatory response of OA chondrocytes has not been fully elucidated. Earlier studies have established the role of the transcription factors C/EBPβ, NF-κB and AP-1 in the transcriptional regulation of IL-6 [131]. Harpagoside had no effect on NF-κB and C/EBPβ activation in IL-1β-stimulated OA chondrocytes. However, a significant suppression in the expression and activation of c-FOS, that is one of the two main components of AP-1 transcription factor, was observed. c-Jun, another major component of AP-1 was not affected by harpagoside in IL-1β-stimulated OA chondrocytes [132].

Gagnier and colleagues reviewed six randomized trials and determined that devil's claw standardized to 60 mg harpagoside was a moderately effective treatment for osteoarthritis of the spine, hip, and knee [128]. Hasseb et al. suggested that harpagoside exert a significant anti-inflammatory effect by inhibiting the inflammatory stimuli mediated by suppressing c-FOS/AP-1 activity in OA chondrocytes under pathological conditions [132].

**Danshen (Salvia miltiorrhiza) Urtica dioica (UD) (Stinging Nettle)**

*Urtica dioica* (UD), often known as common nettle or stinging nettle, is a herbaceous perennial flowering plant in the family Urticaceae [133]. Originally native to Europe, much of temperate Asia and western North Africa, the plant is now found worldwide, including New Zealand and North America [134]. Nettle is covered with hairs called trichomes on leaves and stems that act like hypodermic needles, injecting histamine and other chemicals that cause a burning sensation during contact ("contact urticaria", a form of contact dermatitis)[135]. Nettle leaves have been used to treat hair loss, eczema, gout, urti-
caria, allergic rhinitis, and RA, and roots have been used to treat benign prostatic hypertrophy. The plant has a long history of use as a source for traditional medicine, food, tea, and textile raw material in ancient societies [136]. A wide range of phytochemicals, including flavonoids, agglutinins, lignans, carotenoids, phenolic compounds, and terpenoids, have been isolated from nettle. *U. dioica* and its phytoconstituents were reported for various pharmacological activities which includes hypoglycemic and anti-inflammatory activities [137]. Hox alpha, an acid present in nettle extract, significantly suppresses the expression of MMP-9 and MMP-3 by human chondrocytes under exogenous IL-1β conditions. This may be one of the mechanisms by which nettle is effective in RA. Studies have shown that nettle extracts inhibit IKB proteolytic decomposition by inhibiting IKB kinases or upstream signaling molecules, thereby inhibiting NF-κB pathway activation [138].

Stinging nettle was beneficial in patients with osteoarthritis in 2 general ways: (1) pain relief and (2) disease process modification. The intact leaf hair’s sting could provide a counter irritation that decreases pain by depleting substance P, similar to the effect of capsaicin. An extract of the leaf, despite lacking the intact hairs, still contains multiple potential modulators of inflammatory or pain pathways [139].

Danshen (*Salvia miltiorrhiza*), a traditional Chinese medicine with a number of physiological benefits, is widely used for the treatment of OA disease [140]. The pharmacokinetic and pharmacodynamic studies on the active components of Danshen indicate that Danshen contains mainly two types of constituents, lipid soluble diterpenoid quinines (e.g., tanshinone and cryptotanshinone) and water soluble phenolics (e.g., danshensu, rosmarinic acid, salvianolic acids, protocatechuic acid, and protocatechuic aldehyde)[141,142]. Both components are responsible for the pharmacological activities of Danshen. It has been reported that Danshen has antioxidant and anti-inflammatory effects [143]. Danshen has been reported to prevent articular cartilage degeneration in rabbits with OA by inhibiting oxidative stress [144].

The mechanism of the OA ameliorating effect of Danshen was further investigated. Data showed that the JAK2/STAT3 and AKT pathways were activated by Danshen, and treatment with corresponding inhibitors treatment abrogated the apoptosis inhibition effect of Danshen. This information reveals that the JAK2/STAT3 and AKT pathways are implicated in the OA ameliorating effect of Danshen [140]. Also, indicate that Danshen alleviates the cartilage injury in rabbit OA through inhibition of the NF-κB signaling pathway. Other pathways, such as PTEN, AMPK, and ERK, are also downstream signaling pathways of Danshen [145-147].

Xilin Xu and colleagues explored the effects of Danshen on OA, The results of this study showed that Danshen attenuated OA cartilage destruction in-vivo and reduced oxidative stress and apoptosis of chondrocytes in an OA model in-vitro [140]. Danshen was found to inhibit SNP-induced chondrocyte apoptosis in-vitro, and it rescued apoptosis related proteins impacted by SNP. Danshen can also reduce proteoglycans loss in cartilage tissues [148]. Bai
et al demonstrated that Danshen could prevent the degeneration of articular cartilage by its antioxidant effects in rabbits with OA. It has been suggested that Danshen supplementation may be useful in the treatment of OA [141]. Recently, salvianolic acid B (sal B), a hydrophilic component of Danshen, has also been reported to promote cell growth and attenuate the de-differentiation status of articular chondrocytes [149]. Xiaohong Yang showed the biological activity of Sal B on cultured chondrocytes. Sal B treatments demonstrated enhanced anabolic activity in the chondrocytes by elevating mitochondrial membrane potential and stimulated cell survival and synthetic activity exhibited as increased volumes of nucleic acids by specific labeling and quantitative analysis [149]. Liu et al. reported that S. miltiorrhiza with a higher Sal B content exerts a therapeutic effect in RA patients by suppressing synovial hyperplasia. In addition, Sal B has shown a positive impact on various experimental RA models [150]. Ma et al. reported that in RA, Malondialdehyde (MDA) levels are significantly increased with decreased activity of glutathione (GSH), Superoxide dismutase (SOD), and catalase (CAT). Owing to the free radical-scavenging and Nrf2-modulatory activities of Sal B [151], it reduced oxidative stress by increasing GSH, CAT, and SOD activities and normalizing MDA levels. Therefore, Sal B can protect joint tissue against the deleterious effects of free radicals by elevating endogenous antioxidant levels, thereby maintaining the integrity of synovial or joint tissue and cartilage [152]. Xia ZB et al. Sal B exerts a concentration-dependent effect on the arthritis score, edema, paw swelling, oxidative stress, and inflammatory markers, and ameliorate synovitis and cartilage markers. Therefore, Sal B (especially 40 mg/kg) has potential as an adjuvant therapy for RA together with standard drugs [153].

