The Use of Glucosamine, Devil's Claw (*Harpagophytum procumbens*), and Acupuncture as Complementary and Alternative Treatments for Osteoarthritis

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Abstract
Osteoarthritis is one of the most common chronic inflammatory conditions seen in the general population. Current pharmacological treatments focus on reduction of pain and increased mobility to improve overall quality of life. However, the relief afforded by current standard care is often insufficient and can be associated with significant side effects. Many patients, therefore, seek the option of non-standard therapies, such as nutritional and herbal supplements, acupuncture, and exercise regimens. Glucosamine, *Harpagophytum procumbens*, and acupuncture are among the most commonly used complementary and alternative medicine approaches utilized by patients suffering from osteoarthritis. Their clinical relevance, safety, and potential mechanisms of action are discussed in this review.
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Introduction

This review evaluates the use of three complementary and alternative medicine (CAM) approaches commonly used in the treatment of osteoarthritis (OA) – glucosamine, *Harpagophytum procumbens*, Pedaliaceae (commonly known as devil's claw), and acupuncture. It outlines the pathophysiology of OA and its standard recommended pharmacological and non-pharmacological management, discusses the pharmacology of glucosamine and *H. procumbens*, and evaluates the evidence on the efficacy and safety of these three CAM treatments compared to standard therapy. Based on these evaluations, the question of whether these CAM treatments should be recommended is discussed.

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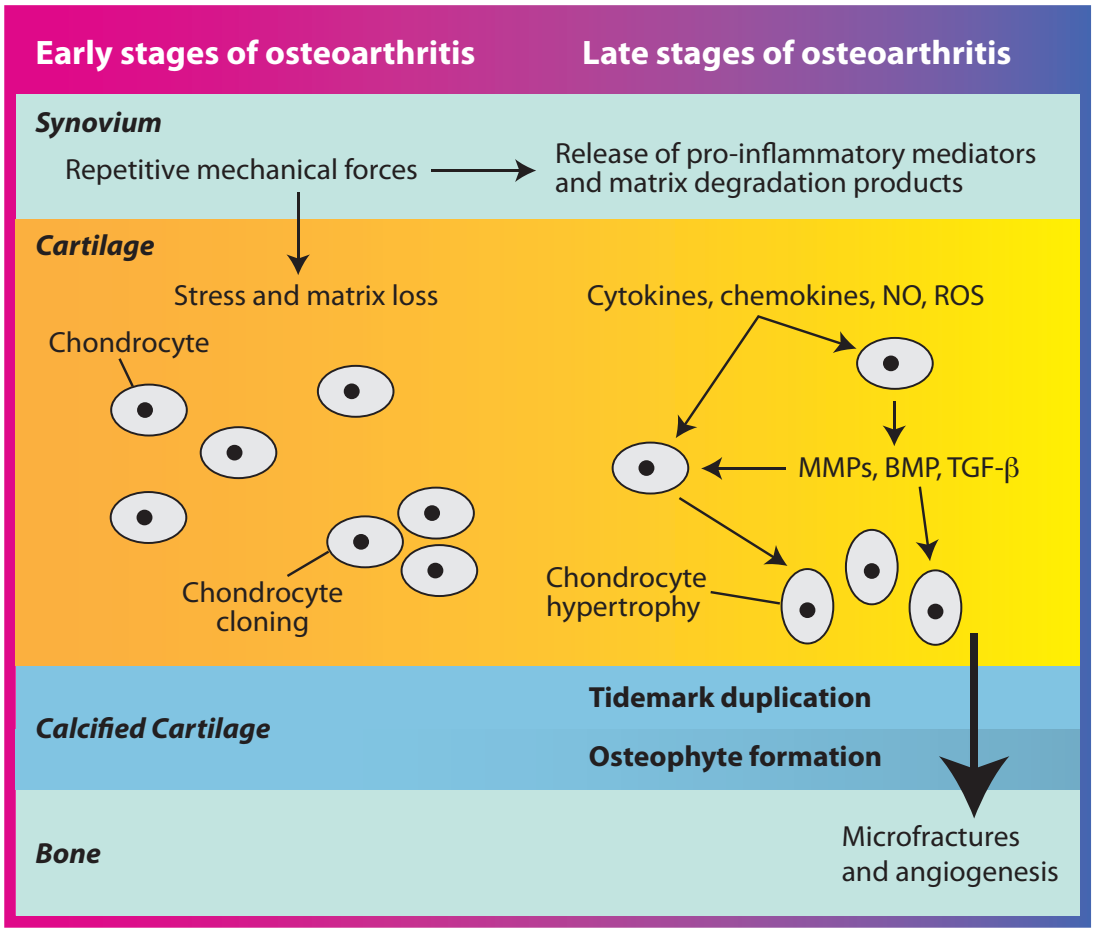
Pathophysiology of Osteoarthritis

