Potential Role of Herbal Medicine in Alleviating Pain and Inflammation in Osteoarthritis: a Review

Mahdi Mahdavī¹, Mahdi Taherian², Hossein Maghsoudi³, Reza Taherian⁴*

Abstract

Osteoarthritis (OA) is a rheumatological disorder accompanied with imbalance between anabolic and catabolic mediators that lead to the destruction of homeostasis of articular cartilage. Currently, Steroids and non-steroidal anti-inflammatory drugs are commonly used in the management of OA. Besides the various side effects of these drugs, they can just moderately alleviate symptoms of OA. Hence, to achieve safe and efficacious drugs, the research tendency toward exploration of novel sources has been grown up. Various previous researches have focused on the use of medicinal plants in the treatment of OA. This review focuses on the most efficacious medicinal plants and drugs considering related laboratory and clinical evidences. More investigations are needed to develop therapeutic agents with disease-modifying properties to treat OA.

Keywords: Osteoarthritis; Pain; Medicinal Plants; Inflammation

Introduction

Osteoarthritis (OA) is a rheumatological disorder accompanied by breakdown of joint cartilage and underlying bone (1). It is the most common degenerative joint disorder that can affect various joints including small (e.g hand) and large (e.g knee) joints (2). OA is one of the major causes of pain, disability and limited function affecting the elderly (3, 4). Pain is especially important because it leads to decreased productivity and impaired quality of life (5). Prevalence of OA is strongly age-dependent with most people older than 65 and roughly 80% of those aged over 75 showing various degrees of OA in radiographic imaging. The disease is not common in people younger than 40 (6). Other than age, there are different predisposing factors for OA including genetic factors, endocrine disorders, joint infection, anatomical and orthopedic disorders (i.e. congenital hip dislocation), muscle weakness, trauma, and previous rheumatoid arthritis (RA). Obesity can increase the mechanical pressure on joints and is a major factor in the progression of OA (7, 8). Symptoms of OA include pain, swelling, warmth and stiffness. The severity of these symptoms depends on the location of affected joints and severity of the disease. Any synovial joint can be affected by OA but the disease commonly affects large load-bearing joints such as knee and hip. Breakdown of articular cartilage is the most prominent anatomical feature of this disease (9). Inflammation of the synovium occurs in early and late stages of OA and is thought to be a key component of the disease having a significant role in the destruction of cartilage matrix.
and subsequent exacerbation of symptoms (10, 11). There is ample evidence pointing to the role of pro-inflammatory cytokines especially interleukin-1b (IL-1b) and tumor necrosis factor-α (TNF-α) in the inflammatory process seen in OA (12). These pro-inflammatory cytokines can increase the level of nitric oxide (NO) and prostaglandin E2 (PGE2), leading to the increased amount of proteolytic enzymes and subsequent cartilage breakdown (13, 14). Activation of proteolytic enzymes such as matrix metalloproteinase (MMP) promotes degradation of the cartilage causing synovitis and creates a vicious cycle leading to more joint damage (13, 15, 16). As mentioned before, pain is a major cause of decreased quality of life in patients with OA, therefore pain killers and anti-inflammatory drugs including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid drugs are widely used to alleviate OA symptoms (5, 17, 18). These drugs have many side effects; for example, acetaminophen can cause liver toxicity (19) and NSAIDs are associated with gastrointestinal (GI) side effects including GI ulcers and bleeding (20). Both conventional NSAIDs and COX-2 inhibitors can increase cardiovascular risk (21). Some studies show NSAIDs can also increase blood pressure (22). Severity and prevalence of NSAID-related gastrointestinal side effects increase with aging, limiting its use in old patients (23). Opioid drugs are believed to increase the risk of cardiovascular accidents and overall mortality. Compared with NSAIDs, opioid drugs are accompanied by a higher risk of bone fractures (24, 25); thus, it can be seen that conventional OA treatments such as NSAIDs have many side effects limiting their use especially in older patients.

Complementary or alternative medicine (CAM) is defined as “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine” (26). CAM has many types, acupuncture (27) and Pulsed electromagnetic field (28) are two examples of CAM. Herbal medicines are also considered a group of CAM. Popular and often self-prescribed, herbal medicines are used in a wide range of conditions. Conventional OA treatments, as mentioned before, can cause various and sometimes life-threatening side effects. Moreover, these treatments are not always optimally effective. Herbal medicines are usually considered food supplements thus are widely available (29). Compared to NSAIDs and corticosteroids, the side effects of such plants are low; hence, these plants can make a substantial contribution to the patients with osteoarthritis. In this review, we will focus on recent updates on herbal medicines as an alternative treatment option for OA. Herbal plants/drugs with both clinical and laboratory evidence of effectiveness in osteoarthritis are summarized in Table 1.