**Centella asiatica (CA)**

*Centella asiatica* (CA) or gotu kola is medicinal plant widely used in India and across Asia for treating a variety of diseases. The aerial parts and roots are used for medicinal purpose, and its chemical constituents have wide therapeutic applications in areas of anti-inflammatory and antioxidant activities [154]. Polyphenols, flavonoids, β-carotene, tannin, and Vitamin C found in CA contribute in significant antioxidant activity of the herb [155]. Madecassoside (MA) is a bioactive triterpenoid saponin with a molecular weight of 975.12kDa that is isolated from the gotu kola [156]. Previous studies have reported that MA exhibits antioxidant and anti-inflammatory activities and is able to suppress the activation of the NF-κB signaling pathway [157]. The researchers examined the protective role of MA in bone marrow cells affected by IL-1β, which showed regulated toxicity associated with chondrocytes by modulating NF-κB signaling in vitro and destroying weak cartilage in vivo. These findings propound that MA has a possible therapeutic effect on OA [156]. Anita Hartog et al. illustrated that CA fraction can prohibit the zymosan-induced cartilage atrophy in-vivo without changing the zymosan-induced inflammatory cell infiltration and joint inflammations. An in-vitro study showed that this cartilage pro-
tective activity might at least partially be due to the inhibition of NO efficiency. Thus, this CA fraction indicates a possible disease-modifying activity which could have advantages for OA patients [158].

Sharma et al. showed CA (150 and 250 mg/kg) exhibited high anti-inflammatory and antioxidant activities both in-vitro and in-vivo. The oral administration of CA inhibited collagen induced arthritis (CIA) progression by reducing the production of pro-inflammatory cytokines, NO, and oxidative stress without any toxicity. The direct oxygen free radical scavenging activity of CA might also contribute to its in-vivo antioxidant activity. Therefore, in light of the above findings, CA can be considered as a new source of anti-arthritis natural antioxidant for clinical application/dietary needs [159].

Discussion and Conclusion
Plants described in this review demonstrated the importance of herbal medicines in the treatment of rheumatoid arthritis and also introduce good source for a new drug or a lead to make a new drug. Treatment with herbal medicines is one of the main components of complementary medicine and alternative medicine with growing public interest.

Many patients use complementary and alternative therapies with the idea that natural remedies that have been used for a long time are harmless; while they have no knowledge of their true clinical efficacy and side effects. Physicians/pharmacists' unfamiliarity with such drugs often limits their ability to guide patients. Most complementary and alternative therapies have not been well studied, and there is no centralized source of information about many of the most widely used herbal remedies. Concomitant use of complementary and alternative therapies with prescription or over-the-counter medications, especially in the elderly who are more likely to take multiple medications, may lead to adverse effects and herb-drug interactions. It may also be important to clarify the mechanism of complementary and alternative therapies in the discovery of new molecular targets for the treatment of diseases.

Effective medicinal plants in the treatment of rheumatic diseases, if used in combination with conventional drugs, can reduce the required dose of artificial drugs and thus reduce the side effects of conventional drugs. For example, nonsteroidal anti-inflammatory drugs are one of the main treatments of rheumatologic diseases such as OA and RA, but their gastrointestinal and cardiovascular side effects limit their use. In addition, unlike OA, there is no cure for OA, and disease modifying the disease modifying drugs used in rheumatoid arthritis includes immunosuppressive drugs (methotrexate, azathioprine) and cyclone with several major side effects.

It is concluded that a number of herbal medicines may be effective for the treatment of symptom and pain associated with OA and RA. The mechanism of action, the interaction of adverse effects, the efficacy and safety of medicinal plants and the potentially beneficial plant active ingredients in the treatment of rheumatic diseases require further attention.
**Conflict of interests**

We confirm that none of the authors has any conflict of interest to disclose.

**Acknowledgment**

This study didn’t receive financially support. We thank Sareh Dortaj Pharmacy student in Dubai Pharmacy College, Dubai UAE for her useful comments.

**References**

[1] Temenoff J, Mikos A. Tissue engineering for regeneration of articular cartilage. Biomaterials 2000;21:431-40.

[2] Adam C, Eckstein F, Milz S, Schulte E, Becker C, Putz R. The distribution of cartilage thickness in the knee-joints of old-aged individuals—measurement by A-mode ultrasound. Clin Biomech 1998;13:1-10.

[3] Kovach I. A molecular theory of cartilage viscoelasticity. Biophys Chem 1996;59:61-73.

[4] Soltz MA, Ateshian GA. Interstitial fluid pressurization during confined compression cyclical loading of articular cartilage. Annals of biomedical engineering 2000;28:150-159.

[5] Eyre D. Articular cartilage and changes in arthritis: collagen of articular cartilage. Arthritis Res Ther 2001;3:40.

[6] Newman AP. Articular cartilage repair. Trans J Am Coll Sports Med 1998;26:309-324.

[7] Wang P, Zhang F, He Q, Wang J, Shiu HT, Shu Y. Flavonoid compound icariin activates hypoxia inducible factor-1α in chondrocytes and promotes articular cartilage repair. PloS one 2016;11:11-16.

[8] Luo Y, Zhang Y, and Huang Y. Icariin Reduces Cartilage Degeneration in a Mouse Model of Osteoarthritis and is Associated with the Changes in Expression of Indian Hedgehog and Parathyroid Hormone-Related Protein. Medical science monitor: Med Sci Monit 2018;24:6695.

[9] Jansen EJ, Emans PJ, Vanhijn LW, Bulstra SK, Kuijer R. Development of partial-thickness articular cartilage injury in a rabbit model. Clin Orthop Relat Res 2008;466:487-494.

[10] Matsiko A, Levingstone TJ, O'Brien FJ. Advanced strategies for articular cartilage defect repair. Materials 2013;6:637-668.