OA is one of the most common forms of arthritis.[1] It commonly develops after age 45, although it can occur in younger people. OA is characterized by the breakdown and eventual loss of cartilage in one or more joints. Cartilage is a protein produced by chondrocytes that serves as a "cushion" between the bones of the joints. The joints are wrapped inside a tough capsule that is filled with synovial fluid. This fluid lubricates the joint and keeps it moving smoothly. In OA, the cartilage becomes brittle and degrades.[2] Pieces of cartilage may even break away and float around inside the synovial fluid, which can lead to inflammation (Figure 1). Eventually, the cartilage can break down to the point that it no longer cushions the two bones at the joint. The catabolism of proteins is due to an increase in proteases under the influence of cytokines.[3-5]

The symptoms of OA most commonly involve pain in the affected joint(s). Joint pain is usually worse later in the day and can be associated with swelling, warmth, stiffness, weakness of the muscles around affected joints, reduced mobility, and creaking of the joint;[6] stiffness can also occur after long periods of inactivity. OA usually affects the hands, spine, hips, and knees. Common risk factors for development of OA are family history (genetic predisposition), previous joint injury, and being overweight. Obesity can also exacerbate existing OA, particularly in the knees.[7,8]

Keywords: CAM, arthritis, osteoarthritis, Harpagophytum, devil's claw, glucosamine, acupuncture, joint disease, DJD, OA

Figure 1. Pathophysiology of Osteoarthritis



Pharmacological and Non-pharmacological Treatment

OA follows a slow progressive course for most patients. According to the Osteoarthritis Research Society International (OARSI) Treatment Guidelines Committee, there is no known cure for OA; treatment should be based on management of the symptoms with a focus on reducing pain.[9] Standard therapy is based on a combination of pharmacological (e.g., acetaminophen, non-steroidal anti-inflammatory drugs {NSAIDs}, glucosamine, etc.) and non-pharmacological methods (e.g., self-management and education about exercise, diet, appropriate footwear, etc.).[9]

Acetaminophen (paracetamol, an aniline analgesic) is generally the first-line pharmacological treatment recommendation. The recommended dose is 0.5-1 g orally, every 4-6 hours as necessary, up to a maximum daily dose of 4 g/day.[9,10] While acetaminophen produces a statistically significant reduction in pain, the absolute pain reduction is small and might be of limited clinical significance.[9] A recent systematic review suggests that acetaminophen is modestly less effective than NSAIDs for OA and that the clinical significance of acetaminophen is questionable because, in the short term, it results in only a five-percent greater improvement from baseline in pain reduction compared to placebo treatment.[10] Acetaminophen appears to have a better gastrointestinal and cardiovascular toxicity profile than NSAIDs; however, it is not devoid of risk, with concerns including hepatotoxicity and kidney damage.[9,10]

Treatment guidelines suggest that NSAIDs should be used with or without concurrent acetaminophen if symptom relief is not sufficient with acetaminophen alone.[9,11] Dose of NSAIDs should be as low as possible to achieve effective results

and long-term use should be avoided if possible.[9] NSAIDs may be only slightly better than placebo in providing short-term pain relief.[9] Furthermore, many NSAIDs are associated with considerable side effects. Gastrointestinal bleeding, the most clinically substantial NSAID side effect, causes approximately 16,500 and 2,200 deaths, and 107,000 and 12,000 hospital admissions in the United States and United Kingdom, respectively, and is of particular concern in older patients.[12,13]

Single intra-articular (IA) corticosteroid injections can also provide rapid relief for up to four weeks.[14] Injections are particularly useful for patients who have an important event to participate in or who need to travel. Patients should be encouraged to rest for at least 24 hours after the injection. Repeated injections appear to be less successful.

