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FILE: ▪ Devil's Claw (*Harpagophytum procumbens*)
▪Anti-inflammatory Activity

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RE: Anti-inflammatory Activity of Devil's Claw Reviewed

Grant L, McBean DE, Fyfe L, Warnock AM. A review of the biological and potential therapeutic actions of *Harpagophytum procumbens*. *Phytother Res*. Mar 2007;21(3):199-209.

Devil's claw (*Harpagophytum procumbens*) is used in herbal medicine as a treatment for tendonitis, osteoarthritis (OA), rheumatoid arthritis (RA), headache, backache, and menstrual pain. The Khoisan people of the Kalahari Desert have used devil's claw as an analgesic and anti-inflammatory preparation for centuries. It is most often used as an ethanolic tincture or dry extract of the tubers. The active constituents are believed to be iridoid glycosides, including harpagoside, procumbide, and harpagide. Although the active constituent or constituents are still not positively identified, harpagoside is used as a marker compound. Extracts of devil's claw usually contain about 2.5% harpagoside. The European Scientific Cooperative on Phytotherapy (ESCOP) recommends 2-5 g of the extract containing at least 1.2% harpagoside or 1-3 g of the herb or equivalent hydroalcoholic or aqueous extract taken three times daily for a minimum of 2-3 months in the treatment of painful joints or tendonitis. Recent studies suggest that devil's claw may be useful in the treatment of other conditions including convulsions and lower back pain. In this review, the authors examine the anti-inflammatory activity of devil's claw.

The earliest animal studies on devil's claw, conducted in the 1970s, indicate that devil's claw extract has an anti-inflammatory effect. While these studies did not use more commonly accepted methods, more recent animal studies have supported the findings of the earlier studies. They indicate a dose-dependent anti-inflammatory effect equivalent to that of phenylbutazone, indomethacin, and aspirin. However, other animal studies indicate no anti-inflammatory effect. One animal study has demonstrated an anti-inflammatory effect with intraduodenal administration of devil's claw extract and no effect with oral administration. Other studies indicate that the active constituents of devil's claw are degraded by stomach acid. However, two more animal studies have demonstrated anti-inflammatory and analgesic effects following oral administration of aqueous devil's claw extract. The authors of this

review write that these inconsistent results may be due to differences in extract composition. A more recent study has indicated that intraperitoneal administration of devil's claw extract suppresses acute inflammation and has an analgesic effect. Additionally, another animal study has demonstrated a significant dose-dependent reduction in blood glucose in normal and diabetic fasting mice.

The majority of animal studies indicate that devil's claw extracts possess anti-inflammatory and analgesic effects against acute and subacute inflammation. However, there has been very little research on chronic inflammation, which is important in the treatment of arthritic conditions.

Devil's claw had no effect on the COX enzyme, showing no effect on prostaglandin synthetase activity in one study. Another in vitro study has demonstrated that devil's claw extract does not affect eicosanoid production through the COX and 5-LOX pathways in healthy subjects. However, another study has shown that devil's claw extract inhibits the biosynthesis of cystemyl-leukotrienes, with the constituent harpagoside being the most active. In addition, another study has shown that harpagoside alone inhibits TXB formation in stimulated blood platelets. A follow-up ex vivo study has found that devil's claw extract (9% harpagoside) reduces Cys-LT levels in blood samples from healthy male subjects in a biphasic pattern. A significant correlation between serum harpagoside levels and LT inhibition was demonstrated. The difference in results among these studies is most likely due to variations in the constituents of the devil's claw extracts. In addition, the authors recommend the use of enteric coated capsules in future studies to guard against possible deterioration by gastric acid. The authors conclude that these mechanism of action studies "tentatively suggest" that devil's claw extract modulates LT and/or TX synthesis, but this effect may not be through a direct effect on the COX and 5-LOX pathways.

In addition, recent studies show that devil's claw extract may directly inhibit the COX-2 enzyme and suggest that the anti-inflammatory effects of devil's claw extract can be attributed to a direct suppression of the iNOS and COX-2 inflammatory enzymes. Overall, the research shows that devil's claw extract has an antioxidant effect by scavenging free radicals and inhibiting the enzymes that produce them. Therefore, part of devil's claw extract's anti-inflammatory effect may relate to its ability to balance levels of free radicals and antioxidants. High levels of free radicals and low levels of serum antioxidants are associated with arthritic conditions, including rheumatoid arthritis. Other studies have demonstrated that devil's claw extract inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha and IL-1beta. In addition, devil's claw extract has been shown to inhibit human leukocyte elastase in a dose-dependent manner, indicating a possible inhibitory effect on neutrophil elastase, which is associated with arthritis. These in vitro and ex vivo studies indicate that devil's claw extract "has significant effects on inflammatory markers," but the mechanism of action for devil's claw extract's observed analgesic and anti-inflammatory effects is still not clear.

