Chapter

Herbal Medicinal Products in the Treatment of Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common form of arthritis, which represents a substantial economic burden for society and significantly affects patients' quality of life. Current conventional treatments of OA may be insufficiently effective and unsafe. In an attempt to overcome these limitations, many patients use herbal medicinal products (HMPs) and dietary supplements. A considerable number of herbal drugs and preparations (e.g., willow bark, *Salicis cortex*; devil's claw root, *Harpagophyti radix*; blackcurrant leaf, *Ribis nigri folium*; nettle leaf/herb, *Urticae folium/herba*; meadowsweet/meadowsweet flower, *Filipendulae ulmariae herba/flos*; rosemary leaf/oil, *Rosmarini folium/aetheroleum*; and juniper oil, *Juniperi aetheroleum*) are traditionally employed to relieve minor articular pain. Active constituents (e.g., sesquiterpene lactones, triterpenic acids, diarylheptanoids, iridoid glycosides, phenolic glycosides, procyanidins, and alkaloids) are not often fully known. Experimental studies suggest that herbal extracts/compounds are able to suppress inflammation, inhibit catabolic processes, and stimulate anabolic processes relevant to OA. Therapeutic benefit of most HMPs is expected solely from the experience of their long-standing traditional use. Efficacy and safety of several HMPs were assessed in clinical trials. The growing body of preclinical and clinical evidence provides rationale for the use of herbal products in the treatment of OA. However, at present, they cannot be recommended to patients with confidence.

Keywords: osteoarthritis, herbal medicinal products, medicinal plants, mechanism of action, active constituents, clinical efficacy

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis and the main cause of disability in elderly. Due to the aging population and obesity (major risk factors), its prevalence increases. It is estimated that symptomatic OA of knee affects approximately 12% of the older population (≥60 years). Symptomatic OA of hand (6.8%, ≥26 years) and hip (9.2%, ≥45 years) is also frequent. OA can influence patients' quality of life significantly, as it is usually accompanied with the pain and loss of physical function. OA often affects knees, hips, hands (distal and proximal interphalangeal joints and the base of thumb), cervical and lumbosacral spine, and feet (first metatarsal phalangeal joint). It is characterized by failure of all joint structures. Articular cartilage loss is the most prominent feature of the disease, but subchondral bone, synovial membrane, associated muscles, and ligaments are also affected. On cellular level, catabolic function of chondrocytes prevails over their

anabolic activity. This imbalance is promoted by pro-inflammatory cytokines, which stimulate chondrocytes to produce enzymes (collagenases and aggrecanases) able to degrade extracellular matrix composed of collagen type II and proteoglycans. Several mediators (e.g., TNF-α, IL-1β, NO, and PGE_2) play an important role in the pathogenesis and progression of OA [1, 2].

Conventional treatment of OA encompasses non-pharmacotherapeutic approach (e.g., physiotherapy, correction of malalignment, weight control, and patient education), pharmacotherapy, and surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs) are medicines used most often for the relief of osteoarthritic symptoms. Although NSAIDs are relatively efficient, their prolonged use or their use in susceptible individuals can cause serious side effects such as gastrointestinal toxicity, cardiovascular events, edema development, reversible renal insufficiency, and modest increase of blood pressure. Topical formulations of NSAIDs are slightly less efficient than the oral ones, but their advantage lies in better safety profile. However, irritation of the skin often occurs at the application area [1].

Some patients experiencing unsatisfactory efficacy and side effects of conventional therapy try to overcome current treatment deficiencies by using modalities of complementary and alternative medicine. In that regard, herbal medicinal products (HMPs) and dietary supplements have become considerably popular for alleviation of OA symptoms [3]. Besides expected direct effects, important indirect benefit of their use may be the decrease of required doses of concomitantly administered conventional drugs, as this may result in reduced side effects. At present, available scientific data are insufficient to support the use of these products in clinical management of OA. The aim of this review is therefore to present current knowledge on herbal treatment options in the therapy of OA, i.e., active constituents of plants and mechanisms of their action relevant to OA, advice for patients using herbal products, and results of clinical trials, if available.

2. Herbal medicinal products for oral use in the treatment of osteoarthritis

Willow bark (*Salicis cortex*) is whole or fragmented dried bark of young branches or whole dried pieces of current-year twigs of various species of genus *Salix* including *S. purpurea* L., *S. daphnoides* Vill., and *S. fragilis* L. [4]. Herbal teas (infusion and decoction), powder, dry aqueous extracts, liquid hydroalcoholic extract, and tincture of willow bark are traditionally used for minor articular pain relief. Duration of the treatment is restricted to 4 weeks. In the case of hypersensitivity (to the willow bark, salicylates, or the other NSAIDs), asthma due to hypersensitivity to salicylates, active peptic ulcer disease, third trimester of pregnancy, glucose-6-phosphate dehydrogenase deficiency, children and adolescents younger than 18 (risk of Reye's syndrome), severe liver or renal dysfunction and coagulation disorders, the use of *Salicis cortex*-based HMPs is contraindicated. Concomitant application of salicylates and other NSAIDs is not recommended, unless advised by the physician. Willow bark preparations may interact with anticoagulants. Their use is not recommended in the first and second trimester of pregnancy, as well as during lactation. Side effects include allergic reactions and gastrointestinal symptoms [5]. The main constituents of willow bark with respect to the pharmacological action are phenolic glycosides (e.g., salicin, salicortin, 2′-O-acetylsalicortin, and/or tremulacin) [6, 7] although the other secondary metabolites (e.g., polyphenolic compounds) may also participate in the total anti-inflammatory activity [8]. Phenolic glycosides are considered as prodrug compounds that are metabolized to salicylic acid in gastrointestinal tract and liver. Beneficial effect is a result of

cyclooxygenase inhibition and diminished production of prostaglandins [9]. Two randomized controlled clinical trials provided low-quality evidence that short-term treatment with standardized willow bark extracts (daily doses corresponded to 240 mg of salicin) was not efficient in reduction of pain and improvement of physical function in patients with OA of hip and knee [3, 10]. Additional well-designed sufficiently powered studies are needed in order to estimate willow bark clinical effect.

Devil's claw root (*Harpagophyti radix*) consists of cut and dried, tuberous secondary roots of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne. [4]. Herbal tea and liquid or solid dosage forms containing different devil's claw root preparations (e.g., dry aqueous or hydroalcoholic extracts, liquid or soft hydroalcoholic extracts, tincture, powder) are used for the relief of minor articular pain, exclusively based upon long-standing traditional use. Patients with known hypersensitivity to devil's claw root or active gastric/duodenal ulcer must not use these products. Additionally, in cases of gallstones, a physician should be consulted prior to use of devil's claw root preparations. Undesirable effects include hypersensitivity, as well as adverse reactions of the central nervous system and gastrointestinal tract [11]. *Harpagophyti radix* contains bitter iridoid glycosides (harpagide and harpagoside), triterpenoids, polyphenolic acids, phenylethyl glycosides, and flavonoids [7]. Devil's claw root preparations exhibited anti-inflammatory activity *in vitro* by decreasing production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and PGE_2 in LPS-stimulated human monocytes [12] and by reducing levels of matrix metalloproteinases (MMP-1, MMP-3, MMP-9) in IL-1β-stimulated human chondrocytes [13]. Aqueous extract of *H. procumbens* downregulated expression of COX-2 and iNOS in the mouse fibroblasts and, as a result, decreased PGE_2 and NO generation [14]. Harpagoside, similarly to devil's claw root extracts, suppressed expression of IL-6 and MMP-13 in human chondrocytes, probably via the inhibition of transcription factor activator protein-1 (AP-1) activity [15]. Antiosteoarthritic properties of three devil's claw root preparations were the subject of four randomized controlled clinical trials. In two studies investigating Flexiloges® (ethanolic (60%) extract, DER 4.5–5.5:1, daily dose 960 mg), there was no improvement in pain scores. However, the pain-relieving activity of Arthrotabs® (aqueous extract, DER 1.5–2.5:1, daily dose 2400 mg) was noticed in another study. Finally, one study indicated that Harpadol® (cryoground powder, daily dose 2610 mg) was comparable to diacerhein in reducing pain [10].