[11] Beris AE, Lykissas MG, Papageorgiou CD, Georgoulis AD. Advances in articular cartilage repair. Injury 2005;36:14-23.

[12] Carballo CB, Nakagawa Y, Sekiya I, Rodeo SA. Basic science of articular cartilage. Clin Sports Med 2017;36:413-425.

[13] Kidd B. Mechanisms of pain in osteoarthritis. Hss Journal 2012;8:26-28.

[14] Sion S, Jones G, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinsan H, Carr AG. Osteoarthritis Lancet 2015;386:376-386.

[15] Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64:1697-1707.

[16] Li Y, Xu L. Advances in understanding cartilage remodeling. F1000Research 2015;4:3-6.

[17] Li H, Wang D, Yuan Y, and Min J. New insights on the MMP-13 regulatory network in the pathogenesis of early osteoarthritis. Arthritis Res Ther 2017;19:248.

[18] Saito T, Tanaka S. Molecular mechanisms underlying osteoarthritis development: Notch and NF-κB. Arthritis Res Ther 2017;19:94.

[19] Marcu KB, Otero M, Olivotto E, Maria Borzi R, Goldring MB. NF-κB signaling: multiple angles to target OA. Curr Drug Targets 2010;11:599-613.

[20] Ogando JJ, Tardáguila M, Alderete AD, Usategui A, Ramos VM, Herrera DJM, Fuente L, León Mg, Escudero C, Caeñete JD, Toribio ML, Cases I, Montano AP, Pavlos JL, Mañes S. Notch-regulated miR-223 targets the aryl hydrocarbon receptor pathway and increases cytokine production in macrophages from rheumatoid arthritis patients. Sci Rep 2016;6:202223.

[21] Mapp PJ, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. Nat Rev Rheumatol 2012;8:390.

[22] Knaan P, Berg W. Chondrocyte hypertrophy and osteoarthritis: role in initiation and progression of cartilage degeneration? Osteoarthritis Cartilage 2012;20:223-232.

[23] Rimpmeester EG, Timur UT, Caron MM, Welting TJ. Recent insights into the contribution of the changing hypertrophic chondrocyte phenotype in the development and progression of osteoarthritis. Front Bioeng Biotechnol 2018;6:18.

[24] Sharma AS, Jagga S, Lee SS, Nam JS. Interplay between cartilage and subchondral bone contributing to pathogenesis of osteoarthritis. Int J Mol Sci 2013;14:19805-19830.

[25] Roseti L, Desando G, Cavallo C, Petretta M, Grigolo B. Articular Cartilage Regeneration in Osteoarthritis. Cells 2019;8:1305.

[26] Makris EA, Gornall AH, Malizos KN, Hu JC, Athanasiou KA. Repair and tissue engineering techniques for articular cartilage. Nat Rev Rheumatol 2015;11:21.

[27] Hunziker EB. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. Osteoarthritis Cartilage 2002;10:432-463.

[28] Schindler OS. Current concepts of articular cartilage repair. Acta Orthop Belg 2011;77:709.

[29] Oldershaw RA. Cell sources for the regeneration of articular cartilage: the past, the horizon and the future. Int J Exp Pathol 2012;93:389-400.

[30] Tuon RS, Chen AF, Klatt BA. Cartilage regeneration. J Am
Herbal medicine used in osteoarthritis and chondrogenesis

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Acad Orthop Surg 2013;21:303.

[31] PourmollaAbasi B, Hashemibeni B, and Esfandiar E. A review study: effect of growth factors on human mesenchymal stem cells differentiation into cartilage tissue Anat Sci J 2015;12:183-190.

[32] Shea CM, Edgar CM, Einhorn TA, Gerstenfeld LC. BMP treatment of CSH10T1/2 mesenchymal stem cells induces both chondrogenesis and osteogenesis J Cell Biochem 2003;90:1112-1127.

[33] Christiansen BA, Bhatti S, Goudarzi R, Emami S. Management of osteoarthritis with avocado/soybean unsaponifiables. Cartilage 2015;6:30-44.

[34] Salehi B, Rescigno A, Dettori T, Calina D, Docea AO, Singh L. Avocado–Soybean Unsaponifiables: A Panoply of Potentialities to Be Exploited. Biomolecules 2020;10:130.

[35] Lippiello L, Nardo IV, Harlan R, Chiuo T. Metabolic effects of avocado/soy unsaponifiables on articular chondrocytes. Evid Based Complementary Altern Med 2008;5:191-197.

[36] Eser O, Songur A, Yaman M, Cosar M, Fidan H, Sahin O, Hakan M, Sadik B. The protective effect of avocado soybean unsaponifiables on brain ischemia/reperfusion injury in rat prefrontal cortex. Br J Neurosurg 2001;15:701-706.

[37] Hashemibeni B, Valiani A, Esmaeli M, Kazemi M, Aliakbari M, and Iranpour FG. Comparison of the efficacy of piascledine and transforming growth factor β1 on chondrogenic differentiation of human adipose-derived stem cells in fibrin and fibrin-alginate scaffolds. Iran J Basic Med Sci 2018;21:212.

[38] Hashemibeni B, Mardani M, Valiani A, Pourzentezari M, Anvari M, Yadegar M, Mangoli E. Effects of Avocado/ Soybean on the Chondrogenesis of Human Adipose-Derived Stem Cells Cultured on Polylactic-Co-Glycolic Acid/ Fibrin Hybrid Scaffold. Appl Biotechnol Rep 2019;6:145-150.

[39] Cho SJ, Oh SH, Pridmore RD, Juillerat MA, Lee CH. Purification and characterization of proteases from Bacillus amyoliquefaciens isolated from traditional soybean fermentation starter. J Agric Food Chem 2003;51:7664-7670.

[40] Taylor JF, Goudarzi R, Yazdi PG, Pedersen BA. In vitro effects of arthrocin, an avocado/soy unsaponifiable agent, on inflammation and global gene expression in human monocytes. Int J Chem 2017:9:31.