It is difficult to compare the results of clinical trials on devil's claw due to variations in study design, extract dose and constituents, and clinical conditions. These studies have been focused on patients with OA or RA of the hip or knee, chronic non-specific low back pain,

or various types of musculoskeletal pain. Five clinical trials on devil's claw extract in the treatment of OA or RA of the hip or knee have demonstrated positive results. These trials include one open trial and four double-blind clinical trials using daily doses of devil's claw extracts in the range of 2,000-4,500 mg containing 30-57mg of harpagoside with durations of 4-20 weeks. The open trial shows significant overall improvement in pain and symptom-related parameters, including improvements on the WOMAC osteoarthritis scale, the VAS pain scale, and physician assessments. There were two reports of minor adverse effects that may have been related to the study medication. The two double-blind placebo-controlled clinical trials enrolled patients with "rheumatic articulation of the knee or hip" and "acute exacerbation of coxarthritis." They demonstrate significant reductions in pain and improvements in mobility for patients receiving the devil's claw extracts, as demonstrated by improvements in VAS scores, reduction of ibuprofen use, and improvements in a finger-floor measure of pain and joint mobility. In one study, the patients received ibuprofen and devil's claw or ibuprofen alone, and significant reductions in ibuprofen use were observed in the devil's claw group. The two double-blind comparative trials compared the efficacy of devil's claw extract with the conventional medications phenylbutazone and diacerin in the treatment of rheumatic joints, gouty arthritis, and OA of the knee or hip. Both studies have shown improvements in pain. The diacerin study has found no difference between diacerin and devil's claw groups in pain and mobility improvements. In addition, the devil's claw group used less rescue medication and had fewer adverse events. The findings were similar in the phenylbutazone study, with similar improvements in pain between the two groups and fewer adverse events in the devil's claw group.

One open trial on devil's claw (960 mg/day) and chronic non-radicular back pain has demonstrated a significant reduction in perceived pain and a significant improvement in mobility with three mild adverse events. Five double-blind clinical trials have been conducted on devil's claw extract and chronic non-specific back pain, all of them by the same group. The trials include daily doses of 4,500-9,000 mg (30-100 mg harpagoside) of devil's claw products, including the proprietary product Doloteffin® (Ardeypharm GmbH, Germany), for at least four weeks. Overall, the results indicate that devil's claw extract is effective in treating chronic low back pain. In the placebo-controlled trials, improvements in Arhus pain scores and increases in the numbers of pain-free patients, compared with the placebo groups, were observed. The comparative trials have shown equivalency in efficacy between devil's claw extract and a standard non-steroidal anti-inflammatory drug (NSAID) and the COX-2 inhibitor Vioxx® (rofecoxib). Similar improvements were observed in the numbers of pain-free patients and the Arhus scale. Overall, fewer adverse effects were observed in the devil's claw groups. It should be noted that Vioxx has been removed from the world market due to concerns over safety. A one year follow-up study by the same group has found that patients receiving devil's claw extract continued to experience overall improvements in pain without serious adverse events.

Several trials have been conducted on devil's claw extract and the treatment of various forms of musculoskeletal pain. A small 1981 open trial (n=13) has found no apparent benefit for devil's claw in treatment of a variety of rheumatic conditions. The other studies show improvements in mobility, pain, and other symptoms. An open trial that enrolled patients with arthrosis of the hip, knees, fingers, or spine (n=630) has shown significant

improvements in pain after six months of treatment with devil's claw extract (3,000-9,000 mg/day). Similarly, another open trial enrolling patients with OA and RA has demonstrated significant improvements in symptoms, mobility, and morning stiffness without adverse events after 30 days of treatment with 750 mg/day of powdered devil's claw roots. A fourth open trial enrolling patients with low back pain, osteoarthritic knee pain, or hip pain has shown significant improvements in pain and mobility with only minor adverse events after eight weeks of treatment with Doloteffin devil's claw extract (60 mg harpagoside/day). The benefits were greatest in patients with hip arthrosis and knee arthrosis. In addition, double-blind, placebo-controlled clinical trials have demonstrated benefits for patients with various forms of musculoskeletal pain. A 1984 study has demonstrated significant improvements in severity of pain, compared with the placebo group in patients with general arthrosis after three weeks of treatment with 2,400 mg/day of devil's claw extract. Another trial involving patients with OA, chronic low back pain, or myalgia has shown that devil's claw extract (2,460 mg/day) is more effective than a placebo in suppressing pain. In addition, a clinical trial on devil's claw extract (4,500 mg/day containing 30 mg harpagoside) and tendonitis of the shoulder, neck, and/or back has shown significantly less pain in the treatment group, compared with the placebo group.

Overall, a number of double-blind placebo-controlled clinical trials have demonstrated that devil's claw treatment is effective in improving mobility and relieving pain in a variety of conditions, including non-specific back pain, arthrosis of the knee and hip, general arthritic complaints, and muscle soreness. Clinical trial findings support the German Commission E and ESCOP indications for devil's claw preparations. Double-blind clinical trials also show possible equivalence between devil's claw extract and conventional drugs in the treatment of arthritis of the knee and hip and low back pain. Further trials are needed to confirm these results. Treatment with devil's claw extract may be more cost-effective and safer than pharmaceutical treatments. Overall, devil's claw extracts are well-tolerated with clinical trials showing no serious adverse events and some minor gastrointestinal adverse effects. Long-term use of devil's claw extract also appears to be well-tolerated, and there are no reports of drug-herb interactions between devil's claw extracts and conventional drugs for arthritic conditions. However, further studies on possible devil's claw drug-herb interactions and hepatoxicity are needed. In addition, more research is needed to confirm the mechanism(s) of action for devil's claw's effects.

—Marissa N. Oppel, MS

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