Blackcurrant leaf (*Ribis nigri folium*) is a dried leaf of *Ribes nigrum* L. [4]. Phytochemical analysis showed that it contains polyphenolic compounds (flavonoids, proanthocyanidins, hydroxycinnamic acid derivatives) and traces of essential oil [6]. Blackcurrant leaf is used in traditional medicine to reduce minor articular pain [16]. Hydroalcoholic extract of this herbal drug exerted beneficial effects in carrageenan-induced acute inflammation, cotton pellet granuloma, and Freund's adjuvant-induced arthritis in rats. It also acted as an antinociceptive agent in the acetic acid-induced writhing test in mice [17]. Prodelphinidins (*Ribis nigri folium* constituents) stimulated synthesis of type II collagen and proteoglycans, and decreased the generation of PGE_2 in human chondrocytes [18]. Documented anti-inflammatory, analgesic, and anabolic effects give credence to reported folkloric use.

Meadowsweet herb (*Filipendulae ulmariae herba*—whole or cut, dried flowering tops) and meadowsweet flower (*Filipendulae ulmariae flos*, syn. *Spiraeae flos*—dried flowers) are herbal drugs obtained from *Filipendula ulmaria* (L.) Maxim. (syn. *Spiraea ulmaria* L.), which are traditionally used in treatment of minor articular pain [4, 19–21]. They are characterized by high content of polyphenols, particularly flavonoids and ellagitannins. Phenolic glycosides and salicylic acid are also present [6, 22]. *In vitro* anti-inflammatory action of

meadowsweet preparations was mediated by inhibition of complement activation, reduction of the production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and, to a certain degree, inhibition of cyclooxygenase and PGE_2 generation [6, 23, 24]. In animal model of carrageenan-induced acute inflammation, lyophilized flower infusion of *F. ulmaria* exerted analgesic activity [25]. There is no literature data related to clinical effects of meadowsweet in OA.

Nettle leaf (*Urticae folium*) is whole or a cut dried leaf of *Urtica dioica* L., *Urtica urens* L., or their mixture [4], whereas nettle herb (*Urticae herba*) is dried cut or fragmented aerial part of *Urtica dioica* L., *Urtica urens* L., their hybrids or mixtures, collected or harvested during the flowering period [26]. Both herbal drugs are employed in folkloric medicine for alleviation of minor articular pain. Side effects include gastrointestinal and allergic reactions [26, 27]. Constituents of nettle leaf and/or herb are caffeic acid esters, flavonoids, minerals, free amino acids, etc. [6]. Reputed benefit of nettle preparations in the treatment of OA complaints is supported by experimental findings that they suppressed activation of transcription factor NF-κB and inhibited IL-1β-stimulated production of MMP-1, MMP-3, and MMP-9 in human chondrocytes [28, 29]. Furthermore, oral intake of nettle leaf extract by healthy volunteers, during a three-week period, reduced production of pro-inflammatory cytokines (TNF-α, IL-1β) in whole blood *ex vivo* after LPS challenge [30].

Ash leaf (*Fraxini folium*) is by definition a dried leaf of *Fraxinus excelsior* L. or *Fraxinus angustifolia* Vahl (syn. *Fraxinus oxyphylla* M. Bieb), or of hybrids of these two species or of a mixture [4]. It is employed in ethnomedicine as herbal tea (infusion or decoction) to reduce minor articular pain [31]. Constituents occurring in ash leaf are coumarins, iridoids, secoiridoids, flavonoids, lignans, simple phenolic compounds, etc. [32]. Evidence from pharmacological studies that could explain recorded traditional use is scarce. Certain support was provided by experimental observation that esculin, a coumarin present in both species, decreased NO production in macrophages by inhibition of transcription factor NF-κB activation. Additionally, esculin was able to suppress inflammatory response (reduce levels of TNF-α and IL-6) induced by injecting LPS to mice [33].

Mixture of avocado and soybean unsaponifiables. Antiosteoarthritic properties of a mixture of avocado and soybean unsaponifiables (ASU) were extensively examined in the past. Phytochemical analysis of its composition revealed the presence of phytosterols (β-sitosterol, campesterol, and stigmasterol), fat-soluble vitamins, triterpene alcohols, and possibly furan fatty acids. Experimental studies provided significant evidence of ASU anabolic and anticatabolic action in cartilage. ASU stimulated the synthesis of extracellular matrix components (collagen and aggrecan) and inhibited production of pro-inflammatory molecules (TNF-α, IL-1β, IL-6, IL-8, MIP-1β, NO, and PGE_2) probably by interfering with signaling of transcription factor NF-κB. Cartilage degradation may be decreased as a result of ASU ability to inhibit matrix metalloproteinases (MMP-2, MMP-3, and MMP-13) and stimulate expression of tissue inhibitor of metalloproteinases-1. Beneficial activity may also be related to the capacity of ASU to affect levels of transforming growth factor-β and vascular endothelial growth factor [34]. Four randomized controlled clinical studies recruiting 651 participants provided moderate-quality evidence that ASU proprietary product Piascledine® (mixture of unsaponifiable fractions of fatty oils of *Persea gratissima* (P) and *Glycine max* (G), 1/3 P + 2/3 G; daily dose 300 mg) generated small improvement in osteoarthritic symptoms with questionable clinical significance, after a treatment lasting 3–12 months. Adverse events of herbal intervention were not probably increased compared to the placebo group. Moderate-quality evidence showed that Piascledine® in higher daily dose (600 mg) also reduced OA symptoms. Available data did not support assumption

that it significantly improved joint structure. There is limited evidence that it prevented joint space narrowing [10].

Indian frankincense (*Olibanum indicum*) is an air-dried gum-resin exudate, obtained by incision of the stem or branches of *Boswellia serrata* Roxb. ex Colebr. [4], which is used in the treatment of OA [35]. To assure optimal absorption, it is recommended to use Indian frankincense preparations with food. Cases of neutropenia were documented after long-term use of dry extract in a daily dose of up to 10 g. It contains pentacyclic triterpenic acids, i.e., β-boswellic acid (BA), 11-keto-β-boswellic acid (KBA), and acetyl-11-keto-β-boswellic acid (AKBA) [35]. These secondary metabolites could be responsible for the therapeutic activity, particularly BA that reaches relatively high concentration in the human plasma. BA, KBA, and AKBA acted as inhibitors of mPGES-1 and, hence, PGE_2 synthesis. They reduced the activity of cathepsin G [36], a serine protease whose relevance in OA has been suggested in a recent study [37]. The suppressing effect of AKBA on production of TNF-α in monocytes was also reported [36]. Crude *Boswellia serrata* extract downregulated inflammatory cytokines (TNF-α, IL-1β, and IL-6) in peripheral blood mononuclear cells [38]. Results of investigations using animal models of inflammation and arthritis (e.g., adjuvant arthritis in Lewis rats, formaldehyde-induced arthritis in rats, dextran-induced edema in rats, and carrageenan-induced edema in rats and mice) are in accordance with the *in vitro* observed anti-inflammatory activity [36]. Two randomized placebo-controlled clinical trials conducted with Indian frankincense proprietary product 5-Loxin® (standardized to contain at least 30% AKBA) indicated that oral application of this enriched extract in a daily dose of 100 mg decreased pain and improved function in OA patients (n = 85) after 90 days treatment. The results of studies examining proprietary product Aflapin® (enriched with non-volatile oil and standardized to contain at least 20% AKBA) are consistent. New studies may change the estimations [10]. Concentration of MMP-3 in synovial fluid of patients using 5-Loxin® decreased, suggesting that therapeutic activity could be linked to the attenuation of cartilage destruction [39].