Intra-articular hyaluronic acid injections can also be given weekly for 3-5 weeks, depending on the preparation.[15] Hyaluronic acid has been shown to provide slower onset but more prolonged (up to 12 weeks) relief of symptoms than corticosteroids.[16,17]

OARSI pharmacological intervention recommendations also include three additional pharmacological interventions.

- Topical use of NSAIDs and capsaicin as adjuncts or alternatives to oral analgesic/anti-inflammatory agents in knee OA
- Treatment with glucosamine and/or chondroitin sulfate in patients with knee or hip OA
- The use of weak opioids and narcotic analgesics for the treatment of refractory pain in patients with hip or knee OA, when other pharmacological agents have been ineffective or are contraindicated

OARSI treatment guidelines emphasize that optimal management of OA requires a combination of both pharmacological and non-pharmacological modalities. Self-management, education, and information about OA and its treatment are a core part of non-pharmacological treatment recommendations. OARSI treatment guidelines recommend 11 non-pharmacological treatments for OA (see side bar).[9]

OARSI treatment guidelines recommend the use of several CAM interventions, including glucosamine and acupuncture.[9] *Harpagophytum procumbens* is also a CAM intervention that can be considered as adjunct therapy. The remainder of this review will focus on these three CAM interventions for OA.

OARSI Non-pharmacological Treatment Recommendations[9]

All patients with hip and knee OA should be given information access and education about treatment objectives and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.

The clinical status of patients with hip or knee OA can be improved if patients are contacted regularly by phone.

Patients with symptomatic hip and knee OA may benefit from referral to a physical therapist for evaluation and instruction in appropriate exercises to reduce pain and improve functional capacity. This evaluation may result in provision of assistive devices such as canes and walkers, as appropriate.

Patients with hip and knee OA should be encouraged to undertake continuous regular aerobic, muscle strengthening, and range of motion exercises. For patients with symptomatic hip OA, exercises in water can be effective.

Overweight patients with hip and knee OA should be encouraged to lose weight and maintain the weight loss.

Walking aids can reduce pain in patients with hip and knee OA. Patients should be given instruction in the optimal use of a cane or crutch in the contralateral hand. Frames or wheeled walkers are often preferable for those with bilateral disease.

In patients with knee OA and mild/moderate varus or valgus instability, a knee brace can reduce pain, improve stability, and diminish the risk of falling.

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OARSI Non-pharmacological Treatment Recommendations[9] *– Continued*

Every patient with hip or knee OA should receive advice concerning appropriate footwear. In patients with knee OA, insoles can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.

Some thermal modalities may be effective for relieving symptoms in hip and knee OA.

Transcutaneous electrical nerve stimulation (TENS) can help with short-term pain control in some patients with hip or knee OA.

Acupuncture may be of symptomatic benefit in patients with knee OA.

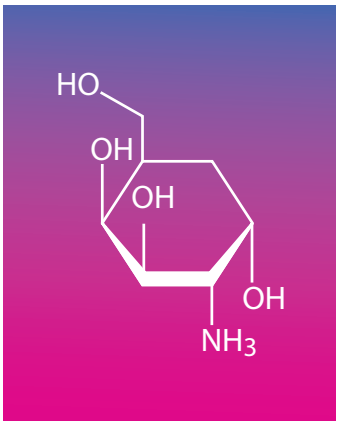
Glucosamine

Description and Pharmacology

Glucosamine is a naturally occurring amino-monosaccharide (Figure 2), a constituent of the glycosaminoglycan chains in aggrecan and other proteoglycans found in the synovial fluid and articular cartilage of joints.[18] Aggrecan and other proteoglycans trap water in the matrix of cartilage, providing it with the deformable resilience that is necessary for function. In the early phases of OA, there is an increase in the production of structural molecules such as aggrecan and collagen, but this appears to be overcome by an increase in catabolism by proteases under the influence of cytokines.[19] *In vitro* experiments of chondrocyte cultures show an increase in aggrecan synthesis with the addition of glucosamine, suggesting that glucosamine plays a critical role in increasing synovial fluid availability and maintaining joint lubrication.[20-22] Pharmacokinetic studies suggest that glucosamine is generally a substrate for the synthesis of mucopolysaccharides and proteoglycans rather than a source of energy. Hence, there is a latency of 4-8 weeks before the therapeutic effect emerges.[23,24]

