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Review

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

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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

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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 diarthroidal 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 neovascularization 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 propeptide 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 medicin 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).

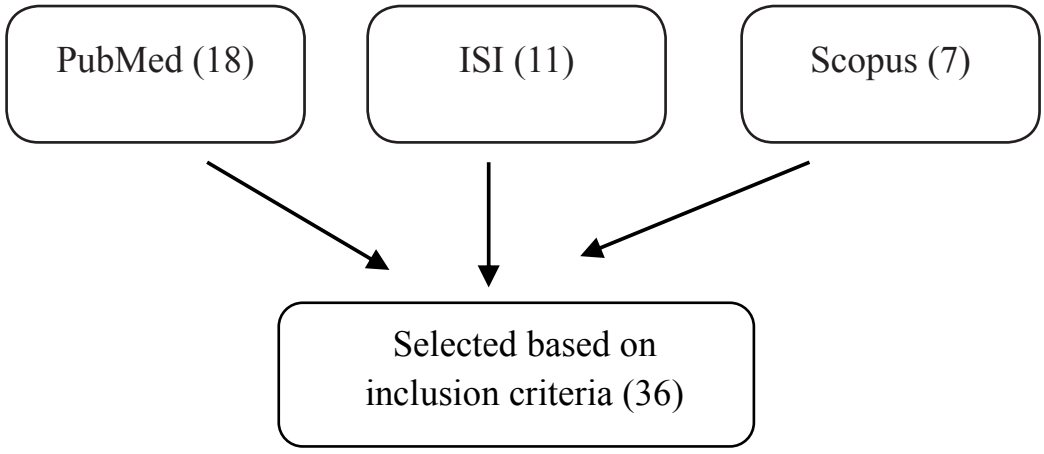

Figure 1. Schematic diagram of applied studies for accomplishment of this review

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 grandiflorum	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 lipooxygenase5, 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 lipooxygenase5 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 kappaB
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

10	Urtica Dioica	Urticaceae	Leaves	Neophytadiene, Phtaleic acid, Dibutyl phthalate, Bis (2-ethyl hexyls') maleate, 1,2-benzenocli 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 glycetin) 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]. The favor

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

dex. 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 expressions 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 effec

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 human cartilage sparing effects and is non-toxic to human cartilage cells. Pretreatment 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 demnstrated 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 cassi

Cinnamomum cassia has multi-component characteristics, and its mech¬anism 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 procyanidins 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]. In a

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 proinfalmmatory 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 Rhomatoid Arthritis [113].

Grape Seeds (GS)

Grape seeds (GS) are rich sources of proanthocyanidins, which include polyhydroxycylan 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 indistinctively 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 pro teoglycans 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 dedifferentiation 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]. Mateen 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 erosion. 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-arthritic 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 elderlies 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.

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