Pycnogenol® is standardized bark extract of French maritime pine (*Pinus pinaster* Aiton) rich in polyphenolic compounds (procyanidins, taxifolin, catechin, and phenolic acids) [40]. Pharmacokinetic studies demonstrated that certain anti-inflammatory constituents of Pycnogenol® (ferulic acid and caffeic acid) and procyanidins gut microbiota metabolite δ-(3,4-dihydroxy-phenyl)-γ-valerolactone were able to reach synovial fluid [40, 41]. δ-(3,4-Dihydroxy-phenyl)-γ-valerolactone concentration-dependently reduced nitrite production and iNOS expression. Its affinity to accumulate in macrophages, monocytes, and endothelial cells were demonstrated [42]. Investigation conducted in patients with severe OA showed that expression of matrix metalloproteinases (MMP-3 and MMP-13) and IL-1β in chondrocytes was decreased after intake of Pycnogenol®, as well as level of ADAMTS-5 in serum [43]. Plasma obtained from volunteers taking Pycnogenol® orally for 5 days decreased activation of transcription factor NF-κB in macrophages and inhibited COX-1 and COX-2 [44, 45]. Additionally, gene expression of COX-2 and 5-LOX, leukotriene biosynthesis, and phospholipase A_2 activity in polymorphonuclear leukocytes (isolated from the blood of volunteers) were reduced [46]. Moderate-quality evidence obtained from three randomized controlled clinical trials indicated that Pycnogenol® (daily doses 100 or 150 mg) decreased pain and improved physical function in patients with OA of knee and that it probably reduced consumption of NSAIDs. The effect size after three-month treatment was estimated to be large and clinically important. However, quality of evidence is insufficient to make any firm conclusion. It should be noted that the content of marker compound (procyanidins) differed in the investigated products [3, 10].

Rosehip (*Rosae pseudofructus cum fructibus*) is obtained from *Rosa canina* L. It represents pseudofruit, composed of achenes enclosed in a fleshy receptacle or hypanthium. Phytochemical investigations revealed that rosehip contains sugars, organic acids, pectins, procyanidins, catechins, flavonoids, carotenoids, triterpene acids, unsaturated fatty acids, and a galactolipid [7, 35]. *R. canina* hip preparations inhibited activation of transcription factor NF-κB, decreased expression of matrix metalloproteinases (MMP-1, MMP-3, MMP-9, and MMP-13) in chondrocytes, suppressed expression of COX-2 in human monocytes and chondrocytes, decreased generation of PGE_2 and NO in murine macrophages, and reduced levels of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) and chemokine CCL5 in various assays. Dried powder of *R. canina* hips given to animals during 3 weeks exerted activity in rat arthritis model (monoiodoacetate-induced) and suppressed production of MMP-3 and MMP-13. Rosehip preparations also displayed activity in animal models of acute inflammation [47]. Active constituents belong to different groups of compounds; e.g., galactolipid was able to modulate chemokines (CCL5 and IL-8), matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) and aggrecanase ADAMTS-4 expression, whereas fatty acids (linoleic and linolenic) inhibited cyclooxygenases [47, 48]. It seems that reputed antirheumatic effect of rosehip is a sum of actions of several individual constituents. Data obtained from three clinical trials examining effects of rosehip powder provided modest and somewhat conflicting evidence that orally administered product (daily dose 5 g) is superior to placebo in the treatment of osteoarthritic pain [10].

Turmeric rhizome (*Curcumae longae rhizoma*) consists of whole, peeled, shortly boiled or steamed and dried rhizome of *Curcuma longa* L. (syn. *C. domestica* Valeton) [4]. Characteristic constituents are curcuminoids (phenolic diarylheptanoids), essential oil rich in turmerones (sesquiterpene ketones), and polysaccharides. It is popular in Ayurveda and Chinese medicine as an anti-inflammatory agent [7]. Curcumin *in vitro* prevented the apoptosis of chondrocytes and decreased the production of matrix metalloproteinases and monocyte chemoattractant protein. It also suppressed expression of pro-inflammatory cytokines, cyclooxygenase, and PGE_2 in chondrocytes. These effects were probably mediated by inhibition of IkB phosphorylation and thus transcription factor NF-κB activation. Regulation of AP-1 and protein kinase C was described as well. *In vivo* curcumin suppressed carrageenan-induced edema and formaldehyde-induced arthritis [49, 50]. Meta-analyses of randomized controlled trials indicated that curcumin was able to decrease circulating levels of pro-inflammatory cytokines TNF-α and IL-6 [51, 52]. Curcuminoids and *Curcuma longa* extract decreased oxidative stress in patients with OA, which suggested that antioxidant activity participated in turmeric beneficial action [53, 54]. A four-week multicenter randomized double-blind controlled clinical study showed that ethanol extract of turmeric rhizome (daily dose 1500 mg, 75–85% curcuminoids) was not inferior compared to ibuprofen (daily dose 1200 mg) in the management of knee OA. The number of side effects was similar in both groups, but incidence of gastrointestinal side effects was significantly higher in patients treated with ibuprofen [55]. Authors of a systematic review and meta-analysis concluded that a short-term treatment with curcumin and extract of *Curcuma longa* produced significant and clinically meaningful reduction of pain and improvement of physical function in patients with OA of knee. The quality of evidence was estimated to be very low to moderate. Characteristics of available studies limit possibility to make firm conclusion on the efficacy of turmeric rhizome preparations [3].

Ginger (*Zingiberis rhizoma*) is dried, whole or cut rhizome of *Zingiber officinale* Roscoe, with the cork removed, either completely or from wide, flat surfaces only [4]. It is characterized by the presence of essential oil and a mixture of pungent

tasting phenolic compounds (gingerols, gingerdiols, gingerdiones, dihydrogingerdiones, and shogaols) [7]. In a recent *in vitro* study, it has been shown that ginger extract was able to attenuate oxidative stress and reduce succeeding cell death of chondrocytes resulting from a mitochondrial apoptosis [56]. Ginger preparations also inhibited LPS-induced PGE_2 formation in U937 cells and decreased levels of TNF-α and IL-1β in murine peritoneal macrophages [57]. *In vivo*, they suppressed carrageenan- and fresh egg albumin-induced edema in rats and exhibited analgesic action in models of chemically and thermally induced pain in mice [58, 59]. Ginger essential oil reduced acetic acid-induced writhing response in animals [57]. Intraperitoneally administered 6-gingerol exhibited analgesic and anti-inflammatory action, i.e., decreased formalin-induced licking time in late phase and suppressed carrageenan-induced edema and acetic acid-induced writing response [60]. *In vitro* assay showed considerable potential of 6-gingerol to inhibit prostaglandin biosynthesis [61]. Therapeutic effect of ginger in patients with OA was investigated in two randomized controlled cross-over clinical studies. In one trial, ibuprofen treatment was reported to be more effective than acetone extract of ginger root (DER 20:1, daily dose 510 mg) in terms of pain reduction and consumption of NSAIDs. Available data did not allow reanalysis. Another trial showed that CO_2 extract of ginger root (daily dose: 1000 mg of extract, 40 mg of gingerol) significantly differed from placebo after a six-month study [10]. Although clinical trials investigating ginger were performed, its clinical benefit at this moment cannot be assessed with confidence.

