Review Article

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

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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

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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 labarotory 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 prespective, curcumin can deacreas 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 labarotory evidence of effectiveness in osteoarthritis

Plant/product name	Family	Potential active constituents in osteoarthritis	Supporting studies	
			In vitor/ In vivo	Clinical
Curcuma longa	Zingibaraceae	Curcumin	Mathy-Hartert et al (32), Csaki et al (33), Yeh et al (37)	Kuptniratsaikul et al (40), Pinsornsak et al (39) Nakagawa et al (41).
Zingiber officinale	Zingibaraceae	Curcumin, capsaicin	Verma et al (43), Jung et al (45), Lantz et al (46),	Altman et al (49), Bartels et al (50),
Harpagophytum procumbens	Sesame	Harpagoside	Gyurkovska et al (52)	Brien et al (56)
Rosa canina	Rosaceae	Galactolipid	Willich et al (58), Daels-Rakotoarison et al (60), Orhan et al (61)	Marstrand et al (63), Winther et al (65), Petcharat et al (66).
Rosmarinus officinalis	Lamiaceae	Phenolic acids	Nogueira de Melo et al (70), Amaral et al (71)	Lukaczer et al (72)
Capsaicin	Capsicum	Capsaicinoid	Spiller et al (79), Kim et al (80)	Kosuwon et al (81), Mason et al (82), Laslettet et al (83)
Urtica dioica	Urticaceae	Flavonoid	Riehemann et al (84)	Randall et al (86), Jacquet et al (87)
SKI 306X	Herbal drug	Comprised of Clematis mandshurica, Prunella vulgaris and Trichosanthes kirilowii	Choi et al (73)	Jung et al (74)
Phytodolor	Herbal drug	Comprised of Solidago virgaurea ,Populus tremula and Fraxinus excelsior	Long et al (76)	Cameron et al (75)
Glycine max/Persea americana	Herbal drug	Comprised of Avocado and soybean	Au et al (88), Ownby et al (89), Altinel et al (91)	Appelboom et al (93). Maheu et al (94). Christensen et al (95).

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- ,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 neutrophilic 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, stiffnes 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, stiffnes 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 adition,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 metalloproteinase s(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.

References

1. Cooper C, Javaid MK, Arden N. Epidemiology of osteoarthritis. Atlas of osteoarthritis: Springer; 2014. p. 21-36.
2. Martel-Pelletier J, Barr AJ, Cicuttini FM, et al. Osteoarthritis. 2016;2:16072.
3. Aigner T, Rose J, Martin J, Buckwalter J. Aging theories of primary osteoarthritis: from epidemiology to molecular biology. Rejuvenation Research. 2004;7(2):134-45.
4. Brooks PM. Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications. Current opinion in rheumatology. 2002;14(5):573-7.
5. Malfait A-M, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nat Rev Rheumatol. 2013;9(11):654-64.
6. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best practice & research Clinical rheumatology. 2006;20(1):3-25.
7. Lotz MK. New developments in osteoarthritis: posttraumatic osteoarthritis: pathogenesis and pharmacological treatment options. Arthritis research & therapy. 2010;12(3):211.
8. Yusuf E, Nelissen R, Ioan-Facsinay A, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Annals of the rheumatic diseases. 2009.
9. Buckwalter JA, Mankin HJ, Grodzinsky AJ. Articular cartilage and osteoarthritis. Instructional Course Lectures-American Academy of Orthopaedic Surgeons. 2005;54:465.
10. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Therapeutic Advances in Musculoskeletal Disease. 2013;5(2):77-94.
11. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012;51(2):249-57.
12. Houard X, Goldring MB, Berenbaum F. Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. Current rheumatology reports. 2013;15(11):375.
13. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nature Reviews Rheumatology. 2010;6(11):625-35.
14. Gardner GC. Inflammatory arthritis in the era of the biologics. Clinical and Applied Immunology Reviews. 2005;5(1):19-44.
15. Huang K, Wu L. Aggrecanase and aggrecan degradation in osteoarthritis: a review. Journal of International Medical Research. 2008;36(6):1149-60.
16. Roughley P. The structure and function of cartilage proteoglycans. Eur Cell Mater. 2006;12(9).
17. Gemmell HA, Jacobson BH, Hayes BM. Effect of a topical herbal cream on osteoarthritis of the hand and knee: a pilot study. Journal of manipulative and physiological therapeutics. 2003;26(5):322.
18. Lai LH, Chan FLK. What is the optimal anti-inflammatory

