Chronic Pain Management:

Use of a Devil’s claw agent to inhibit cytokine release

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The severity of chronic pain can be mild to severe and it can be episodic or continuous. In some cases the pain partially affects the patient’s well-being, level of function, and quality of life and in others it is completely incapacitating. The goal of pain management is to rapidly provide relief and improve the quality of life, including the ability to participate in day-to-day activities. Analgesics and other medications are commonly used in the treatment of chronic pain. There are a number of pharmacological choices for the treatment of pain with a wide range of effectiveness. Reducing the severity of pain to a tolerable level may be challenging as it may take several types of pharmacological treatments given in combination or involve upward titration of a drug before a patient obtains adequate relief. In many cases pain medications effectively reduce the severity of the pain but in others the same medications are not tolerated by the patient. There is also a personal aspect to the severity of pain and each person may respond in a different manner to a specific pharmacological agent. The physician must often seek an alternative drug or reduce the dose of the suspect agent.

Additional pharmacological agents are needed to provide physicians with alternative analgesics for the management of chronic pain. This issue has resulted in a review of the safety and efficacy data to identify potential botanical agents. There are many botanical agents that have shown good efficacy in well-controlled clinical trials but not many can be safely used in a patient population; especially one taking multiple pharmaceutical drugs. Some botanical agents have unique mechanisms of action due to
their content of multiple medicinal ingredients. In addition, the mechanism of action is rarely a single target and usually involves multiple sites of pharmacological activity. This often translates into good safety in human subjects that are relatively healthy but in people taking multiple medications there may be additional risks.

There are many herbal references that discuss the anti-inflammatory and analgesic benefits of *Boswellia* species, *Curcuma longa*, *Harpagophytum procumbens*, and *Salix* species. These agents have good pain relief benefits when used at an appropriate dose but the majority have safety issues that are not negligible in a chronic pain or elderly population. All of these will have additive effects with other analgesic and anti-inflammatory agents. Some of these will target cytokine release and this is of interest for patients with chronic inflammatory conditions.

*Curcuma longa* may inhibit platelet aggregation and potentially cause increased bruising and bleeding. Health Canada requires a label precautionary statement to consult a health practitioner prior to use if you have stomach ulcers or excess stomach acid.

*Salix alba* (Willow bark) can enhance anti-platelet effects. The European Medical Agency (EMA) concluded that Willow bark can interact with oral anticoagulants (heparin, coumarine derivatives) and that it can be of therapeutic importance. The EMA further states that there are statistically significant associations between the use of Willow bark and bleeding events. This lead to their recommendation that the combined use of Willow bark with acetylsalicylic acid and other NSAIDs is not recommended. Health Canada requires products to bear precaution statements regarding use with anticoagulants or products containing acetylsalicylic acid or other salicylates.

*Boswellia* has a relatively good safety profile but it is a moderate-to-potent inhibitor of cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4. It must be used cautiously in patients taking drugs metabolized by cytochrome P450 enzymes.

*Harpagophytum procumbens* (Devil’s claw) has a very good safety profile. Health Canada does not require any precautionary statements with regards to drug interactions (including interaction with anticoagulants) and bleeding risk. This agent does not cause the inhibition or induction of cytochrome P450 enzymes. There is a single case report of purpura in a patient taking warfarin with Devil’s claw in the literature. This case as well as all the body of evidence was assessed by Health Canada and the EMA. The EMA concluded that they could not find any study or reported cases suggesting an interaction with oral anticoagulants or sulfonylureas. They further stated that no signal, even weak, had emerged from the literature to suggest a link. Even though there are no contraindications, it is always better to be cautious when administering a botanical supplement to a person taking an anticoagulant or antiplatelet medication. Other authors\(^2\) have come to the same conclusion, that this botanical agent will have significant pharmacodynamic anti-inflammatory and analgesic properties that may allow a reduction in drug dose and drug adverse effects for many NSAIDs. As a general precaution, companies typically state on the product label not to use in patients with gastric or duodenal ulcers.
Many of the adverse events related to the use of Devil’s claw are attributed to allergic rather than dose-dependent effects. The adverse effects consist of mild gastrointestinal upset, diarrhea, or anorexia. The gastrointestinal adverse effects should be minimized by the use of an enteric coated product.