Cat's claw (*Uncaria tomentosa* and *U. guianensis*), South American vines that share the same common name, are used traditionally to treat inflammatory conditions (e.g., arthritis) [62]. Active constituents of these medicinal plants are considered to be oxindole alkaloids (isorhynchophylline, rhynchophylline and their N-oxides, mitraphylline) and the quinovic acid glycosides [63]. According to the monograph of the World Health Organization, cat's claw bark (*Uncariae cortex*) consists of the dried stem bark of *Uncaria tomentosa* (Willd.) DC. (Rubiaceae) [64]. *In vitro* studies in murine macrophages showed that *U. tomentosa* and *U. guianensis* preparations suppressed TNF-α and PGE_2 formation [62] and that aqueous bark extract of *U. tomentosa* inhibited activation of transcription factor NF-κB [65]. The observed anti-inflammatory activity was further supported by *in vivo* experiments. *U. tomentosa* bark extracts (spray-dried hydroalcoholic and aqueous freeze-dried) suppressed carrageenan-induced paw edema in mice [66]. Using *in vivo* model of acute inflammation, fractions of *U. tomentosa* bark extract yielded quinovic acid glycoside as one of pharmacologically active compounds [67]. Mitraphylline, pentacyclic oxindole alkaloid, decreased blood levels of pro-inflammatory cytokines (IL-1β and TNF-α) in the LPS-challenged mice [68]. Double-blind placebo-controlled study in 45 patients within 4 weeks compared pain-relieving property of freeze-dried aqueous extract of *U. guianensis* bark (daily dose 100 mg) to placebo. A significant decrease in activity-related OA knee pain occurred in a group receiving *U. guianensis* preparation in the first week of trial. On the other hand, *U. guianensis* preparation did not reduce the pain at rest or at night. Serious side effects were not observed [62]. Clinical data were insufficiently reported for reanalysis [10]. Preclinical studies suggested that *U. tomentosa* (especially pentacyclic chemotype) could exert immunostimulatory action; therefore, patients under risk of transplanted organ rejection should be advised not to use cat's claw products [63].

Bromelain is a mixture of proteolytic enzymes obtained from the fruit and stem of pineapple (*Ananas comosus* L.) and other species of Bromeliaceae family [7]. Experimental evidence suggests that bromelain anti-inflammatory properties may be mediated by its ability to decrease levels of bradykinin and PGE_2 and to modulate cell surface adhesion molecule implicated in arthritis. Investigations in animals

confirmed that bromelain acted as an analgesic agent [69]. Anti-osteoarthritic property of orally administered bromelain (daily dose 500 mg) was compared with therapeutic activity of diclofenac (daily dose 100 mg) in a randomized single-blind active-controlled pilot study in 40 patients with mild-to-moderate knee OA. After a four-week treatment, there was no difference in symptoms relief between bromelain-treated and diclofenac-treated groups [70]. Bromelain (800 mg/day) was also compared with placebo in a randomized double-blind three-month long pilot study that included patients with moderate-to-severe OA of knee. The authors suggested that bromelain was not efficacious as an adjunctive treatment, but, due to the trial limitations, proposed that new studies should be performed [71]. Recent systematic review of clinical trials, examining dietary supplements used in the management of OA, has shown that the short-term treatment with bromelain was not effective in alleviation of pain and function improvement. Evidence quality was low [3].

Purified purple passion fruit peel extract, obtained from South American climbing vine *Passiflora edulis*, contains considerable amounts of flavonoids and anthocyanins. Its therapeutic effects (daily dose 150 mg) in patients with OA of knee were examined in a randomized double-blind placebo-controlled short-term study. The observed reduction of pain and improvement of physical function were significant and clinically meaningful. The quality of provided evidence was moderate [3, 72].

3. Herbal medicinal products for topical use in the treatment of osteoarthritis

Capsicum (*Capsici fructus*) is a dried ripe fruit of *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small-fruited varieties of *Capsicum frutescens* L. [4]. With respect to its medicinal properties, the most important compounds are capsaicinoids (capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicins I and II, caprylic acid vanillylamide, etc.). Triglycerides, carotenoids, ascorbic acid, flavonoids, and a complex mixture of volatile compounds are also present [35]. Standardized products of capsicum (semisolid or liquid dosage forms, medicated plasters) are intended for the relief of muscle (e.g., low back pain) and osteoarthritic pain. They should be used continuously until relief of pain is achieved, but not longer than 3 weeks and with a subsequent, at least two-week break period. Its use is contraindicated in cases of broken skin, wounds, eczema, and hypersensitivity to herbal substance or capsaicinoids. The plasters and semisolid dosage forms are not intended for concomitant use with other products for external administration. Topical application of capsicum HMPs initially causes skin irritation that is manifested by erythema and warmth sensation. Next stage is characterized by prolonged (hours to weeks) desensitization to pain stimuli. Side effects include skin hypersensitivity and allergic reactions [35, 73]. Capsaicin acts as an agonist of vanilloid receptors on C-type nerve fibers and thus it leads to depletion of neuropeptide substance P and consequent antinociception [7]. Standardized product containing capsicum tincture (Capsica gel®, 0.0125% of capsaicin) was investigated in a cross-over, randomized, placebo-controlled trial recruiting 99 patients with the OA of knee, within 9 weeks. Gel (2 inches) was applied topically three times per day. The conducted study provided moderate-quality evidence that the product probably did not decrease pain and improve function. Adverse events were common and included skin irritation and burning sensation [74, 75]. Creams containing higher concentration of capsaicin (0.025–0.075%) are indicated in the treatment of OA symptoms [1].

Arnica flower (*Arnicae flos*) is, whole or partially broken, dried flower-head of *Arnica montana* L. [4]. This herbal drug is employed traditionally for relief of bruises, sprains, and localized muscular pain. Semisolid and liquid dosage forms based on arnica preparations (tinctures or ethanolic liquid extract) are applied cutaneously. The use of arnica HMPs is contraindicated in patients with known hypersensitivity to arnica and other plants belonging to Asteraceae family. They should not be applied on broken skin. Reported side effects include allergic skin reactions [76]. Main constituents of arnica flower-heads are pseudoguianolide-type sesquiterpene lactones helenalin and 11α,13-dihydrohelenalin [7]. Contribution of these secondary metabolites to the anti-inflammatory effect is likely as it was shown that helenalin and 11α,13-dihydrohelenalin had the ability to interfere with the activation of transcription factor NF-κB [77]. *In vitro* experiments conducted on the pig skin indicated that sesquiterpene lactones can penetrate into it, and thus further support this assumption [78, 79]. Better permeation through stratum corneum (the outermost layer of the skin) was achieved when sesquiterpene lactones were applied in the form of arnica tinctures than as pure compounds [78]. Arnica flower preparations at low concentration/s were able to reduce levels of pro-inflammatory cytokines (IL-1 and TNF-α) in human mononuclear cells and of mRNA of matrix metalloproteinases (MMP-1 and MMP-13) in human and bovine articular chondrocytes [80, 81]. Whole plant methanolic extract suppressed expression of iNOS and COX-2 in LPS-stimulated murine macrophages [82]. Presented literature data may help to rationalize the use of arnica in management of diseases with underlying inflammation. Moderate evidence from a single, double-blind randomized controlled clinical trial showed that topical application of arnica gel (A. Vogel Arnica Gel®, 50 g herbal tincture/100 g gel, extraction solvent 50% ethanol, and DER 1:20) three times per day probably decreased pain and improved function related to hand OA as ibuprofen gel (5%), with a similar number of adverse events [74, 83].