[41] Henrotin Y. Avocado/Soybean Unsaponifiables (Piacleidine® 300) show beneficial effect on the metabolism of osteoarthritic cartilage, synovium and subchondral bone: An overview of the mechanisms. AIMS Medical Science 2018;5:33-52.

[42] Ernst E. Avocado-soybean unsaponifiables (ASU) for osteoarthritis—a systematic review. Clin Rheumatol 2003;22:285-288.

[43] Mahau E, Cadet C, Marty M, Moyse D, Kerloch I, Coste P, Dougdos M, Mazieres B, Spector T, Halhol H, Grouin J, Lequesne M. Randomised, controlled trial of avocado–soybean unsaponifiable (Piascledine) effect on structure modification in hip osteoarthritis: the ERADIAS study. Ann Rheum Dis 2014;73:376-384.

[44] Henrotin YE, Sanchez C, Deberg, Piccardi N, Guillou GB, Msika P, Reginester G. Avocado/soybean unsaponifiables increase aggrecan synthesis and reduce catabolic and proinflammatory mediator production by human osteoarthritic chondrocytes. J Rheumatol 2003;30:1825-1834.

[45] Gabay O, Gosset M, Levy A, Salvat C, Sanchez C, Pigenet A, Sautet A, Jacques C, Berenbaum F. Stress-induced signaling pathways in hyalin chondrocytes: inhibition by Avocado–Soybean Unsaponifiables (ASU). Osteoarthr Cartil 2008;16:373-384.

[46] Lasserre CK, Miller CC, Ejeil A, Gogly B, Dridi M, Piccardi N, Guillou B, Pellat B, Godeau G. Effect of avocado and soybean unsaponifiables on gelatinase A (MMP-2), stromelysin 1 (MMP-3), and tissue inhibitors of matrix metalloproteinase (TIMP-1 and TIMP-2) secretion by human fibroblasts in culture. J Periodontol 2001;72:1685-1694.

[47] Bahrami M, Valiani A, Amirpour N, Rani MZR, Hashemibeni B. Cartilage tissue engineering via icariin and adipose-derived stem cells in fibrin scaffold. Adv Biomed Res 2018;7.

[48] Ownybl SL, Fortuno LV, Au AY, Grzanna MW, Rashmir-Raven AM, Frondoza CG. Expression of pro-inflammatory mediators is inhibited by an avocado/soybean unsaponifiables and epigallocatechin gallate combination. Inflammation 2014;11:8.

[49] Darestani RT, Bakhshi H, Sahraee R. Comparing the efficacy and safety of Diclofenac and Piaseclined in patients with knee osteoarthritis. Pajoohshahdeh 2013;17:272-278.

[50] Zhang DW, Cheng Y, Wang NL, Zhang JC, Yang MS, Yao XS. Effects of total flavonoids and flavonol glycosides from Epimedium koreanum Nakai on the proliferation and differentiation of primary osteoblasts. Phytomedicine 2008;15:55-61.

[51] Qin Z, Liao D, Chen Y, Zhang C, An R, Zeng Q, Li X. A widely metabolomic analysis revealed metabolic alterations of epimedium pubescens leaves at different growth stages. Molecules 2020;25:137.

[52] Hashemibeni B, Pourzentezari M, Valiani A, Zamani M, Mardani M. Effect of icariin on the chondrogenesis of human adipose derived stem cells on poly (lactic-co-glycolic) acid/fibrin composite scaffold. Int J Adv Biotechnol Res 2017;8:595-605.

[53] Hsieh TP, Sheu SY, Sun JS, Chen MH, Liu MH. Icariin isolated from Epimedium pubescens regulates osteoblasts anabolism through BMP-2, SMAD4, and Cbfα1 expression. Phytomedicine 2010;17:414-423.

[54] Zhao J, Ohba S, Shinkai M, Chung UI, Nagamune T. Icariin in fibrin and fibrin-alginate scaffolds. Iran J Basic Med Sci 2014;11:8.

[55] Li D, Yuan T, Zhang X, Xiao Y, Wang R, Fan Y. Icariin: a potential promoting compound for cartilage tissue engineering. J Tradit Chin Med 2013;33:611-615.
Herbal medicine used in osteoarthritis and chondrogenesis

M. Anvari et al.

[56] Liu MH, Sun JS, Tsai SW, Sheu SY, Chen MH. Icariin protects murine chondrocytes from lipopolysaccharide-induced inflammatory responses and extracellular matrix degradation. Nutr Res Rev 2010;30:57-65.

[57] Zhang L, Zhang X, Li KF, Li DX, Xiao YM, Fan YJ, Xhan XD. Icariin promotes extracellular matrix synthesis and gene expression of chondrocytes in vitro. Phytother Res 2012;26:1385-1392.

[58] Zhang J, Zhang D, Wu C, Liu A, Zhang C, Jiao J, Shang M. Icariin-conditioned serum engineered with hyaluronic acid promote repair of articular cartilage defects in rabbit knees. BMC Complement Altern 2019;19:1-9.

[59] Sun P, Liu Y, Deng X, Yu C, Dai N, Yuan X, Chen L, Yu S, Si W, Wang X, Wu D, Liu S, Pang H. An inhibitor of cathepsin K, icariin suppresses cartilage and bone degradation in mice of collagen-induced arthritis. Phytotherapy 2013;20:975-979.

[60] Mi B, Wang J, Liu Y, Liu J, Hu L, Panayi AC, Liu G, Zhou W. Icariin activates autophagy via down-regulation of the NF-κB signaling-mediated apoptosis in chondrocytes. Front Pharmacol 2018;9:605.

[61] Wang Z, Ding L, Zhang S, Jiang T, Yang Y, Li R. Effects of icariin on the regulation of the OPG-RANKL–RANK system are mediated through the MAPK pathways in IL-1β-stimulated human SW1353 chondrosarcoma cells. Int J Mol Med 2014;34:1720-1726.

[62] Zeng L, Rong XF, Li RH, Wu XY. Icariin inhibits MMP-1, MMP-3 and MMP-13 expression through MAPK pathways in IL-1β-stimulated SW1353 chondrosarcoma cells. Mol Med Rep 2017;15:2853-1858.