**Curcuma longa**

*Curcuma longa* is a plant that naturally grows in India and southeast Asia. Curcumin is a metabolite of *C. longa* that has considerable anti-inflammatory effects and is thought to be responsible for anti-inflammatory effects of *C. longa* (30). In traditional Chinese medicine, curcumin has been used for its anti-inflammatory effects (31). From molecular perspective, curcumin can decrease the level of pro-inflammatory mediators such as IL-6, IL-8, NO, PGE2, and TNF-α. In addition, it has an inhibitory effect on NF-κB activation pathway (an important pathway causing inflammation) (32-35). Furthermore, curcumin can protect joint cartilage by inhibiting the production of MMPs and thus preventing cartilage breakdown (36, 37). Moreover, it can also increase the production of glycosaminoglycan and type 2 collagen that are two important structural elements in joint cartilage, and can also decrease the apoptosis rate of chondrocytes (36, 38). *C. longa* has been used as an adjuvant therapy for OA and has been shown to have potentially beneficial effects for treatment of OA (39-41). These in vitro and in vivo results show promising anti-OA effects for *C. longa*.

**Zingiber officinale**

*Zingiber officinale* commonly known as ginger, is a plant that is native to southern Asia and India. Ginger has an anti-inflammatory effect through reducing prostaglandin and leukotriene production by inhibiting 5-lipoxygenase. It can also reduce levels of IL-8, IL-1 and TNF-α (42, 43). In some studies ginger reduced the levels of NO and PGE2 and their subsequent inflammatory effects (44, 45). Ginger can
Table 1: Herbal plants/drugs with both clinical and laboratory evidence of effectiveness in osteoarthritis

<table>
<thead>
<tr>
<th>Plant/product name</th>
<th>Family</th>
<th>Potential active constituents in osteoarthritis</th>
<th>Supporting studies</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zingiber officinale</td>
<td>Zingibaraceae</td>
<td>Curcumin, capsaicin</td>
<td>Verma et al (43), Jung et al (45), Lantz et al (46)</td>
<td>Altman et al (49), Bartels et al (50),</td>
</tr>
<tr>
<td>Harpagophytum procumbens</td>
<td>Sesame</td>
<td>Harpagoside</td>
<td>Gyurkovska et al (52)</td>
<td>Brien et al (56)</td>
</tr>
<tr>
<td>Rosmarinus officinalis</td>
<td>Lamiaceae</td>
<td>Phenolic acids</td>
<td>Nogueira de Melo et al (70), Amaral et al (71)</td>
<td>Lukaczer et al (72), Kosuwon et al (81), Mason et al (82), Laslett et al (83),</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Capsicum</td>
<td>Capsaicinoid</td>
<td>Spiller et al (79), Kim et al (80)</td>
<td>Randall et al (86), Jacquet et al (87)</td>
</tr>
<tr>
<td>Urtica dioica</td>
<td>Urticaceae</td>
<td>Flavonoid</td>
<td>Riehemann et al (84)</td>
<td></td>
</tr>
<tr>
<td>SKI 306X</td>
<td>Herbal drug</td>
<td>Comprised of Clematis mandshurica, Prunella vulgaris and Trichosanthes kirilowii</td>
<td>Choi et al (73)</td>
<td>Jung et al (74)</td>
</tr>
<tr>
<td>Phytodolor</td>
<td>Herbal drug</td>
<td>Comprised of Solidago virgaurea, Populus tremula and Fraxinus excelsior</td>
<td>Long et al (76)</td>
<td>Cameron et al (75)</td>
</tr>
</tbody>
</table>

reduce the activity of cyclooxygenase-2 (COX2) enzyme. COX2 is an enzyme responsible for the
production of many inflammatory mediators including prostaglandins thus by inhibiting this enzyme, like the drug celecoxib, ginger can decrease the level of inflammation (46). Ginger has a positive effect on pain control that is comparable to Diclofenac 100 mg in patients with OA plus it has no life-threatening side effects (47). Ginger extract has been compared to Ibuprofen and Indomethacin in patients with OA in previous studies. The results have shown Ibuprofen, Indomethacin, and ginger extract equally improve the pain score (48, 49). Ginger was shown to be superior to placebo in terms of reducing pain and disability among OA patients and with no serious side effects, it has been suggested as a complementary treatment for OA (50).