Rosemary leaf (*Rosmarini folium*) is whole, dried leaf of *Rosmarinus officinalis* L. [4]. Its chemistry is characterized by the presence of essential oil, phenolic diterpenes (e.g., carnosol, carnosolic acid, and rosmanol), hydroxycinnamic derivatives, flavonoids, and triterpenoids [6]. Rosemary leaf bath additive is applied as an adjuvant to relieve minor muscular and articular pain, exclusively based upon long-standing traditional use [84]. Several rosemary compounds exhibited anti-inflammatory action *in vitro*. Rosmarinic acid decreased levels of PGE_2 and NO in rat chondrocytes [85]. Phenolic diterpene carnosol decreased concentrations of PGE_2 and NO, and reduced gene expression of iNOS, IL-1α, IL-6, and CCL5 in LPS-stimulated macrophages. In addition, it interfered with transcription factor NF-κB activation and influenced expression of anabolic and catabolic genes in chondrosarcoma cell line SW1353 and in primary human chondrocytes [86].

Comfrey root (*Symphyti radix*) is obtained from *Symphytum officinale* L., a traditional medicinal plant that can be found throughout Europe, parts of Asia, and as a naturalized plant in North America. It contains allantoin, mucilage polysaccharides, phenolic acids (e.g., rosmarinic acid), glycopeptides, amino acids, triterpene saponins, and pyrrolizidine alkaloids with 1,2-unsaturated necine ring structures. Identity of active principles is not sufficiently known although it is assumed that allantoin and rosmarinic acid play an important role in biological activity [87]. Taking into account considerable hepatotoxic and carcinogenic potential of pyrrolizidine alkaloids, their content in comfrey products has to be specified, as daily exposure has to be below 0.35 μg [88]. Anti-inflammatory action of comfrey preparations was demonstrated in preclinical studies when they dose-dependently inhibited complement activation and suppressed carrageenan-induced rat paw edema [87]. Moderate evidence from a double-blind, randomized, bicenter,

placebo-controlled trial with 220 participants indicated that comfrey root gel Kytta-Salbe® f probably reduced pain related to knee OA after 3 weeks of external application (6 g daily, 3 × 2 g) [74, 89]. Investigated proprietary product contained 35% of liquid extract (DER 1:2, ethanol 60% V/V, allantoin 0.2–0.5%) and <0.35 ppm of pyrrolizidine alkaloids [89].

Essential oils such as juniper oil, *Juniperi aetheroleum*; rosemary oil, *Rosmarini aetheroleum*; eucalyptus oil, *Eucalypti aetheroleum*; peppermint oil, *Menthae piperitae aetheroleum*; sweet birch oil, *Betulae lentae aetheroleum;* and wintergreen oil, *Gaultheriae aetheroleum* are employed for external treatment of articular pain and rheumatism. They are used in the form of bath additives and semisolid and liquid dosage forms. When applied to skin, essential oils act as irritants, which cause local increase of blood flow, reddening of the skin, and sensation of warmth thus antagonizing pain. Juniper oil must be avoided in the case of severe renal diseases [6, 7, 90, 91].

4. Conclusion

Osteoarthritis (OA) is a slowly developing degeneration disease affecting joint cartilage and adjacent tissues. It is one of the most prevalent diseases and most common causes of disability in the elderly, associated with worsening symptoms of joint pain, stiffness, and limitation of articular movement. Therefore, it imposes a significant functional and economic burden not only on affected patients but also on health-care systems.

Contemporary therapy protocols involve an array of non-pharmacological, pharmacological, and surgical measures. Although non-pharmacological treatments represent a basis for OA treatment, pharmacotherapy is considered to be an important adjunct. Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently a cornerstone in OA pharmacotherapy. None of the therapeutic options are curative, but the aim of treatment is to relieve the pain, improve quality of life, and reduce the loss of physical functionality.

NSAIDs often have serious adverse effects, with gastrointestinal complications as the most frequently reported. Some patients do not respond well to conventional medical therapy. Facing unsatisfactory efficacy and adverse effects of conventional therapy, they try to overcome current treatment deficiencies by using herbal medicinal products.

Preclinical studies showed that a number of herbal extracts and respective constituents exhibited pharmacological properties that could be relevant for their beneficial effect in OA. They interfered with cytokine (IL-1β, TNF-α, and IL-6), PGE_2, and NO production, modulated biosynthesis and activity of collagenases and aggrecanases, stimulated formation of extracellular matrix, and inhibited activation of transcription factor NF-κB. Active constituents are not often defined satisfactorily, but it could be said that they belong to various groups of secondary metabolites such as sesquiterpene lactones, triterpenic acids, galactolipids, diarylheptanoids, iridoid glycosides, phenolic glycosides, procyanidins, and alkaloids. Trials in humans support observations from *in vitro* and animal studies.

Unfortunately, this area is still far under-researched and needs further and better attention. Existing studies were frequently based on flawed research design, unclear and incomplete selection criteria, inadequate definition of the herbal interventions, or post hoc manipulation of data to support the authors' preferred conclusions [10]. The same authors urge on high quality and adequately powered clinical studies, advising future researchers that particular attention should be given to the detail of study design, which would ensure that participant samples are well

defined according to American College of Rheumatology (ACR) criteria and that participants are recruited without bias [10]. Furthermore, herbal preparations should be reported in detail, including dose, extraction method, and chemical characterization of active principle(s). Finally, study results should be recorded using reliable, valid outcome measures that combine pain and functional impairments in the identification of treatment response (as proposed by OMERACT-OARSI initiative) for comparing the efficacy of different medicinal plant products [10].

Herbal medicines that have been shown to be effective in the treatment of pain associated with OA could help lowering or ceasing the consumption of NSAIDs, reducing at the same time the incidence and severity of their adverse effects. This would also produce necessary long-term safety data, which are needed for most of the herbal medicinal products.