A Devil’s claw herbal product is contraindicated for use during pregnancy because of the lack of clinical trial evidence to recommend safe use. This is the case for the majority of herbs.

These extracts should be used cautiously in patients with arrhythmias or taking antiarrhythmic agents, due to potential negative inotropic effects of Devil’s claw. In rabbits, Devil’s claw has been associated with negative chronotropic, as well as positive and negative inotropic effects. These effects have not been reported in human studies but this could simply be due to a low incidence of occurrence or limited pharmacovigilence. Although no precautionary statements are required by Health Canada, it is theoretically possible that Devil’s claw could result in additive effects with anti-arrhythmic drugs. This herbal agent should be used cautiously in patients taking calcium channel blockers, such as Verpamil. It is always important to be cautious even though there are no reported incidents in humans.

Devil’s claw (Harpagophytum procumbens) extracts can be used as a Non-Steroidal Anti-Inflammatory Drug (NSAID). Research has shown that the active ingredients have COX-2 inhibition activity and are a potent inhibitor of cytokine release. Clinical trials have shown that this agent is effective in managing pain associated with osteoarthritis, rheumatoid arthritis and low back pain.

The pharmacological mechanism of action is complex. The relation between serum harpagoside levels and the inhibition of leukotriene biosynthesis was shown in a clinical trial in healthy human volunteers. Based on pharmacokinetic studies, the elimination half-life of harpagoside is 5.6 hours. Studies demonstrated that the medicinal ingredient inhibits cyclo-oxygenase-2, assists the extracellular matrix construction (e.g., synthesis of Glycosaminoglycans (GAGs)), and the synthesis of hyaluronic acid. Mechanistic studies demonstrated that concentrated extracts could reduce IL-1B-induced TNF expression and reduce LPS induced TNF expression. Relative to prescription COX-2 inhibitors, Devil’s claw is a weak inhibitor of COX-2 mediated prostaglandin E2 biosynthesis and a potent cytokine release inhibitor.

The botanical ingredient was studied in over 20 clinical trials in patients with osteoarthritis, rheumatoid arthritis and low back pain. These studies lead the Natural Standard™ database and UpToDate™ to conclude that ‘There is a growing body of scientific evidence suggesting that Devil’s claw is safe and beneficial in the short-term management of pain related to degenerative joint disease or osteoarthritis. It may be equally effective as drug therapies, such as non-steroidal anti-inflammatory drugs (or may allow for dose reductions or cessation of these drugs in some patients).’

An enteric-coated standardized extract is important for protecting the medicinal ingredients from acid hydrolysis, ensuring lot-to-lot consistency, and a fixed amount of the iridoid glycoside, harpagosides, which are
associated to the therapeutic properties of the herb. Based on the body of clinical evidence, patients should receive between 50 to 100 mg harpagosides per day\textsuperscript{9}. Optimal dosing requires giving the product three times a day because of the half-life of the harpgosides. There was no efficacy when less than 30 mg harpagoside was given per day in patients\textsuperscript{9} there by suggesting a minimal effective dose of 10 mg harpagoside three times per day.

The clinical trials used non-enteric coated extracts of Devil’s claw and in the majority of the studies the product was administered in three doses per day. In one study it was compared to Vioxx (Rofecoxib) in patients with low back pain\textsuperscript{10}. The study was double-blind and randomized. Eighty eight patients either received 12.5 mg of Vioxx versus 2.4 grams of a Devil’s claw extract (60 mg harpagosides per day) per day for 6 weeks. A rescue therapy of 400 mg per day of Tramadol was allowed. Efficacy was evaluated using the Arhus index, pain scales and a health assessment questionnaire. The investigators found no statistical differences between groups.

In a double-blind, randomized, multicentre clinical trial, 122 patients with osteoarthritis (OA) of the knee and hip either received 100 mg Diacerhein\textsuperscript{1} or 2.6 grams Devil’s claw per day (57 mg harpagosides per day) for 4 months\textsuperscript{11}. Efficacy endpoints included: spontaneous pain using a visual analog scale (VAS); Lequesne Index, functional disability of movement assessed on a VAS; amount of taken rescue medication (acetaminophen-caffeine with or without diclofenac). Sixty-five percent of subjects on Devil’s claw and 60% on Diacerhein had considerable improvements in OA symptoms. There were no significant differences for pain, functional disability, or Lequesne score. Subjects taking Devil’s claw were using statistically significantly less analgesic medications (p=0.01). Adverse effects (mainly diarrhea) that were considered to be due to treatment were reported in 8.1% and 26.7% of Devil’s claw and Diacerhein patients, respectively (p=0.017).