**Harpagophytum procumbens**

*Harpagophytum procumbens* also known as devil's claw is a plant native to southern parts of Africa. Harpagoside is one of the main chemical compounds of devil's claw and is responsible for a significant portion of medical and anti-inflammatory effects of this plant (51). The medical effects of this plant are from an extract obtained from its roots. Devil’s claw’s Root’s extract is thought to be able to decrease the production of inflammatory cytokines (i.e. TNF-α, IL-1β and IL-6) PGE2 and NO. Moreover, it can prevent arachidonic acid from being metabolized to prostaglandins and thromboxanes (prostaglandins and thromboxanes are molecules with inflammatory effects) thus reducing the inflammation (52-54). Devil’s claw has shown "encouraging" potential to reduce the pain of OA and daily usage of 60 mg harpagoside showed “moderately strong evidence” for being effective in the treatment of knee, hip and spine OA (55). Some RCTs and review articles also show the effectiveness of devil's claw as an anti-inflammatory and potential treatment for OA (54, 56). There are several contraindications for using devil's claw. Patients with gastric and duodenal ulcers, gallstone and cardiac disease are advised not to use this plant or its extracts (56).

**Rosa canina**

Being native to western Asia and Europe, *Rosa canina* is a wild rose species that has shown potential to be an adjuvant therapeutic choice for treating OA. Rose hip (rose hip is an accessory fruit of this plant) has been able to reduce the levels of ESR and CRP, two important inflammatory markers, in patients with OA and rheumatoid arthritis (57, 58). Studies have shown that *R. canina* extracts reduce the activity of COX-1 and COX-2 enzymes and are able to act like a reactive oxygen scavenger (reactive oxygen scavengers reduce the levels of reactive oxygen species (ROS) and oxidative stress) (59, 60). Moreover, rose hip has been able to reduce the chemotaxis of polymorphonuclear leucocytes and monocytes (61). Galactolipid is an active component of rosehip powder which its inhibitory potential has been confirmed by laboratory and in vitro studies (62). Some studies have shown that *R. canina* extract was able to reduce OA symptoms such as pain and stiffness in OA patients (63). In two double-blind, randomized, placebo-controlled clinical trials, rose hip powder ameliorated OA symptoms, pain being one of them, and reduced the usage of conventional analgesic drugs (64, 65). In another study rose hip powder was able to improve symptoms of knee OA after 3 weeks of treatment (66).

**Rosmarinus officinalis**

*Rosmarinus officinalis* commonly known as rosemary is an herb native to the Mediterranean region. Phenolic acids have substantial role in anti-inflammatory and antioxidant capacity of rosemary (67, 68). Inhibition of C3b attachment in complement system by rosemary can decrease the activation of complement system and reduce the subsequent inflammatory response caused by activation of this system (69). Rosemary can also inhibit the migration of leukocytes and thus reduce the inflammation (70). Infiltration of tissues by neutrophils is an important cause of inflammation as neutrophils can release a wide range of inflammatory mediators and harm tissues. Rosemary can inhibit tissue neutrophil infiltration it also decreases the level of inflammatory cytokines such as IL-1 and TNF-α (71). In an open-label trial, the effects of rosemary extract were investigated in patients with OA, RA and fibromyalgia. Level of hs-CRP was significantly decreased in these patients during 4 weeks of treatment. also, a reduction in inflammation and improvement of pain score were observed during the treatment but remission has not occurred in fibromyalgia scores (72). More studies are needed to confirm the positive effects of rosemary on OA patients.
SKI 306X (Clematis mandshurica, Prunella vulgaris, and Trichosanthes kirilowii)

SKI 306X is an herbal drug made of Clematis mandshurica, Prunella vulgaris, and Trichosanthes kirilowii. It can protect cartilage proteoglycan from being destroyed by inflammation. As mentioned before, IL-1 is an inflammatory cytokine that rises in patients with OA. This cytokine can mediate a sequence of reactions that lead to degradation of joint proteoglycan. SKI 306X can protect cartilage proteoglycan from being destroyed by IL-1 mediated reactions and its effects were comparable to the effects of diclofenac. When used in animal models of OA, SKI 306X decreased the infiltration of leucocytes and subsequent inflammation of synovial tissue and joint (73). When used in patients with OA, SKI 306X showed superior effects to placebo for controlling OA symptoms such as pain. Additionally, it had similar analgesic effects with daily usage of diclofenac 300 mg, this herbal medicine was well tolerated by patients and no adverse effects were observed (55, 74).