[63] Zu Y, Mu Y, Li Q, Zhang ST, Yan HJ. Icariin alleviates osteoarthritis by inhibiting NLRP3-mediated pyroptosis. J Orthop Surg Res 2019;14:307.

[64] Zarfeshany A, Asgary S, Javanmard SH. Potent health effects of pomegranate. Adv Biomed Res 2014;3:100.

[65] Shuid AN, Mohamed IN. Pomegranate use to attenuate bone loss in major musculoskeletal diseases: an evidence-based review. Curr Drug Targets 2013;14:1565-1578.

[66] Ahmed S, Wang N, Hafeez BB, Cheruvu VK, Haqqi TM. Punica granatum L. extract inhibits IL-1β-Induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NF-kappaB in human chondrocytes in vitro. J Nutr 2005;135:2096-2102.

[67] Kamekura S, Kawasaki Y, Hoshi K, Shimoka T, Chikuda H, Maruyama Y. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum 2006;54:2462-2470.

[68] Tetsunaga T, Nishida K, Furumatsu T, Naruse K, Hirohata S, Yoshida A, Saito T, Ozaki T. Regulation of mechanistic stress-induced MMP-13 and ADAMTS-5 expression by RUNX-2 transcriptional factor in SW1353 chondrocyte-like cells. Osteoarthr Cartil 2011;19:222-232.

[69] Rasheed Z, Akhtar N, Anbazhagan AN, Ramamurthy S, Shukla M, Haqqi TM. Polyphenol-rich pomegranate fruit extract (POMx) suppresses PMACI-induced expression of pro-inflammatory cytokines by inhibiting the activation of MAP Kinases and NF-κB in human KU812 cells. inflammation 2009;6:1.

[70] Zarfeshany A, Asgary S, Javanmard SH. Potent health effects of pomegranate. Adv Biomed Res 2014;3:36-38.

[71] Spilmont M, Léotoing L, Davicco MJ, Lebecque P, Mercier S, Noirault SM, Pilet P, Rios L, Wittran Y, Coxam V. Pomegranate seed oil prevents bone loss in a mice model of osteoporosis, through osteoblastic stimulation, osteoclastic inhibition and decreased inflammatory status. J Nutr Biochem 2013;24:1840-1848.

[72] Hadipour-Jahromy M, Mozaffari-Kermani R. Chondroprotective effects of pomegranate juice on monoiodoacetate-induced osteoarthritis of the knee joint of mice. Phytother Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 2010;24:182-185.

[73] Garbacki N, Angenot L, Bassleer C, Damas J, Tits M. Effects of prodelphinidins isolated from Ribes nigrum on osteoclastic inhibition and decreased inflammatory status. J Nutr Biochem 2013;365:434-441.

[74] Katani M, Zolfaghari B, Soleimani M, Valiani A, and Hashembeni B. The effect of pomegranate extract on producing type II collagen in differentiation of adipose-derived stem cells into chondrocytes. Journal of Isfahan Medical School 2018;35:1540-5.

[75] Razavi SZE, Karimi M, Kamalinejad M. The efficacy of topical oliban oil (Boswellia Carterii B.) in relieving the symptoms of knee osteoarthritis. Physical Medicine, Rehabilitation, and Electrodiagnosis 2019;1:7-13.

[76] Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS)–validation and comparison to the WOMAC in total knee replacement. Health Qual Life Out 2003;1:17.
Herbal medicine used in osteoarthritis and chondrogenesis

M. Anvari et al.

[81] Kaboli PJ, Doebbeling BN, Saag KG, Rosenthal GE. Use of complementary and alternative medicine by older patients with arthritis: a population-based study. Arthritis Care Res 2001;45:398-403.

[82] Striggow F, Schmidt W, Mack T. Method of treating cerebral ischemia with hydrogenation products of frankincense extracts. ed: Google Patents, 2010.

[83] Qurishi Y, Hamid A, Zargar M, Singh SK, Saxena AK. Potential role of natural molecules in health and disease: Importance of boswellic acid. J Med Plants Res 2010;4:2778-2785.

[84] Safayhi H, Mack T, Sabieraj J, Anazodo MI, Subramanian LR, Ammon H. Boswellic acids: novel, specific, nonreducing inhibitors of 5-lipoxygenase. J Pharmocol Exp Ther 1992;261:1143-1146.

[85] Pelletier JP, Boileau C, Boily B, Brunet J, Mineau F, Geng C, Reboul C, Laufer S, Lajeunesse D, Pelletier JM. The protective effect of licoflone on experimental osteoarthritis is correlated with the downregulation of gene expression and protein synthesis of several major cartilage catabolic factors: MMP-13, cathepsin K and aggrecanases. Arthritis Res Ther 2005;7:1091.

[86] Syrovets T, Büchele B, Krauss C, Laumonier Y, Simmet T. Acetylsalicylic acids inhibit lipopolysaccharide-mediated TNF-α induction in monocytes by direct interaction with hsp kinases. J Immunol 2005;174:498-506.

[87] Wang Q, Pan X, Wong H, Wagner C, Lahey L, Robinson W, Sokolove J. Oral and topical boswellic acid attenuates mouse osteoarthritis. Osteoarthr Cartil 2014;22:128-132.

[88] Sengupta K, Kolla JN, Krishnaraju AV, Yalamanchili N, Rao CV, Golakoti T, Raychaudhuri S, Raychaudhuri SP. Cellular and molecular mechanisms of anti-inflammatory effect of Aflapin: a novel Boswellia serrata extract. Mol Cell Biochem 2011;354:189-197.

[89] Walker-Bone K, Javaid K, Arden N, Cooper C. Medical management of osteoarthritis. BMJ 2000;321:936-940.

[90] Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee: a clinical evaluation. Altern Complement Ther 2002;8:341-348.

[91] Badria FA, El-Farahaty T, Shabana AA, Hawas SA, El-Batoty MF. Boswelia–curcumin preparation for treating knee osteoarthritis: a clinical evaluation. Alterm Complement Ther 2002;8:341-348.