A recent proteomic analysis revealed that glucosamine modulates 18 proteins in chondrocyte cultures. An increase in protein expression was noted for peroxiredoxin-1, heat-shock protein beta-1, and collagen alpha-1 (IV) chain precursor; whereas, both mitochondrial superoxide dismutase and cytoplasmic action showed decreased protein expression. In general, glucosamine influences signal transduction and protein-folding processes positively, while decreasing both metabolism and redox processes.[25]

Figure 2. Glucosamine Structure



Efficacy and Safety

Studies of glucosamine for OA have yielded mixed results. A variety of meta-analyses have been conducted on glucosamine. Some have shown that glucosamine may provide better pain relief and improve function compared to placebo, while others have not reported benefit.[26-33] A possible explanation for the mixed findings is a study reporting that glucosamine sulfate consistently produced better symptomatic benefits compared to glucosamine hydrochloride,[28] which suggests that the form of glucosamine being used might possibly influence results. Several studies involving either acetaminophen or NSAIDs as the comparator have shown that glucosamine sulfate was at least equal to, and in some studies superior to, NSAIDs in providing symptomatic pain relief.[34-36] Regarding safety, the majority of studies and meta-analyses concluded that the use of glucosamine preparations in OA is linked to only minor and transient side effects.[31,33,37-41] The above information is reviewed in more detail below.

A meta-analysis conducted in 2000 found weak evidence that glucosamine is more efficacious than placebo in reducing pain or disability from OA.[26] Many of the studies included in this meta-analysis were conducted for intermediate durations (at least four weeks of intervention) and involved an adequate number of patients (total of 1,710 patients from 15 clinical trials). Reviews/meta-analyses conducted in 2005 and 2006 did not completely agree on the efficacy of glucosamine.[28,29] A combined narrative analysis summarizing findings from previous meta-analyses concluded that current evidence was inconclusive and therefore did not support recommending glucosamine preparations for the treatment of OA.[29]

In contrast to these findings, a 2005 Cochrane meta-analysis that included 25 randomized clinical trials (RCT) reported that glucosamine preparations showed a 22-percent improvement in pain and 11-percent improvement in function compared to baseline measurements.[28]

Several meta-analyses conducted in 2008 concluded that, although several studies indicate glucosamine has little benefit in providing pain relief for OA, over 40 studies indicate that glucosamine *is* effective in providing relief of pain and improvement of joint health among sufferers of OA.[31,32]

Glucosamine is often combined with chondroitin in dietary supplements. The rationale is that both molecules act as a structural building block for proteoglycans and other macromolecules that are part of the cartilage matrix.[42] Based on prior controversial clinical trial data, a 2008 National Institutes of Health (NIH)-funded Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) study was conducted that involved 1,583 patients with OA. This study concluded that glucosamine sulfate, in combination with chondroitin, is effective in treating moderate-to-severe knee pain at a recommended dose of 500 mg glucosamine sulfate three times daily. The researchers also concluded that one should allow 6-8 weeks for initial effects and six months for full benefits to be achieved.[43]

A 2008 article reviewed 20 randomized controlled trials on efficacy and safety of glucosamine in sufferers of OA, involving more than 2,500 patients.[33] Although the results were inconsistent, the findings were mostly positive for a benefit in reducing OA pain and disease progression as indicated by reduced joint-space narrowing.