Another interesting trial was performed by Schröffer et al\textsuperscript{3,12}. The trial included 50 patients randomized into two groups of 25 and treated with 1230 mg Devil’s claw extract and phenybutazone (300 mg per day for the first four days, then 200 mg), respectively. Devil’s claw was found equally effective or superior to phenybutazone after 28 days of treatment.

Clinical investigations performed by Chamberland\textsuperscript{13} demonstrated that a concentrated extract could be used in the management of acute and chronic pain in patients not taking any pain medications. These patients received Devil’s claw and an antispasmodic herb three times a day and California poppy at night. In the pilot acute pain study, the majority of patients reported a significant improvement in the VAS. The delta –VAS\textsuperscript{2} in patients suffering from acute pain (neck, upper back, wrist, or shoulder pain or fibromyalgia) was 2.2. A delta-VAS greater than 2 is considered clinically significant by physicians specializing in pain management. Physical examination of the patients also revealed improved cervical motion and reduced swelling and tenderness.

The pilot chronic pain study included patients with osteoarthritis and low back pain.

\textsuperscript{1} Diacerhein is an inhibitor of IL-1.

\textsuperscript{2} Delta VAS = VAS Day 7 – VAS – Day 0.
Improvements were observed at Day 14 and Day 28. This gradual improvement is consistent with the mechanism of action of the Devil’s claw. Patients show improvement over a 1 to 2 month period. This progressive improvement is consistent with its action on cytokine release. These patients showed increase mobility or flexibility, decreased swelling, tenderness or stiffness. The delta-VAS for this group of patients was 2.0.

Our current research is assessing the benefits of this botanical agent in patients with fibromyalgia or other chronic pain conditions in patients with uncontrolled pain despite receiving the medical-pharmacological standard of care.

Clinical research suggests that cytokines may be involved in the pathogenesis of fibromyalgia. Altered levels of cytokines are also associated with symptoms of pain, fatigue and distressed mood in many conditions such as peripheral neuropathies and cancer. In osteoarthritis, IL-1 has an important role in cartilage degradation. TNF-alpha and IL-6 work synergistically with IL-1 to induce matrix breakdown. In rheumatoid arthritis, IL-1 and TNF-alpha also play a role. IL-1 and TNF-alpha mediate inflammation and joint destruction. In back and neck pain, herniation of disc tissue causes inflammation, with release of cytokines; especially TNF-alpha. TNF-alpha is produced by the herniated or degenerating disc.

This botanical agent has been shown to be non-inferior (equivalent) to several NSAIDs in clinical trials. It is a relatively weaker COX-2 inhibitor than VIOXX. It is believed that its clinical potency is derived from its cytokine release inhibition mechanism. The relatively weaker COX-2 inhibitor activity than drugs, such as VIOXX, explains why these have a relatively better safety profile than NSAIDs.

The pharmacological rationale for using Devil’s claw extracts has mainly been based on a typical NSAID-type therapy. These agents provide an anti-inflammatory benefit similar to NSAIDs within an hour of taking the product and in some cases this may provide sufficient relief. The more potent aspect of its activity is associated with its reduction of cytokine release and this will take a longer duration of treatment to observe optimal benefits. This aspect of the agent explains why it needs to be taken over 2 to 3 months to observe optimal and significant clinical benefits in patients. This is required to allow the herbal ingredients to reduce the release of cytokines responsible for the inflammation and pain. The use in patients with fibromyalgia is well supported by its mechanism of action involving two key inflammatory cytokines, IL-1 and TNF-alpha. Case studies reported by physicians support the use in patients with fibromyalgia. As with many pain medications, physicians also report that they cannot predict in which patients this agent will work. It is a trial-and-error approach and they claim to observe significant benefits in about 1 out of 2 patients. This medical practice involves the use of a Devil’s claw product as an adjuvant to the standard of care pain medications.

REFERENCES