[92] Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, Bridgert L, Williams S, Guillemin F, Hill CL, Laslett LL, Jones G, Cicuttini F, Osborne R, Vos T, Buchbinder R, Woolf A, March L. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323-1330.

[93] Zhou G, Li R, Xia T, Ma C, Shen J. Utilizing network pharmacology to explore the underlying mechanism of Cinnamomum cassia Presl in treating osteoarthritis. Int J Clin Exp Med 2019;12:13359-13369.

[94] Hootman JM, Helmick CG, Barbour KE, Theis KA, Borling MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015–2040. Arthritis Rheumatol 2016;68:1582-1587.

[95] Vetal S, Bodhankar SL, Mohan V, Thakurdesai PA. Anti-inflammatory and anti-arthritic activity of type-A procoynadine polyphenols from bark of Cinnamomum zeylanicum in rats. Food Sci Hum Well 2013;2:59-67.

[96] Fiebich B, Heinrich M, Hiller K, Kamranner N. Inhibition of TNF-α synthesis in LPS-stimulated primary human monocytes by Harpagophyllum procumbens extract SteiHap 69. Phytotherapy 2001;8:28-30.

[97] Loew D, Müllerfeld J, Schröder A, Puttkammer S, Kaschin M. Investigations on the pharmacokinetic properties of Harpagophyllum procumbens extracts and their effects on eicosanoid biosynthesis in vitro and ex vivo. Clin Pharmacol Ther 2001;69:356-364.

[98] Tjendraputra E, Tran VH, Liu-Brennan D, Roufogalis BD, Duke CC. Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. Bioorg Chem 2001;29:156-163.

[99] Brien S, Lewith GT, and McGregor G. Devil’s Claw (Harpagophyllum procumbens) as a treatment for osteoarthritis: a review of efficacy and safety. J Altern Complement Med 2006;12:981-993.

[100] Frondoza CG, Sohrabi A, Polotsky A, Phan PV, Hungerford DS, Lindmark L. An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. In Vitro Cell Dev-an. 2004;40:95-101.

[101] Bartels E, Folmer V, Biddal D, Altman RD, Juul C, Tarp S, Zhang W, Christensen R. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. Osteoarthr Cartil 2015;23:13-21.

[102] Lantz RC, Chen G, Sarihan M, Soloyv A, Jolad S, and Timmermann B. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytochemistry 2001;69:142-148.

[103] Grant I, McBean D, Fyfe L, Warnocka. A review of the biological and potential therapeutic actions of Harpagophyllum procumbens. Phytother Res 2007;21:199-209.

[104] Srivastava K, Mustafa T. Ginger (Zingiber officinale) efficacies, safety and mechanisms. Eur Rev Med Pharmacol 2011;15:727-732.

[105] Wigler I, Grotto I, Caspi D, Yaron M. The effects of Zintona (Zingiber officinale Rosc) on human peripheral blood monocytes by Harpagophytum procumbens) as a treatment for osteoarthritis: a randomized, double-blind, placebo-controlled trial. Osteoarthr Cartil 2005;13:451-457.

[106] Gao J, Liu ZJ, Chen T, Zhao D. Pharmaceutical properties of Harpagophyllum procumbens. J Alternative & Complementary Medicine 2010;16:854-858.

[107] Huh J E, Seo DM, Baek YM, Park DS, Lee JD. Utilizing network pharmacology to explore the underlying mechanism of Cinnamomum cassia Presl in treating osteoarthritis. Int J Clin Exp Med 2019;12:13359-13369.

http://jtim.tums.ac.ir
Herbal medicine used in osteoarthritis and chondrogenesis

M. Anvari et al.

[108] Choi S, Heo T, Min BH, Cui J, Choi B, Park S. Alleviation of osteoarthritis by calycosin-7-O-β-D-glucopyranoside (CG) isolated from Astragalus radix (AR) in rabbit osteoarthritis (OA) model. Osteoarthr Cartil 2007;15:1086-1092.

[109] Liu J, Zhao Z, Chen H. Review of Astragalus radix. Chin Herb Med 2011;3:90-105.

[110] Choi L, Lee Y, Heo T. Screening of hyaluronidase inhibitory and free radical scavenging activity in vitro of traditional herbal medicine extracts KSBB Journal 2003.

[111] Park SR, Heo TR. Inhibitory effect of Astragalus radix on matrix degradation in human articular cartilage. J Microbiol Biotechn 2005;15:1258-1266.

[112] Yu SY, OuYang HT, Yang JY, Huang XL, Yang T, Duan JP, Cheng JP, Chen YY, Yang Y, Qiong P. Subchronic toxicity studies of Radix Astragali extract in rats and dogs. J Ethnopharmacol 2007;110:352-355.

[113] Jiang JB, Qiu JD, Yang LH, He JP, Smith JW, LI HQ. Therapeutic effects of astragalus polysaccharides on inflammation and synovial apoptosis in rats with adjuvant-induced arthritis. Int J Rheum Dis 2010;13:396-405.

[114] Unusan N. Proanthocyanidins in grape seeds: An updated review of their health benefits and potential uses in the food industry. J Funct Foods 2020;67:103861.

[115] Sharma V, McNeill JH. To scale or not to scale: the principles of dose extrapolation. Br J Pharmaco 2009;157:907-921.

[116] Pallarès V, Fernández-Iglesias A, Cédó L, Castell-Auví A, Pinent M, Ardèvol A. Grape seed procyanidin extract reduces the endotoxin effects induced by lipopolysaccharide in rats. Free Radic Biol Med 2013;60:107-114.

[117] Aini H, Ochi H, Iwata M, Okawa A, Koga D, Okazaki M. Procyanidin B3 prevents articular cartilage degeneration and heterotopic cartilage formation in a mouse surgical osteoarthritis model. PLoS One 2012:7.

[118] Cho ML, Heo YJ, Park MK, Oh HJ, Park JS, Woo YJ. Grape seed proanthocyanidin extract (GSPE) attenuates collagen-induced arthritis. Immunol Lett 2009;124:102-110.

[119] Suri S, Gill SE, de Camin SM, McWilliams DF, Wilson D, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis 2007;66:1423-1428.