Phytodolor (Solidago virgaurea, Populus tremula, and Fraxinus excelsior)

Phytodolor is an herbal medicine comprised of three herbal plants: Solidago virgaurea, Populus tremula, and Fraxinus excelsior. Two systemic reviews evaluated the efficacy of phytodolor for treating OA. These reviews suggest pain and swelling reduction, increased joint range of motion and a reduction in consumption of NSAIDs in patients receiving Phytodolor compared to those receiving placebo (75, 76). Also in a review of 6 primary studies, positive effects were observed from phytodolor on arthritis pain (29).

Capsaicin (chili pepper)

Capsaicin is an extract of chili pepper with analgesic effects. It reduces pain by selectively modulating peripheral sensory nervous system. Capsaicin depletes substance p,a neurotransmitter responsible for pain sensation from sensory nerve terminals. When first applied to the skin, capsaicin creates a sensation of irritation and burning. These effects are thought to be caused by selective excitation of sensory c fibers. In response to this excitation, c fibers release neuropeptides, thus after repeated use of the capsaicin, these neuropeptides are depleted from c fibers. This process causes the long-lasting analgesic effect seen with the usage of capsaicin (77, 78). Moreover, capsaicin has anti-inflammatory effects. It decreases the levels of PGE2, TNF-α and IL-1b and inhibits the migration of neutrophils. Additionally, it reduces the activity of COX2 enzyme and significantly reduces the release of NO, all of these effects cause a reduction of inflammation (79, 80). Capsaicin can have positive effects on patients with OA. In a cross-over, double-blinded, randomized, controlled trial of 100 patients with mild to moderate knee OA, patients treated with 0.0125% capsaicin gel showed statistically significant improvement in pain, stiffness and joint movement compared to those treated with placebo (81). In a systemic review of six double-blinded, randomized, controlled trials, capsaicin was found to be a "useful adjuvant therapy" in many patients (82). In a study on patients with moderate pain and clinical or radiologically defined OA, topical capsaicin treatment four times daily for 20 weeks was moderately effective in reducing pain intensity regardless of site of application and dose, and was well tolerated (83).

Urtica dioica

Urtica dioica commonly known as stinging nettle is a plant native to northern America, Asia and Europe. Extracts of this plant show potent anti-inflammatory properties through inhibiting the proinflammatory transcription factor NF-κB (84). Oral administration of this plant decreases the level of CRP and can improve inflammatory conditions (85). Significant alleviation of pain and stiffness, anti-inflammatory and analgesic effects were observed in patients with OA by using topical nettle leaf in a randomized clinical trial (86). Phytalgic is a food supplement that contains fish oils, vitamin E, zinc and urtica dioica. After 3 months of treatment, phytalgic reduced the use of NSAIDs and improved pain, stiffness and function compared to placebo (87).

Glycine max/Persea americana

Glycine max commonly known as soybean is a plant native to East Asia. Persea Americana commonly known as Avocado is a fruit native to Central America. Avocado/soybean unsaponifiables (ASU) is believed to have anti-inflammatory effects. It can suppress the expression of IL-1β, TNF-α and COX-2 genes. Moreover, this mixture decreases the production of NO and PGE2 in chondrocytes and macrophages (88).
ASU also decreases pro-inflammatory cytokines and COX-2 expression through the NF-κB signaling pathway (89), phytosterols β-sitosterol, campesterol, and stigmasterol are major components of ASU 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. The identity of the active component(s) remains unknown. The primary contributors to biological activity particularly in chondrocytes are the sterol contents of ASU preparations (90). ASU increases the level of TGF-β1 and TGF-β2 these two play an important role in repairing the cartilage of joint (91). Clinically, ASU reduces joint stiffness and pain. It also improves the function of joint and decreases the usage of NSAIDs. Various randomized, double-blind, multicenter trials have investigated ASU efficacy and safety during and after treatment of patient with symptomatic knee or hip OA. Two studies conducted over a 3-month period reported that standard treatment with 300 mg/day of ASU improved indices of pain, stiffness, and physical function (92, 93). A third trial conducted over 6 months reported improved functioning similar to placebo, measured by the Lequense Functional Index, however, ASU had persistent effects after termination of treatment (94). In addition, some systematic reviews also show that ASU has superior effect compared to placebo in controlling symptoms of OA especially in patients with OA of the knee (95, 96).