Another recent (2010) network meta-analysis included 10 clinical trials comparing glucosamine sulfate and glucosamine hydrochloride, as well as chondroitin sulfate, and their combinations, with placebo. The research concluded that the overall effect on reduction of pain intensity was not clinically significant as evaluated by a visual analog scale, but that these interventions do have an impact on joint space narrowing.[30] One weakness of this study was that it did not include trials that directly compared glucosamine to the effectiveness of NSAIDs.

Studies conducted in 2001 and 2010 compared the efficacy of glucosamine sulfate to NSAIDs such as celecoxib and ibuprofen.[35,36] Both studies concluded that the degree of pain relief from glucosamine sulfate was similar to NSAIDs. Although it was found that pain scores decreased faster during the first two weeks of the study in the ibuprofen group than the glucosamine group, the benefit of ibuprofen reached a plateau after two weeks, while the glucosamine group continued to improve. By week 8 of the study, the pain scores were not significantly different between the ibuprofen and glucosamine sulfate groups compared to placebo.[36]

A 2007 study compared the efficacy of glucosamine or acetaminophen against placebo over a six-month period in 318 patients with knee OA.[34] Pain reduction was reported in 39.6 percent of subjects on glucosamine, 33.3 percent taking acetaminophen, and 21.1 percent on placebo. Glucosamine was slightly more effective in providing pain relief than acetaminophen in this trial. The study also concluded that a 1.5-g once daily dose of glucosamine sulfate was more effective than a 500-mg three times daily dose of glucosamine hydrochloride. The authors hypothesized the difference may be due to the formulation difference rather than the difference in dosing schedule.[34]

As mentioned previously, a factor that may be contributing to the mixed findings with glucosamine is the form used. A review of glucosamine noted that most of the non-significant findings resulted from clinical trials using glucosamine hydrochloride; whereas, most positive trials were performed with a glucosamine sulfate (first sold as the patented Rotta® brand) preparation.[44] For example, a study conducted in 2000, involving 98 patients given a 500-mg dose of glucosamine hydrochloride three times daily or placebo for two months, concluded that glucosamine was no better than placebo in reducing knee OA pain.[45] In a 2005 Cochrane meta-analysis of 25 RCTs, pain reduction was found for the Rotta brand of glucosamine sulfate. No statistical significance compared to

placebo was found for the non-Rotta glucosamine hydrochloride form.[28] An additional significant finding in the 2005 and 2006 reviews was that glucosamine sulfate (Rotta brand) was able to slow radiological progression of OA over a three-year period and that there were no more adverse reactions than placebo during the trial. No studies have compared the Rotta brand with other glucosamine sulfate preparations.

Figure 3. Photograph of *H. procumbens*

Poor results reported in some studies may also be due to short duration (two months or less) and the fact that there is a latency period of 4-8 weeks before therapeutic benefits are seen, as has been established by evidence-based best practice guidelines.[28,29]

A 2008 review of 20 clinical trials reported no significant side effects from the use of glucosamine.[33] This is consistent with other evidence indicating that the long-term use of glucosamine is associated with only minor and infrequent adverse effects – primarily mild and temporary gastrointestinal symptoms.[31] Glucosamine does not carry risks such as gastric bleeding or ulcers, and does not raise the risk of a heart attack, stroke, or kidney disease, as do some NSAIDs.[31]

One potential safety concern with glucosamine involves blood sugar regulation. An initial study in a diabetic animal model raised concerns that glucosamine supplementation might increase insulin resistance.[37] Subsequent studies conducted in 2006 and 2007 in patients with diabetes and OA found that glucosamine did not directly affect blood glucose levels or cause worsening of insulin resistance. In addition, it had no effect on levels of either high-density lipoprotein (HDL) or apolipoprotein A_1, a constituent of HDL.[38,39] However, a recent meta-analysis of clinical studies indicated that glucosamine may decrease insulin sensitivity and increase fasting glucose. The authors noted that these effects were more likely to be detected in studies including subjects with baseline impaired glucose tolerance or insulin resistance. The authors also concluded that further research is needed to provide firm evidence.[40] Until definitive information is available, blood sugar levels should be closely monitored if glucosamine preparations are given to diabetic and glucose-intolerant patients. A further safety consideration is that, since most glucosamine is prepared from shellfish, it should not be recommended to patients with significant seafood allergy, although case reports show that patients do not typically react to glucosamine.[41]