Currently available data are insufficient to acknowledge their use in OA treatment as clinically proven (i.e., with demonstrated efficacy and safety). However, it could be stated that the body of evidence is growing and that expectations on arrival of reliable, efficient, and safe herbal products, fulfilling the criteria of modern medicine in the near future, seem reasonable.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Felson DT. Osteoarthritis. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015. pp. 2226-2233

[2] Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell J, editors. Kelley and Firestein's Textbook of Rheumatology. 10th ed. Philadelphia: Elsevier; 2016

[3] Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: A systematic review and meta-analysis. British Journal of Sports Medicine. 2018;**52**(3): 167-175. DOI: 10.1136/bjsports-2016-097333

[4] European Directorate for the Quality of Medicines (EDQM). European Pharmacopoeia. 8th ed. Strasbourg: Council of Europe; 2013

[5] Committee on Herbal Medicinal Products (HMPC). Final European Union Herbal Monograph on *Salix* [Various Species Including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], cortex. European Medicines Agency; 2017. Reference number: EMA/HMPC/80630/2016

[6] European Scientific Cooperative on Phytotherapy (ESCOP). ESCOP Monographs: The Scientific Foundation for Herbal Medicinal Products. 2nd ed. Exeter, Stuttgart, New York: The European Scientific Cooperative on Phytotherapy, Georg Thieme Verlag, Thieme New York; 2003

[7] Michael H, Joanne B, Simon G, Elizabeth MW. Fundamentals of Pharmacognosy and Phytotherapy. 2nd ed. Edinburgh: Churchill Livingstone; 2012

[8] Shara M, Stohs SJ. Efficacy and safety of white willow bark (*Salix alba*) extracts. Phytotherapy Research. 2015; **29**(8):1112-1116. DOI: 10.1002/ptr.5377

[9] Awang DVC. Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals. 3rd ed. Boca Raton, FL: CRC Press; 2009

[10] Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. Cochrane Database of Systematic Reviews. 2014;**5**. DOI: 10.1002/14651858.CD002947.pub2

[11] Committee on Herbal Medicinal Products (HMPC). Final European Union Herbal Monograph on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix. European Medicines Agency; 2016. Reference number: EMA/HMPC/627057/2015

[12] Fiebich BL, Muñoz E, Rose T, Weiss G, McGregor GP. Molecular targets of the anti-inflammatory *Harpagophytum procumbens* (Devil's claw): Inhibition of TNFα and COX-2 gene expression by preventing activation of AP-1. Phytotherapy Research. 2012;**26**(6): 806-811. DOI: 10.1002/ptr.3636

[13] Schulze-Tanzil G, Hansen C, Shakibaei M. Effect of a *Harpagophytum procumbens* DC extract on matrix metalloproteinases in human chondrocytes *in vitro*. Arzneimittel-Forschung. 2004;**54**(4):213-220. DOI: 10.1055/s-0031-1296962

[14] Jang M-H, Lim S, Han S-M, Park H-J, Shin I, Kim J-W, Kim N-Y, Lee J-S, Kim K-A, Kim C-J. *Harpagophytum procumbens* suppresses lipopolysaccharide-stimulated expressions of cyclooxygenase-2 and inducible nitric oxide synthase in fibroblast cell line L929. Journal of Pharmacological Sciences. 2003;**93**(3): 367-371. DOI: 10.1254/jphs.93.367

[15] Haseeb A, Ansari MY, Haqqi TM. Harpagoside suppresses IL-6 expression

in primary human osteoarthritis chondrocytes. Journal of Orthopaedic Research. 2017;**35**(2):311-320. DOI: 10.1002/jor.23262

[16] Committee on Herbal Medicinal Products (HMPC). Final European Union Herbal Monograph on *Ribes nigrum* L., folium. European Medicines Agency; 2017. Reference number: EMA/HMPC/745353/2016

[17] Mongold JJ, Susplugas P, Taillade C, Serrano JJ. Anti-inflammatory activity of *Ribes nigrum* leaf extract in rats. Plantes médicinales et phytothérapie. 1993;**26**(2):109-116

[18] Garbacki N, Angenot L, Bassleer C, Damas J, Tits M. Effects of prodelphinidins isolated from *Ribes nigrum* on chondrocyte metabolism and COX activity. Naunyn-Schmiedeberg's Archives of Pharmacology. 2002;**365**(6):434-441. DOI: 10.1007/s00210-002-0553-y

[19] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Filipendula ulmaria* (L.) Maxim., flos - First Version. European Medicines Agency; 2011. Reference number: EMA/HMPC/434894/2010

[20] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Filipendula ulmaria* (L.) Maxim., herba - First Version. European Medicines Agency; 2011. Reference number: EMA/HMPC/434881/2010

[21] Committee on Herbal Medicinal Products (HMPC). Final Assessment Report on *Filipendula ulmaria* (L.) Maxim., herba and *Filipendula ulmaria* (L.) Maxim., flos - First Version. European Medicines Agency; 2011. Reference number: EMA/HMPC/434892/2010

[22] Olennikov DN, Kruglova MY. A new quercetin glycoside and other phenolic compounds from the genus *Filipendula*. Chemistry of Natural Compounds. 2013;**49**(4):610-616. DOI: 10.1007/s10600-013-0691-0

[23] Drummond EM, Harbourne N, Marete E, Martyn D, Jacquier J, O'Riordan D, Gibney ER. Inhibition of proinflammatory biomarkers in THP1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. Phytotherapy Research. 2013;**27**(4):588-594. DOI: 10.1002/ptr.4753

[24] Samardžić S, Arsenijević J, Božić D, Milenković M, Tešević V, Maksimović Z. Antioxidant, anti-inflammatory and gastroprotective activity of *Filipendula ulmaria* (L.) maxim. and *Filipendula vulgaris* Moench. Journal of Ethnopharmacology. 2018;**213**:132-137. DOI: 10.1016/j.jep.2017.11.013

[25] Samardžić S, Tomić M, Pecikoza U, Stepanović-Petrović R, Maksimović Z. Antihyperalgesic activity of *Filipendula ulmaria* (L.) maxim. And *Filipendula vulgaris* Moench in a rat model of inflammation. Journal of Ethnopharmacology. 2016;**193**:652-656. DOI: 10.1016/j.jep.2016.10.024

[26] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Urtica dioica* L. and *Urtica urens* L., herba. European Medicines Agency; 2008. Reference number: EMEA/HMPC/170261/2006

[27] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Urtica dioica* L.; *Urtica urens* L., folium. European Medicines Agency; 2010. Reference number: EMA/HMPC/508015/2007

[28] 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

Letters. 1999;**442**(1):89-94. DOI: 10.1016/S0014-5793(98)01622-6

[29] Schulze-Tanzil G, de Souza P, Behnke B, Klingelhoefer S, Scheid A, Shakibaei M. Effects of the antirheumatic remedy Hox alpha - a new stinging nettle leaf extract - on matrix metalloproteinases in human chondrocytes *in vitro*. Histology and Histopathology. 2002;**17**(2):477-485. DOI: 10.14670/HH-17.477

[30] 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**(9):906-910

[31] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Fraxinus excelsior* L. or *Fraxinus angustifolia* Vahl, folium. European Medicines Agency; 2012. Reference number: EMA/HMPC/239271/2011

[32] Committee on Herbal Medicinal Products (HMPC). Final Assessment Report on *Fraxinus excelsior* L. or *Fraxinus angustifolia* Vahl, folium. European Medicines Agency; 2012. Reference number: EMA/HMPC/239269/2011

[33] Li W, Wang Y, Wang X, He Z, Liu F, Zhi W, Zhang H, Niu X. Esculin attenuates endotoxin shock induced by lipopolysaccharide in mouse and NO production *in vitro* through inhibition of NF-κB activation. European Journal of Pharmacology. 2016;**791**:726-734. DOI: 10.1016/j.ejphar.2016.10.013

[34] Christiansen BA, Bhatti S, Goudarzi R, Emami S. Management of osteoarthritis with avocado/soybean unsaponifiables. Cartilage. 2015;**6**(1):30-44. DOI: 10.1177/1947603514554992