therapy for patients with osteoarthritis and increased cardiovascular risk? Nat Clin Pract Gastroenterol Hepatol. 2008;5(5):240-1.
19. Jozwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. Acta poloniae pharmaceutica. 2014;71(1):11-23.
20. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Journal of the American College of Cardiology. 2008;52(18):1502-17.
21. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation. 2007;115(12):1634-42.
22. Friedewald VE, Bennett JS, Christo JP, et al. AJC Editor's consensus: Selective and nonselective nonsteroidal anti-inflammatory drugs and cardiovascular risk. The American journal of cardiology. 2010;106(6):873-84.
23. Ofman JJ, MacLean CH, Straus WL, et al. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. The Journal of rheumatology. 2002;29(4):804-12.
24. Ivers N, Dhalla IA, Allan GM. Opioids for osteoarthritis pain: benefits and risks. Canadian Family Physician. 2012;58(12):e708-e.
25. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Archives of internal medicine. 2010;170(22):1968-76.
26. Ernst E, Resch K, Mills S, et al. Complementary medicine—a definition. Br J Gen Pract. 1995;45(398):506-.
27. Selfe TK, Taylor AG. Acupuncture and Osteoarthritis of the Knee: A Review of Randomized, Controlled Trials. Family & community health. 2008;31(3):247-54.
28. Iannitti T, Fistetto G, Esposito A, Rottigni V, Palmieri B. Pulsed electromagnetic field therapy for management of osteoarthritis-related pain, stiffness and physical function: clinical experience in the elderly. Clinical Interventions in Aging. 2013;8:1289-93.
29. Ernst E. Herbal medicine in the treatment of rheumatic diseases. Rheumatic diseases clinics of North America. 2011;37(1):95-102.
30. 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).
31. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. Biochemical pharmacology. 2008;75(4):787-809.
32. Mathy-Hartert M, Jacquemond-Collet I, Priem F, Sanchez C, Lambert C, Henrotin Y. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. Inflamm Res. 2009;58(12):899-908.
33. Csaki C, Mobasheri A, Shakibaei M. Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1beta-induced NF-kappaB-mediated inflammation and apoptosis. Arthritis Res Ther. 2009;11(6):R165.
34. Aggarwal BB, Gupta SC, Sung B. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. British journal of pharmacology. 2013;169(8):1672-92.
35. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. The international journal of biochemistry & cell biology. 2009;41(1):40-59.
36. Henrotin Y, Clutterbuck AL, Allaway D, et al. Biological actions of curcumin on articular chondrocytes. Osteoarthritis and cartilage. 2010;18(2):141-9.
37. Yeh CC, Su YH, Lin YJ, et al. Evaluation of the protective effects of curcuminoid (curcumin and bisdemethoxycurcumin)-loaded liposomes against bone turnover in a cell-based model of osteoarthritis. Drug Des Devel Ther. 2015;9:2285-300.
38. Buhrmann C, Mobasheri A, Matis U, Shakibaei M. Curcumin mediated suppression of nuclear factor-kappaB promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment. Arthritis Res Ther. 2010;12(4):R127.
39. Pinsornsak P, Niempoog S. The efficacy of Curcuma Longa L. extract as an adjuvant therapy in primary knee osteoarthritis: a randomized control trial. J Med Assoc Thai. 2012;95 Suppl 1:S51-8.
40. Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. J Altern Complement Med. 2009;15(8):891-7.
41. Nakagawa Y, Mukai S, Yamada S, et al. Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. J Orthop Sci. 2014;19(6):933-9.
42. Tjendraputra E, Tran VH, Liu-Brennan D, Roufogalis BD, Duke CC. Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. Bioorganic chemistry. 2001;29(3):156-63.
43. Verma SK, Singh M, Jain P, Bordia A. Protective effect of ginger, Zingiber officinale Rosc on experimental atherosclerosis in rabbits. Indian journal of experimental biology. 2004;42(7):736-8.
44. Pan MH, Hsieh MC, Kuo JM, et al. 6-Shogaol induces apoptosis in human colorectal carcinoma cells via ROS production, caspase activation, and GADD 153 expression. Molecular nutrition & food research. 2008;52(5):527-37.
45. Jung HW, Yoon CH, Park KM, Han HS, Park YK. Hexane fraction of Zingiberis Rhizoma Crudus extract inhibits the production of nitric oxide and proinflammatory cytokines in LPS-stimulated BV2 microglial cells via the NF-kappaB pathway. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2009;47(6):1190-7.
46. Lantz RC, Chen GJ, Sarihan M, Solyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2007;14(2-3):123-8.
47. Drozdov VN, Kim VA, Tkachenko EV, Varvanina GG. Influence of a specific ginger combination on gastropathy conditions in patients with osteoarthritis of the knee or hip. The Journal of Alternative and Complementary Medicine. 2012;18(6):583-8.
48. Haghighi A, Tavalaei N, Owlia MB. Effects of ginger on primary knee osteoarthritis. Indian Journal of Rheumatology. 2006;1(1):3-7.
49. Altman RD, Marcussen K. Effects of a ginger extract on knee