Harpagophytum procumbens

Description and Pharmacology

Harpagophytum procumbens has historically been used as an analgesic, a remedy for fevers and allergies, and as a stimulant for gastric enzymes and digestion.[46] Figure 3 is an image of this herb. The *British Herbal Pharmacopoeia* recommends *H. procumbens* as a diuretic and sedative, while the German Food and Drug Administration as well as the Commission E approve *H. procumbens* for dyspepsia, appetite stimulation, and degenerative disorders of the musculoskeletal system.[47]

H. procumbens belongs to the Pedaliaceae family and, in addition to the common name devil's claw, is also known as grapple plant, wood spider, and harpago. It is native to the southern part of the African continent and may be found in the Kalahari sands of Namibia, Botswana, South Africa, Zambia, and Zimbabwe.[47] The tuberous roots of the plant are used for medicinal purposes. The major chemical constituents of *H. procumbens* are iridoid glycosides, sugars, triterpenoids, phytosterols, and aromatic acids.[46]

The major chemical component thought to be responsible for the anti-inflammatory activity is harpagoside, a monoterpene glucoside (Figure 4).[48,49] However, clinical trials have shown that constituents other than harpagoside, such as the triterpenoid glycoside β-sitosterol, may also be responsible for the anti-inflammatory effect.[50]

Harpagoside inhibits lipopolysaccharide-induced inducible nitric oxide and cyclooxygenase-2 (COX-2) expression via nuclear factor kappaB suppression, thereby inhibiting inflammation.[51,52] This mechanism is also believed to be in part responsible for the analgesic and chondro-protective effect of *H. procumbens* via inhibition of inflammatory mediators such as COX-2, leukotrienes, tumor necrosis factor-alpha (TNF-α), and interleukin-1β.[48] Studies yielding the best results utilized *H. procumbens* standardized hydro-alcoholic extracts containing 50-100 mg harpagoside daily.[49,53]

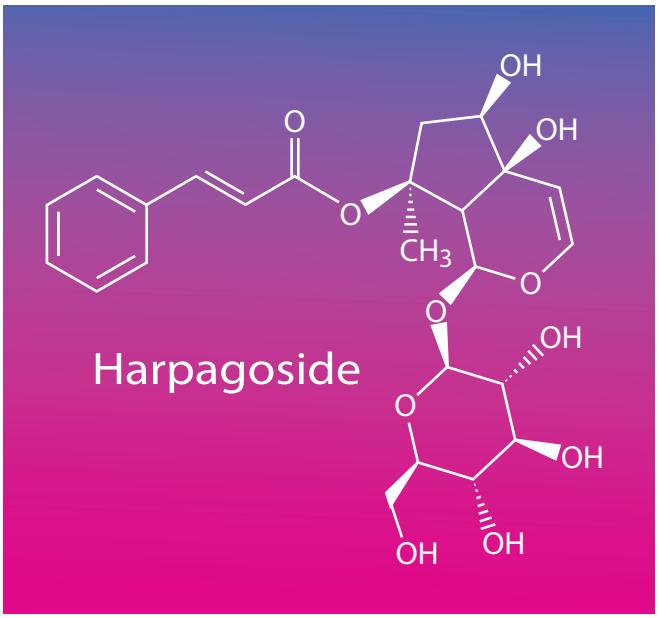
Efficacy and Safety

A 2000 study demonstrated the safety and efficacy of Harpadol®, an *H. procumbens* powdered extract containing a total daily dosage of 57 mg of harpagoside.[54] The study involved 122 patients suffering from knee and hip OA given Harpadol daily for four months. Results showed a significant and progressive reduction in pain, which resulted in a significant decrease in use of NSAIDs or other pain-relieving medications. The Harpadol preparation was well tolerated and patients experienced fewer adverse NSAID-type side effects.