[35] European Scientific Cooperative on Phytotherapy (ESCOP). ESCOP Monographs. The Scientific Foundation for Herbal Medicinal Products. 2nd ed. Supplement 2009 ed. Exeter, Stuttgart, New York: The European Scientific Cooperative on Phytotherapy, Georg Thieme Verlag, Thieme New York; 2009

[36] Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. *Boswellia serrata*: An overall assessment of *in vitro*, preclinical, pharmacokinetic and clinical data. Clinical Pharmacokinetics. 2011;**50**(6):349-369. DOI: 10.2165/11586800-000000000-00000

[37] Huang S, Thomsson-Hulthe K, Jin C, Struglics A, Kalamajski S, Schmidt TA, Karlsson NG. Degradation of lubricin by cathepsin G: A potential mechanism for lubricin degradation in osteoarthritis patients' synovial fluid. Osteoarthritis and Cartilage. 2018;**26**:S195-S196. DOI: 10.1016/j.joca.2018.02.417

[38] Gayathri B, Manjula N, Vinaykumar KS, Lakshmi BS, Balakrishnan A. Pure compound from *Boswellia serrata* extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFα, IL-1β, NO and MAP kinases. International Immunopharmacology. 2007;**7**(4):473-482. DOI: 10.1016/j.intimp.2006.12.003

[39] Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, Dey D, Raychaudhuri SP. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin® for treatment of osteoarthritis of the knee. Arthritis Research & Therapy. 2008;**10**:R85. DOI: 10.1186/ar2461

[40] Rohdewald PJ. Review on sustained relief of osteoarthritis symptoms with a proprietary extract from pine bark, Pycnogenol. Journal of Medicinal Food. 2018;**21**(1):1-4. DOI: 10.1089/jmf.2017.0015

[41] Mülek M, Seefried L, Genest F, Högger P. Distribution of constituents and metabolites of maritime pine bark extract (Pycnogenol®) into serum, blood cells, and synovial fluid of patients with severe osteoarthritis: A randomized controlled trial. Nutrients. 2017;**9**(5):443. DOI: 10.3390/nu9050443

[42] Uhlenhut K, Högger P. Facilitated cellular uptake and suppression of inducible nitric oxide synthase by a metabolite of maritime pine bark extract (Pycnogenol). Free Radical Biology & Medicine. 2012;**53**(2):305-313. DOI: 10.1016/j.freeradbiomed.2012.04.013

[43] Jessberger S, Högger P, Genest F, Salter DM, Seefried L. Cellular pharmacodynamic effects of Pycnogenol® in patients with severe osteoarthritis: A randomized controlled pilot study. BMC Complementary and Alternative Medicine. 2017;**17**:537. DOI: 10.1186/s12906-017-2044-1

[44] Grimm T, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Ďuračková Z, Högger P. Inhibition of NF-κB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol). Journal of Inflammation. 2006;**3**:1. DOI: 10.1186/1476-9255-3-1

[45] Schäfer A, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Ďuračková Z, Högger P. Inhibition of COX-1 and COX-2 activity by plasma of human volunteers after ingestion of French maritime pine bark extract (Pycnogenol). Biomedicine & Pharmacotherapy. 2006;**60**(1):5-9. DOI: 10.1016/j.biopha.2005.08.006

[46] Canali R, Comitato R, Schonlau F, Virgili F. The anti-inflammatory pharmacology of Pycnogenol® in humans involves COX-2 and 5-LOX mRNA expression in leukocytes. International Immunopharmacology. 2009;**9**(10):1145-1149. DOI: 10.1016/j.intimp.2009.06.001

[47] Cheng BCY, Fu X-Q, Guo H, Li T, Wu Z-Z, Chan K, Yu Z-L. The genus *Rosa* and arthritis: Overview on pharmacological perspectives. Pharmacological Research. 2016;**114**: 219-234. DOI: 10.1016/j.phrs.2016.10.029

[48] Schwager J, Hoeller U, Wolfram S, Richard N. Rose hip and its constituent galactolipids confer cartilage protection by modulating cytokine, and chemokine expression. BMC Complementary and Alternative Medicine. 2011;**11**:105. DOI: 10.1186/1472-6882-11-105

[49] Chin K-Y. The spice for joint inflammation: Anti-inflammatory role of curcumin in treating osteoarthritis. Drug Design, Development and Therapy. 2016;**10**:3029-3042. DOI: 10.2147/DDDT.S117432

[50] Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. Alternative Medicine Review. 2009; **14**(2):141-153

[51] Derosa G, Maffioli P, Simental-Mendía LE, Bo S, Sahebkar A. Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Research. 2016; **111**:394-404. DOI: 10.1016/j.phrs.2016.07.004

[52] Sahebkar A, Cicero AFG, Simental-Mendía LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Research. 2016;**107**:234-242. DOI: 10.1016/j.phrs.2016.03.026

[53] Panahi Y, Alishiri GH, Parvin S, Sahebkar A. Mitigation of systemic

oxidative stress by curcuminoids in osteoarthritis: Results of a randomized controlled trial. Journal of Dietary Supplements. 2016;**13**(2):209-220. DOI: 10.3109/19390211.2015.1008611

[54] Srivastava S, Saksena AK, Khattri S, Kumar S, Dagur RS. *Curcuma longa* extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: A four-month, double-blind, randomized, placebo-controlled trial. Inflammopharmacology. 2016;**24**(6):377-388. DOI: 10.1007/s10787-016-0289-9

[55] Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragulpoontawee M, Lukkanapichonchut P, Chootip C, Saengsuwan J, Tantayakom K, Laongpech S. Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. Clinical Interventions in Aging. 2014;**9**: 451-458. DOI: 10.2147/CIA.S58535

[56] Hosseinzadeh A, Juybari KB, Fatemi MJ, Kamarul T, Bagheri A, Tekiyehmaroof N, Sharifi AM. Protective effect of ginger (*Zingiber officinale* roscoe) extract against oxidative stress and mitochondrial apoptosis induced by interleukin-1β in cultured chondrocytes. Cells, Tissues, Organs. 2017;**204**(5–6):241-250. DOI: 10.1159/000479789

[57] Kubra IR, Rao LJM. An impression on current developments in the technology, chemistry, and biological activities of ginger (*Zingiber officinale* roscoe). Critical Reviews in Food Science and Nutrition. 2012;**52**(8): 651-688. DOI: 10.1080/10408398.2010.505689

[58] Mascolo N, Jain R, Jain SC, Capasso F. Ethnopharmacologic investigation of ginger (*Zingiber officinale*). Journal of Ethnopharmacology. 1989;**27**(1):129-140. DOI: 10.1016/0378-8741(89)90085-8

[59] Ojewole JAO. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of *Zingiber officinale* (Roscoe) rhizomes (Zingiberaceae) in mice and rats. Phytotherapy Research. 2006;**20**(9): 764-772. DOI: 10.1002/ptr.1952

[60] Young H-Y, Luo Y-L, Cheng H-Y, Hsieh W-C, Liao J-C, Peng W-H. Analgesic and anti-inflammatory activities of [6]-gingerol. Journal of Ethnopharmacology. 2005;**96**(1): 207-210. DOI: 10.1016/j.jep.2004.09.009

[61] Kiuchi F, Shibuya M, Sankawa U. Inhibitors of prostaglandin biosynthesis from ginger. Chemical and Pharmaceutical Bulletin. 1982;**30**(2): 754-757. DOI: 10.1248/cpb.30.754

[62] Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJS, Sandoval M. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: Mechanisms of action of the species *Uncaria guianensis*. Inflammation Research. 2001;**50**(9):442-448. DOI: 10.1007/PL00000268