pain in patients with osteoarthritis. Arthritis & Rheumatology. 2001;44(11):2531-8.
50. Bartels EM, Folmer VN, Bliddal H, et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis and cartilage. 2015;23(1):13-21.
51. Huang TH-W, Tran VH, Duke RK, et al. Harpagoside suppresses lipopolysaccharide-induced iNOS and COX-2 expression through inhibition of NF-κB activation. Journal of ethnopharmacology. 2006;104(1):149-55.
52. Gyurkovska V, Alipieva K, Maciuk A, et al. Anti-inflammatory activity of Devil's claw in vitro systems and their active constituents. Food Chemistry. 2011;125(1):171-8.
53. Loew D, Möllerfeld J, Schrödter A, Puttkammer S, Kaszkin M. Investigations on the pharmacokinetic properties of Harpagophytum extracts and their effects on eicosanoid biosynthesis in vitro and ex vivo. Clinical Pharmacology & Therapeutics. 2001;69(5):356-64.
54. McGregor G, Fiebich B, Wartenberg A, Brien S, Lewith G, Wegener T. Devil's claw (Harpagophytum procumbens): an anti-inflammatory herb with therapeutic potential. Phytochemistry Reviews. 2005;4(1):47-53.
55. Ernst E. Complementary or alternative therapies for osteoarthritis. Nat Clin Pract Rheum. 2006;2(2):74-80.
56. Brien S, Lewith GT, McGregor G. Devil's Claw (Harpagophytum procumbens) as a treatment for osteoarthritis: a review of efficacy and safety. Journal of alternative and complementary medicine (New York, NY). 2006;12(10):981-93.
57. Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital (stand. powder of a subspecies of Rosa canina fruits), reduces pain and improves general wellbeing in patients with osteoarthritis—a double-blind, placebo-controlled, randomised trial. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2004;11(5):383-91.
58. Willich S, Rossnagel K, Roll S, et al. Rose hip herbal remedy in patients with rheumatoid arthritis–a randomised controlled trial. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2010;17(2):87-93.
59. Jäger AK, Eldeen IM, van Staden J. COX- 1 and- 2 activity of rose hip. Phytotherapy Research. 2007;21(12):1251-2.
60. Daels- Rakotoarison D, Gressier B, Trotin F, et al. Effects of Rosa canina fruit extract on neutrophil respiratory burst. Phytotherapy research. 2002;16(2):157-61.
61. Orhan DD, Hartevioğlu A, Küpeli E, Yesilada E. In vivo anti-inflammatory and antinociceptive activity of the crude extract and fractions from Rosa canina L. fruits. Journal of ethnopharmacology. 2007;112(2):394-400.
62. Schwager J, Richard N, Wolfram S. 145 Anti-inflammatory and chondro-protecitve effects of rose hip powder and its constituent galactolipids gopo. Osteoarthritis and cartilage. 2008;16:S76.
63. Marstrand C, Warholm L, Kharazmi A, Winther K. The anti-inflammatory capacity of Rose-hip is strongly dependent on the seeds-a comparison of animal and human studies. Osteoarthritis and cartilage. 2013;21:S216-S7.
64. Warholm O, Skaar S, Hedman E, Molmen HM, Eik L. The Effects of a Standardized Herbal Remedy Made from a Subtype of Rosa canina in Patients with Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Current therapeutic research, clinical and experimental. 2003;64(1):21-31.