In a 2002 uncontrolled trial, a tableted medication, Doloteffin® (2,400 mg aqueous extract of *H. procumbens* tubers standardized to 50 mg harpagoside daily), was given to 250 patients with OA of the knee or hip for eight weeks.[55] Patients with hip pain experienced a 54-percent improvement, while those with knee pain demonstrated 38-percent improvement compared to baseline. In a similar 2003 trial, Doloteffin (equivalent to 50 mg harpagoside daily) was given to 75 OA patients for 12 weeks.[53] Total pain score was reduced by 22.9 percent, while there was a 35-percent improvement in movement limitation. The results of these trials are limited by the lack of a control group.

Meta-analyses conducted in 2007 of a total of 14 clinical trials tested the validity of *H. procumbens* as an effective anti-inflammatory and analgesic preparation, particularly in the relief of arthritic symptoms.[56-58] These analyses concluded that the majority of studies appear to indicate *H. procumbens* is an effective anti-inflammatory and analgesic preparation in the treatment of acute and subacute inflammation. Clinical trials support *H. procumbens* as a beneficial treatment for the alleviation of pain and improvement of mobility in a variety of musculoskeletal conditions. Analysis of *in vitro* and *ex vivo* studies indicate that *H. procumbens* has significant effects on numerous pro-inflammatory markers; however, the exact mechanism(s) need to be further elucidated.[59] One clinical study found that quality of life was significantly improved from baseline to such a degree that 60 percent of patients in the study either reduced or stopped concomitant pain medication.[49]

Figure 4. Harpagoside Structure



Safety and adverse effects associated with the use of *H. procumbens* were examined in a 2007 review.[60] Twenty-eight clinical trials were included in the analysis, 20 of which were identified as reporting some form of adverse effect. The incidence of adverse events for *H. procumbens* was no greater than for placebo treatment in any trial. Minor adverse effects, mainly gastrointestinal in nature, occurred in three percent of patients. There were no reports of chronic toxicity.

Currently no serious drug interactions have been reported for *H. procumbens*. However, due to the pharmacology and mechanism of action of *H. procumbens*, there may be some potential drug interactions that health professionals should be aware of.

- Evidence suggests that *H. procumbens* is an inhibitor of COX-2. This inhibition may increase the risk of bleeding when taken with drugs that also increase the risk of bleeding, such as NSAIDs or anticoagulants.[51]
- *H. procumbens* extracts may lower blood sugar levels. Caution is advised when using this herb along with other hypoglycemic medications.[61]

- *H. procumbens* may increase stomach acidity and therefore affect drugs used to decrease stomach acid secretion (e.g., H_2 receptor antagonists, proton pump inhibitors, and antacids).[62]
- *H. procumbens* may affect heart rhythm and force of contraction; therefore, caution is advised for patients taking anti-arrhythmics or digoxin.[62]

Acupuncture

OA has a major impact on patients' mobility and quality of life, but the anti-inflammatory drugs used to treat it are also associated with a number of side effects, some of which are potentially dangerous (e.g., gastric bleeds associated with NSAIDs such as aspirin). As a result, in recent years, patients have turned increasingly to acupuncture to relieve the chronic pain associated with OA.

Efficacy and Safety

In 2006, a randomized, controlled clinical trial examined the use of acupuncture as an extension of routine medical care in a large number of patients with chronic pain due to OA of the knee or hip. The study groups consisted of a total of 3,633 patients, with 357 assigned to acupuncture, 355 to control group, and 2,921 patients (who declined randomization) assigned to a non-randomized acupuncture group. Patients treated with acupuncture in addition to routine care in both the randomized and non-randomized groups showed significant improvements in symptoms and quality of life compared with patients who received routine care alone (control group). Furthermore, patients in the control group who received acupuncture only after three months showed similar improvements at six months.[63]

A recent health technology assessment concluded that acupuncture can decrease pain levels in OA sufferers compared to no treatment at all.[64] However, this decrease in pain may only be temporary (e.g., for four weeks after the end of treatment).[65]

A 2007 meta-analysis concluded that acupuncture seems to have a genuine biological effect, as suggested by the small short-term improvements in pain and function compared with placebo.[66] Improvements provided by acupuncture compared with placebo were statistically significant when pooled. More importantly, however, a clear heterogeneity of the results was noted, which was attributed to variability of acupuncture and sham acupuncture protocols.