[63] Barnes J, Anderson LA, Phillipson JD. Herbal Medicines. 3rd ed. London, Grayslake: Pharmaceutical Press; 2007

[64] World Health Organization (WHO). WHO Monographs on Selected Medicinal Plants. Vol. 3. Geneva: WHO Press; 2007

[65] Sandoval-Chacón M, Thompson JH, Zhang XJ, Liu X, Mannick EE, Sadowska-Krowicka H, Charbonnet RM, Clark DA, Miller MJ. Antiinflammatory actions of cat's claw: The role of NF-kappaB. Alimentary Pharmacology & Therapeutics. 1998; **12**(12):1279-1289

[66] Aguilar JL, Rojas P, Marcelo A, Plaza A, Bauer R, Reininger E, Klaas CA, Merfort I. Anti-inflammatory activity of two different extracts of *Uncaria*

tomentosa (Rubiaceae). Journal of Ethnopharmacology. 2002;**81**(2): 271-276. DOI: 10.1016/S0378-8741(02)00093-4

[67] Aquino R, De Feo V, De Simone F, Pizza C, Cirino G. Plant metabolites. New compounds and anti-inflammatory activity of *Uncaria tomentosa*. Journal of Natural Products. 1991;**54**(2):453-459. DOI: 10.1021/np50074a016

[68] Rojas-Duran R, González-Aspajo G, Ruiz-Martel C, Bourdy G, Doroteo-Ortega VH, Alban-Castillo J, Robert G, Auberger P, Deharo E. Anti-inflammatory activity of Mitraphylline isolated from *Uncaria tomentosa* bark. Journal of Ethnopharmacology. 2012; **143**(3):801-804. DOI: 10.1016/j.jep.2012.07.015

[69] Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a treatment for osteoarthritis: A review of clinical studies. Evidence-based Complementary and Alternative Medicine. 2004;**1**(3):251-257. DOI: 10.1093/ecam/neh035

[70] Kasemsuk T, Saengpetch N, Sibmooh N, Unchern S. Improved WOMAC score following 16-week treatment with bromelain for knee osteoarthritis. Clinical Rheumatology. 2016;**35**(10):2531-2540. DOI: 10.1007/s10067-016-3363-1

[71] Brien S, Lewith G, Walker AF, Middleton R, Prescott P, Bundy R. Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: A randomized placebo-controlled pilot study. The Quarterly Journal of Medicine. 2006;**99**(12): 841-850. DOI: 10.1093/qjmed/hcl118

[72] Farid R, Rezaieyazdi Z, Mirfeizi Z, Hatef MR, Mirheidari M, Mansouri H, Esmaelli H, Bentley G, Lu Y, Foo Y, Watson RR. Oral intake of purple passion fruit peel extract reduces pain and stiffness and improves physical function in adult patients with knee osteoarthritis. Nutrition Research. 2010; **30**(9):601-606. DOI: 10.1016/j.nutres.2010.08.010

[73] Committee on Herbal Medicinal Products (HMPC). Final European Union herbal Monograph on *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small fruited varieties of *Capsicum frutescens* L., fructus. European Medicines Agency; 2015. Reference number: EMA/HMPC/674139/2013

[74] Cameron M, Chrubasik S. Topical herbal therapies for treating osteoarthritis. Cochrane Database of Systematic Reviews. 2013;**5**. DOI: 10.1002/14651858.CD010538

[75] Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. Journal of the Medical Association of Thailand. 2010;**93**(10): 1188-1195

[76] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Arnica montana* L., flos. European Medicines Agency; 2014. Reference number: EMA/HMPC/198793/2012

[77] Lyss G, Schmidt TJ, Merfort I, Pahl HL. Helenalin, an anti-inflammatory sesquiterpene lactone from Arnica, selectively inhibits transcription factor NF-kappaB. Biological Chemistry. 1997; **378**(9):951-961. DOI: 10.1515/bchm.1997.378.9.951

[78] Wagner S, Suter A, Merfort I. Skin penetration studies of Arnica preparations and of their sesquiterpene lactones. Planta Medica. 2004;**70**(10): 897-903. DOI: 10.1055/s-2004-832613

[79] Wagner S, Merfort I. Skin penetration behaviour of sesquiterpene

lactones from different Arnica preparations using a validated GC-MSD method. Journal of Pharmaceutical and Biomedical Analysis. 2007;**43**(1):32-38. DOI: 10.1016/j.jpba.2006.06.008

[80] Jäger C, Hrenn A, Zwingmann J, Suter A, Merfort I. Phytomedicines prepared from Arnica flowers inhibit the transcription factors AP-1 and NF-kappaB and modulate the activity of MMP1 and MMP13 in human and bovine chondrocytes. Planta Medica. 2009;**75**(12):1319-1325. DOI: 10.1055/s-0029-1185668

[81] Klaas CA, Wagner G, Laufer S, Sosa S, Della Loggia R, Bomme U, Pahl HL, Merfort I. Studies on the anti-inflammatory activity of phytopharmaceuticals prepared from Arnica flowers. Planta Medica. 2002; **68**(5):385-391. DOI: 10.1055/s-2002-32067

[82] Verma N, Tripathi SK, Sahu D, Das HR, Das RH. Evaluation of inhibitory activities of plant extracts on production of LPS-stimulated pro-inflammatory mediators in J774 murine macrophages. Molecular and Cellular Biochemistry. 2010;**336**(1–2):127-135. DOI: 10.1007/s11010-009-0263-6

[83] Widrig R, Suter A, Saller R, Melzer J. Choosing between NSAID and arnica for topical treatment of hand osteoarthritis in a randomised, double-blind study. Rheumatology International. 2007;**27**(6):585. DOI: 10.1007/s00296-007-0304-y

[84] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Rosmarinus officinalis* L., folium. European Medicines Agency; 2010. Reference number: EMA/HMPC/13633/2009

[85] Chen W-P, Jin G-J, Xiong Y, Hu P-F, Bao J-P, Wu L-D. Rosmarinic acid down-regulates NO and PGE_2 expression via MAPK pathway in rat chondrocytes. Journal of Cellular and Molecular Medicine. 2018;**22**(1): 346-353. DOI: 10.1111/jcmm.13322

[86] Schwager J, Richard N, Fowler A, Seifert N, Raederstorff D. Carnosol and related substances modulate chemokine and cytokine production in macrophages and chondrocytes. Molecules. 2016;**21**(4):465. DOI: 10.3390/molecules21040465

[87] Staiger C. Comfrey: A clinical overview. Phytotherapy Research. 2012; **26**(10):1441-1448. DOI: 10.1002/ptr.4612

[88] Committee on Herbal Medicinal Products (HMPC). Final European Union Herbal Monograph on *Symphytum officinale* L., radix. European Medicines Agency; 2015. Reference number: EMA/HMPC/572846/2009

[89] Grube B, Grünwald J, Krug L, Staiger C. Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: Results of a double-blind, randomised, bicenter, placebo-controlled trial. Phytomedicine. 2007;**14**(1):2-10. DOI: 10.1016/j.phymed.2006.11.006

[90] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Juniperus communis* L., aetheroleum. European Medicines Agency; 2010. Reference number: EMA/HMPC/12402/2010

[91] Committee on Herbal Medicinal Products (HMPC). Final Community Herbal Monograph on *Rosmarinus officinalis* L., aetheroleum; 2010. Reference number: EMA/HMPC/235453/2009