65. Winther K, Apel K, Thamsborg G. A powder made from seeds and shells of a rose-hip subspecies (Rosa canina) reduces symptoms of knee and hip osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial. Scandinavian journal of rheumatology. 2005;34(4):302-8.
66. Petcharat A, Wongsuphasawat K. The efficacy of a standardized Rose-hip powder containing seeds and shells compared with glucosamine sulfate in patients with osteoarthritis of the knee-a blinded, parallel, randomized study. Osteoarthritis and cartilage. 2013;21:S216.
67. Peng CH, Su JD, Chyau CC, et al. Supercritical fluid extracts of rosemary leaves exhibit potent anti-inflammation and anti-tumor effects. Bioscience, biotechnology, and biochemistry. 2007;71(9):2223-32.
68. Moreno S, Scheyer T, Romano CS, Vojnov AA. Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. Free radical research. 2006;40(2):223-31.
69. Sahu A, Rawal N, Pangburn MK. Inhibition of complement by covalent attachment of rosmarinic acid to activated C3b. Biochemical pharmacology. 1999;57(12):1439-46.
70. Nogueira de Melo GA, Grespan R, Fonseca JP, et al. Rosmarinus officinalis L. essential oil inhibits in vivo and in vitro leukocyte migration. Journal of medicinal food. 2011;14(9):944-6.
71. Amaral GP, de Carvalho NR, Barcelos RP, et al. Protective action of ethanolic extract of Rosmarinus officinalis L. in gastric ulcer prevention induced by ethanol in rats. Food and Chemical Toxicology. 2013;55:48-55.
72. Lukaczer D, Darland G, Tripp M, et al. A pilot trial evaluating Meta050, a proprietary combination of reduced iso-alpha acids, rosemary extract and oleanolic acid in patients with arthritis and fibromyalgia. Phytotherapy research : PTR. 2005;19(10):864-9.
73. Choi JH, Choi JH, Kim DY, et al. Effects of SKI 306X, a new herbal agent, on proteoglycan degradation in cartilage explant culture and collagenase-induced rabbit osteoarthritis model. Osteoarthritis and cartilage. 2002;10(6):471-8.
74. Jung YB, Roh KJ, Jung JA, et al. Effect of SKI 306X, a new herbal anti-arthritic agent, in patients with osteoarthritis of the knee: a double-blind placebo controlled study. Am J Chin Med. 2001;29(3-4):485-91.
75. Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. The Cochrane database of systematic reviews. 2014;5:CD002947-CD.
76. Long L, Soeken K, Ernst E. Herbal medicines for the treatment of osteoarthritis: a systematic review. Rheumatology. 2001;40(7):779-93.
77. Rains C, Bryson HM. Topical Capsaicin. Drugs & Aging. 1995;7(4):317-28.
78. National Center for Biotechnology Information. PubChem Compound Database; CID=1548943 hpnnngcaO, 2017). capsaicin. pubmed. 2017.
79. Spiller F, Alves MK, Vieira SM, et al. Anti-inflammatory effects of red pepper (Capsicum baccatum) on carrageenan- and antigen-induced inflammation. The Journal of pharmacy and pharmacology. 2008;60(4):473-8.
80. Kim CS, Kawada T, Kim BS, et al. Capsaicin exhibits anti-inflammatory property by inhibiting IkB-a degradation in LPS-