**Herbal medicine, a possible option for treating OA**

Diseases affecting the musculoskeletal system are a major cause of disability worldwide, especially in elder population. OA is the most common musculoskeletal disorder that causes significant financial burden on health care systems. Elderliness and obesity are major risk factors for OA and a considerable percent of elder population have clinical or radiological signs of OA. This disease is accompanied by a number of symptoms with pain being the most important one. Joint pain caused by OA reduces the patient’s quality of life and causes remarkable morbidity for patients (97). As of present date, there is no effective treatment for curing OA. Alleviating the symptoms is the main goal of current OA treatment protocols. NSAIDs and opioids are the most common effective drugs used for treating OA. However, unfortunately these drugs are not very effective in OA patients and can only cause small or at their best, modest relief of symptoms. Moreover, advanced OA often requires joint replacement to reduce pain and disability (98). NSAIDs and opioids can cause serious and life threatening side effects specially in elder population. NSAIDs can cause ulcers in gastrointestinal system. Additionally, NSAIDs increase the risk of cardiovascular diseases and can increase the risk of blood clot formation in arteries. NSAIDs can impair the effects of aspirin’s platelet inhibition and thus increase the risk of mortality in patients using aspirin (99). Nephrotoxicity is another major side effect of NSAIDs (100). Opioids, especially after long term use, cause tolerance and physical dependence. They also impair the function of immune system and increase the risk of infections. Hormonal changes, hyperalgesia, constipation and bladder dysfunction are some of the other adverse effects of opioids (101). Because of the relatively low effects of common drugs used for treating OA and their adverse effects that can cause significant morbidity and mortality specially for elder patients, researchers are looking for safer and more effective therapies for OA. Usage of glucosamine and chondroitin sulfate is an example of these new therapies. But in a large study, it had no superior effect compared to placebo for pain and functional improvement (102). Herbal medicine is another therapeutic option that researchers around the world are trying to use as an adjuvant or complementary therapy for OA. Usage of dietary supplements and herbal remedies have become important research subjects in rheumatology and orthopaedics. Herbal medicines contain dozens of chemical substances with different effects including anti-bacterial, anti-fungal and anti-inflammatory effects (103). Herbal medicines are vastly used because of their lower price, wide availability and popular belief that they have less side effects than chemical drugs (104). Herbal remedies have been traditionally used for OA treatment. Inflammation and oxidative stress can lead to the destruction of joint cartilage and thus are important factors in the pathogenesis of OA (105). Different herbal medicines can improve the
symptoms of OA by different mechanisms of action. They can decrease oxidative stress (i.e., NO), prevent cartilage degradation by destructive metalloproteinases (e.g., MMP-3, MMP-9), reduce the levels of inflammatory cytokines such as TNF-α, IL-1α, IL-6, IL-8, and inhibit the NF-κB inflammatory pathway. Moreover, they have analgesic and anti-nociceptive effects. Although believed to be mostly harmless, herbal medicines may in fact cause several side effects. Usage of contaminated herbs, interaction with other drugs and harmful active substances in some herbs can lead to development of side effects including nephrotoxicity and potential cardiac problems (106). Between all herbal products, capsaicin is one of the new herbs recommended by many guidelines to manage pain in OA patients (107) but for other herbal drugs, including those reviewed in this article, the current evidence is sparse and therefore seems to be insufficient to reliably judge the efficacy of these therapies in OA. The data regarding several herbal remedies (e.g. Harpagophytum procumbens), however, seem to be sufficiently encouraging to warrant large-scale, definitive studies of these medicines.

Conclusion

The number of elder people is rapidly growing around the world. This growth results in an increased incidence of age-related diseases such as OA. Common drugs used to treat OA, have small to moderate effects and considerable side effects specially in older patients, leading many patients to use other treatment options. Herbal medicine is a popular treatment option for many patients. Believed to be "natural", usage of herbal medicines is growing worldwide. Although there are some evidence for positive effects of herbal medicines on OA, more reliable studies and clinical trials are needed to prove the definite alleviating role of herbal medicines and identify possible side effects.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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