[120] Lu J, Zhang K, Chen S, Wen W. Grape seed extract inhibits VEGF expression via reducing HIF-1α protein expression. Carcinogenesis2009;30:636-644.

[121] Woo YJ, Joo YB, Jung YO, Ju JH, Cho ML, Oh HJ, Jhon JY, Park MK, Park JS, Kang CM, M. Sung MS, Park SH, Kim HY, Min JK. Grape seed procyanidin extractameliorates monosodium iodoacetate-induced osteoarthritis. Exp Mol Med 2001;43:561.

[122] Dumond H, Presle N, Pottier P, Paquelet S, Terlain B, Nettet P, Gepstein A, Livne E, Jouzeau J. Site specific changes in gene expression and cartilage metabolism during early experimental osteoarthritis. Osteoarthr Cartil 2004;12:284-295.

[123] Li WG, Zhang XY, Wu YJ, Tian X. Anti-inflammatory effect and mechanism of proanthocyanidins from grape seeds. Acta Pharmacol Sin 2001;22:1117-1120.

[124] Miller MJ, Bobrowski P, Shukla M, Gupta K, Haqqi TM. Chondroprotective effects of a proanthocyanidin rich Amazonian genonutrient reflects direct inhibition of matrix metalloproteinases and upregulation of IGF-1 production by human chondrocytes. Inflammation 2007;4:16.

[125] Toker H, Yuce YB, Alpan AL, Gevrek F, Elmasetas M. Morphometric and histopathological evaluation of the effect of grape seed proanthocyanidin on alveolar bone loss in experimental diabetes and periodontitis. J Periodontal Res 2018;53:478-486.

[126] Ahmad SF, Zohir KM, Abdel-Hamied HE, Ashour AE, Bakheet SA, Atta SM, Abdallah AR. Grape seed proanthocyanidin extract has potent anti-arthritis effects on collagen-induced arthritis by modifying the T cell balance. Int Immunopharmacol 2013;17:79-87.

[127] Gagnier JJ, Tuder MW, Berman B, Bombardier C. Herbal medicine for low back pain: a Cochrane review. Spine 2007;32:82-92.

[128] Gagnier JJ, Chrubasik S, Manheimer E. Harpagophytum procumbens for osteoarthritis and low back pain: a systematic review. BMC Complement Altern M 2004;4:13.

[129] Anauate MC, Torres LM, Mello SBV. Effect of isolated fractions of Harpagophyton procumbens DC (devil's claw) on COX-1, COX-2 activity and nitric oxide production on whole-blood assay. Phytother Res 2010;24:1365-1369.

[130] Inaba K, Murata K, Naruto S, Matsuda H. Inhibitory effects of devil's claw (secondary root of Harpagophyton procumbens) extract and harpagoside on cytokine production in mouse macrophages. J Nat Med 2010:64:219-222.

[131] Grassl C, Luckow B, Schlondorff D, Dendorfer U. Transectional regulation of the interleukin-6 gene in mesangial cells. Clin J Am Soc Nephro 1999;10:1466-1477.

[132] Haseeb A, Ansari MY, Haqqi TM. Harpagoside suppresses IL-6 expression in primary human osteoarthritis chondrocytes. J Orthop 2017;35:311-320.

[133] Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-κB. Febs Lett. 1999;442:89-94.

[134] Teucher T, Obertreis B, Ruttkowski T, Schmitz H. Cytokine secretion in whole blood of healthy subjects following oral administration of Urtica dioica L. plant extract. Arzneimittel-Forschung 1996;46:906-910.

[135] Shiozawa S, Shimizu K, Tanaka K, Hino K. Studies on the contribution of c-fos/AP-1 to arthritic joint destruction J Clin Invest 1997;99:1210-1216.

[136] Miller MJ, Bobrowski P, Shukla M, Gupta K, Haqqi TM. Chondroprotective effects of a proanthocyanidin rich Amazonian genonutrient reflects direct inhibition of matrix metalloproteinases and upregulation of IGF-1 production by human chondrocytes. Inflammation 2007;4:16.
Herbal medicine used in osteoarthritis and chondrogenesis

M. Anvari et al.

[137] Ahmed KM, Parsuraman S. Urtica dioica L.,(Urticaceae): a stinging nettle. Sys Rev Pharm 2014;5:6.

[138] Efthimiou P, Kakar M, and MacKenzie CR. Complementary and alternative medicine in rheumatoid arthritis: no longer the last resort!. HSS journal 2010;6:108-111.

[139] Rayburn K, Fleischbein E, Song J, Allen B, Kundert M, Leiter C, Bush T. Stinging nettle cream for osteoarthritis. Altern Ther Health Med 2009;15:60.

[140] Xu X, Lv H, Li X, Su H, Zhang X, Yang J. Danshen attenuates cartilage injuries in osteoarthritis in vivo and in vitro by activating JAK2/STAT3 and AKT pathways. Exp Anim 2018;67:127-137.

[141] Bai B, Li Y. Danshen prevents articular cartilage degeneration via antioxidation in rabbits with osteoarthritis. Osteoarthritis Cartilage 2016;24:514-520.

[142] Luo H, Kong W, Hu Y, Chen P, Wu X, Wan L, Yang M. Quality evaluation of Salvia miltiorrhiza Bge. by ultra high performance liquid chromatography with photodiode array detection and chemical fingerprinting coupled with chemometric analysis. J Sep Sci 2015;38:1544-1551.

[143] Chun-Yan S, Qian-Liang M, Rahman K, Ting H, Lu-Ping Q. Salvia miltiorrhiza: Traditional medicinal uses, chemistry, and pharmacology. Chin J Nat Medicines 2015;13:163-182.

[144] Basedow M, Williams H, Shanahan EM, Runciman WB, Esterman A. Australian GP management of osteoarthritis following the release of the RACGP guideline for the non-surgical management of hip and knee osteoarthritis. BMC Res Notes 2015;8:536.

[145] Huang MQ, Zhou CJ, Zhang YP, Zhang XQ, Xu W, Lin J, Wang PJ. Salvianolic acid B ameliorates hyperglycemia and dyslipidemia in db/db mice through the AMPK pathway. Cell Physiol Biochem 2016;40:933-943.