Neurobiological mechanisms invoking the release of endogenous opioids and depression of stress hormone release are believed to be the basis of acupuncture analgesia. A study published in 2009 compared plasma β-endorphin and cortisol levels with self-assessment scores of pain intensity before and after 10 days of electro-acupuncture treatment in patients suffering from chronic pain as a result of OA of the knee. Forty patients of both genders (age >40 years) with primary OA of the knee were recruited into a single-blinded, sham-controlled study. In the case of the electro-acupuncture group, the points were selected according to the Traditional Chinese Medicine Meridian Theory. In the sham group, needles were inserted at random points away from true acupoints and no current was passed through the needles. Both groups were treated for 10 days with one session every day lasting for 20-25 minutes. Electro-acupuncture resulted in subjective improvement in pain, stiffness, and disability. Of clinical importance was an improvement in objective measures of pain and stress/pain associated biomarkers in the electro-acupuncture group compared to sham treatment, demonstrating acupuncture-associated physiological changes beyond placebo effects.[67]

Side effects associated with acupuncture tend to be uncommon, mild, and reversible, and may include sleepiness, fainting, nausea, vomiting, temporary aggravation of symptoms, and bleeding, bruising, and/or pain at the needle site.[68,69] Other side effects may include infection and dermatitis.[70] Although extremely rare, evidence of serious, potentially life threatening complications associated with acupuncture have been reported, and include punctured organs, serious infection (e.g., hepatitis or bacterial infections), spinal cord injury, and shortness of breath.[68]

Conclusion

Substantial evidence suggests that glucosamine, *H. procumbens*, and acupuncture are mildly to moderately effective and well-tolerated CAM treatment options for OA. Although evidence is contradictory, the majority of studies appear to indicate that glucosamine and *H. procumbens* are effective anti-inflammatory and/or analgesic preparations in the treatment of OA. There is some evidence to suggest that glucosamine and *H. procumbens* are as effective as some standard analgesic and anti-inflammatory preparations. A favorable consequence of adjunctive or alternative therapy with glucosamine, *H. procumbens*, or

acupuncture may be a reduction in the use of other first-line pain medications, which in turn may lead to a reduction of side effects associated with these medications.

Another advantage of CAM therapy with glucosamine, *H. procumbens*, and acupuncture is that they offer alternative, moderately effective, and safe treatments for patients who do not tolerate standard pain medications like acetaminophen or NSAIDs. Evidence also suggests that glucosamine and *H. procumbens* might slow the progression of OA and therefore improve long-term quality of life.

Information on the cost-effectiveness of glucosamine for OA is mixed and insufficient to draw definitive conclusions. The cost-effectiveness of glucosamine sulfate compared to acetaminophen was evaluated as a subanalysis of the effect comparison between the treatments (industry-sponsored GUIDE study). The finding in this study was that glucosamine is a highly cost-effective alternative when compared with acetaminophen.[71] A drawback is that it was based on an industry-sponsored effectiveness study, which may be biased toward glucosamine effectiveness. A more comprehensive meta-analysis of glucosamine sulfate in addition to current care practice suggests that the gain in quality of life is not well determined. This meta-analysis focused on specific endpoints such as total knee replacement surgery rather than decreased use of medication and healthcare-related costs.[72]

A clinical trial compared the cost effectiveness of (1) advice and exercise alone to (2) advice, exercise, and either true acupuncture or non-penetrating acupuncture in 352 patients with OA of the knee. The authors concluded that, despite the additional costs incurred by adding acupuncture, it was a feasible and cost-effective treatment.[73] There are no cost-effectiveness studies available for *H. procumbens* treatment.

Although there are certain potential drug interactions and co-existing conditions to consider before recommending the use of glucosamine and *H. procumbens*, these interventions are generally well tolerated with few reported side effects. Side effects are mainly confined to minor gastrointestinal complaints, which are either transient or can be suitably managed. Side effects associated with acupuncture appear to be primarily restricted to minor skin irritations and sleepiness; however, more severe adverse effects are possible.

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