stimulated peritoneal macrophages. Cell Signal. 2003;15(3):299-306.
81. 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 = Chotmaihet thangphaet. 2010;93(10):1188-95.
82. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ : British Medical Journal. 2004;328(7446):991-.
83. Laslett LL, Jones G. Capsaicin for osteoarthritis pain. Progress in drug research Fortschritte der Arzneimittelforschung Progres des recherches pharmaceutiques. 2014;68:277-91.
84. 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.
85. Chrubasik S, Enderlein W, Bauer R, Grabner W. Evidence for antirheumatic effectiveness of Herba Urticae dioicae in acute arthritis: a pilot study. Phytomedicine : international journal of phytotherapy and phytopharmacology. 1997;4(2):105-8.
86. Randall C, Randall H, Dobbs F, Hutton C, Sanders H. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. Journal of the Royal Society of Medicine. 2000;93(6):305-9.
87. Jacquet A, Girodet PO, Pariente A, Forest K, Mallet L, Moore N. Phytalgic, a food supplement, vs placebo in patients with osteoarthritis of the knee or hip: a randomised double-blind placebo-controlled clinical trial. Arthritis Res Ther. 2009;11(6):R192.
88. Au RY, Al-Talib TK, Au AY, Phan PV, Frondoza CG. Avocado soybean unsaponifiables (ASU) suppress TNF-alpha, IL-1beta, COX-2, iNOS gene expression, and prostaglandin E2 and nitric oxide production in articular chondrocytes and monocyte/macrophages. Osteoarthritis Cartilage. 2007;15(11):1249-55.
89. Ownby SL, Fortuno LV, Au AY, Grzanna MW, Rashmir-Raven AM, Frondoza CG. Expression of pro-inflammatory mediators is inhibited by an avocado/soybean unsaponifiables and epigallocatechin gallate combination. Journal of Inflammation. 2014;11(1):8.
90. Lippiello L, Nardo JV, Harlan R, Chiou T. Metabolic effects of avocado/soy unsaponifiables on articular chondrocytes. Evid Based Complement Alternat Med. 2008;5(2):191-7.
91. Altinel L, Saritas ZK, Kose KC, Pamuk K, Aksoy Y, Serteser M. Treatment with unsaponifiable extracts of avocado and soybean increases TGF-beta1 and TGF-beta2 levels in canine joint fluid. The Tohoku journal of experimental medicine. 2007;211(2):181-6.
92. Blotman F, Maheu E, Wulwik A, Caspard H, Lopez A. Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A prospective, multicenter, three-month, randomized, double-blind, placebo-controlled trial. Revue du rhumatisme (English ed). 1997;64(12):825-34.
93. Appelboom T, Schuermans J, Verbruggen G, Henrotin Y, Reginster JY. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective, placebo-controlled study. Scandinavian journal of rheumatology. 2001;30(4):242-7.
94. Maheu E, Mazieres B, Valat JP, et al. Symptomatic efficacy of avocado/soybean unsaponifiables in the treatment of osteoarthritis of the knee and hip: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial with a six-month treatment period and a two-month followup demonstrating a persistent effect. Arthritis Rheum. 1998;41(1):81-91.
95. Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. Osteoarthritis and cartilage. 2008;16(4):399-408.
96. Ernst E. Avocado-soybean unsaponifiables (ASU) for osteoarthritis - a systematic review. Clin Rheumatol. 2003;22(4-5):285-8.
97. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The lancet. 2012;380(9859):2197-223.
98. Hawker GA, Wright JG, Coyte PC, et al. Differences between men and women in the rate of use of hip and knee arthroplasty. New England Journal of Medicine. 2000;342(14):1016-22.
99. Ong CKS, Lirk P, Tan CH, Seymour RA. An Evidence-Based Update on Nonsteroidal Anti-Inflammatory Drugs. Clinical Medicine and Research. 2007;5(1):19-34.
100. Ejaz P, Bhojani K, Joshi VR. NSAIDs and kidney. The Journal of the Association of Physicians of India. 2004;52:632-40.
101. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain physician. 2008;11(2 Suppl):S105-20.
102. Wood AM, Brock TM, Heil K, Holmes R, Weusten A. A review on the management of hip and knee osteoarthritis. International journal of chronic diseases. 2013;2013.
103. Wang X, Zhang A, Zhou X, et al. An integrated chinmedomics strategy for discovery of effective constituents from traditional herbal medicine. 2016;6:18997.
104. Farzaei MH, Khanavi M, Moghaddam G, et al. Standardization of Tragopogon graminifolius DC. extract based on phenolic compounds and antioxidant activity. Journal of Chemistry. 2014;2014.
105. Marchev AS, Dimitrova PA, Burns AJ, Kostov RV, Dinkova-Kostova AT, Georgiev MI. Oxidative stress and chronic inflammation in osteoarthritis: can NRF2 counteract these partners in crime? Annals of the New York Academy of Sciences. 2017;1401(1):114-35.
106. Bent S. Herbal Medicine in the United States: Review of Efficacy, Safety, and Regulation: Grand Rounds at University of California, San Francisco Medical Center. Journal of General Internal Medicine. 2008;23(6):854-9.
107. Mushtaq S, Choudhary R, Scanzello CR. Non-surgical treatment of osteoarthritis-related pain in the elderly. Current Reviews in Musculoskeletal Medicine. 2011;4(3):113-22.