[146] Shen Q, Ma X, Hua Y, Chen M, Wang Y, Zhou Q, Ye W, Zhu X. Aquaporin 3 Expression Induced by Salvia Miltiorrhiza via ERK1/2 Signal Pathway in the Primary Human Amnion Epithelium Cells from Isolated Oligohydramnios. Curr Mol Biol 2016;16:312-319.

[147] Ye YT, Zhong W, Sun P, Wang D, Wang C, Hu LM, Qian JQ. Apoptosis induced by the methanol extract of Salvia miltiorrhiza Bunge in non-small cell lung cancer through PTEN-mediated inhibition of PI3K/Akt pathway. J Ethnopharmacol 2017;200:107-116.

[148] Xu X, Lv H, Li X, Su H, Zhang X, Yang J. Danshen attenuates osteoarthritis-related cartilage degeneration through inhibition of NF-αB signaling pathway in vivo and in vitro. Biochem Cell Biol 2017;95:644-651.

[149] Yang X, Liu S, Li S, Wang P, Zhu W, Liang P, Tan J, Cui S. Salvianolic acid B regulates gene expression and promotes cell viability in chondrocytes. J Cell Mol Med 2017;21:1835-1847.

[150] Liu QS, Luo XY, Jiang H, Xing Y, Yang MH, Yuan GH, Tang Z, Wang H. Salvia miltiorrhiza injection restores apoptosis of fibroblast-like synoviocytes cultured with serum from patients with rheumatoid arthritis. Mol Med Rep 2015;11:1476-182.

[151] Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PloS One 2016;11.

[152] Lin M, Zhai X, Wang G, Tian X, Gao D, Shi L, Wu H, Fan Q, Peng J, Liu K, Yau J. Salvianolic acid B protects against acetaminophen hepatotoxicity by inducing Nrf2 and phase II detoxification gene expression via activation of the PI3K and PKC signaling pathways. J Pharmacol Sci 2015;127:203-210.

[153] Xia ZB, Yuan YJ, Zhang QH, Li H, Dai JL, Min LK. Salvianolic acid B suppresses inflammatory mediator levels by downregulating NF-αB in a rat model of rheumatoid arthritis. Medical science monitor: Med Sci Mon Int Med J Exp Clin Res 2018;24:2524.

[154] Prakash V, Jaiswal N, Srivastava M. A review on medicinal properties of Centella asiatica. Asian J Pharm Clin Res 2017;10:69.

[155] Chandrika UG, Kumara PAP. Gotu kola (Centella asiatica): nutritional properties and plausible health benefits. In Advances in food and nutrition research 2015;76:125-157.

[156] Moqbel SAA, He Y, Xu L, Ma C, Ran J, Xu K, Wu L. Rat Chondrocyte Inflammation and Osteoarthritis Are Ameliorated by Madecassoside. Oxid Med Cell Longev 2020;2020.

[157] Cao W, Li XQ, Zhang XN, Hou Y, Zeng AG, Xie YH, Wang SW. Madecassoside suppresses LPS-induced TNF-α production in cardiomyocytes through inhibition of ERK, p38, and NF-αB activity. Int Immunopharmacol 2010;10:722-729.

[158] Hartog A, Smit HF, van Der Kraan PM, Hoijer MA, and Garrsen J. In vitro and in vivo modulation of cartilage degradation by a standardized Centella asiatica fraction. Exp Biol Med 2009;234:617-623.

[159] Sharma S, Gupta R, Thakur SC. Increased HOx alpha-a new stinging nettle leaf extract-on matrix metalloproteinases in human chondrocytes in vitro. Histol Histopathol 2002. 1177-1182.

[155] Liu QS, Luo XY, Jiang H, Xing Y, Yang MH, Yuan GH, Tang Z, Wang H. Salvia miltiorrhiza injection restores apoptosis of fibroblast-like synoviocytes cultured with serum from patients with rheumatoid arthritis. Mol Med Rep 2015;11:1476-182.

[151] Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PloS One 2016;11.

[152] Lin M, Zhai X, Wang G, Tian X, Gao D, Shi L, Wu H, Fan Q, Peng J, Liu K, Yau J. Salvianolic acid B protects against acetaminophen hepatotoxicity by inducing Nrf2 and phase II detoxification gene expression via activation of the PI3K and PKC signaling pathways. J Pharmacol Sci 2015;127:203-210.

[153] Xia ZB, Yuan YJ, Zhang QH, Li H, Dai JL, Min LK. Salvianolic acid B suppresses inflammatory mediator levels by downregulating NF-αB in a rat model of rheumatoid arthritis. Medical science monitor: Med Sci Mon Int Med J Exp Clin Res 2018;24:2524.

[154] Prakash V, Jaiswal N, Srivastava M. A review on medicinal properties of Centella asiatica. Asian J Pharm Clin Res 2017;10:69.

[155] Chandrika UG, Kumara PAP. Gotu kola (Centella asiatica): nutritional properties and plausible health benefits. In Advances in food and nutrition research 2015;76:125-157.

[156] Moqbel SAA, He Y, Xu L, Ma C, Ran J, Xu K, Wu L. Rat Chondrocyte Inflammation and Osteoarthritis Are Ameliorated by Madecassoside. Oxid Med Cell Longev 2020;2020.

[157] Cao W, Li XQ, Zhang XN, Hou Y, Zeng AG, Xie YH, Wang SW. Madecassoside suppresses LPS-induced TNF-α production in cardiomyocytes through inhibition of ERK, p38, and NF-αB activity. Int Immunopharmacol 2010;10:722-729.

[158] Hartog A, Smit HF, van Der Kraan PM, Hoijer MA, and Garrsen J. In vitro and in vivo modulation of cartilage degradation by a standardized Centella asiatica fraction. Exp Biol Med 2009;234:617-623.

[159] Sharma S, Gupta R, Thakur SC. Attenuation of collagen induced arthritis by Centella asiatica methanol fraction via modulation of cytokines and oxidative stress. Biomed Environ Sci 2014;27:926-938.