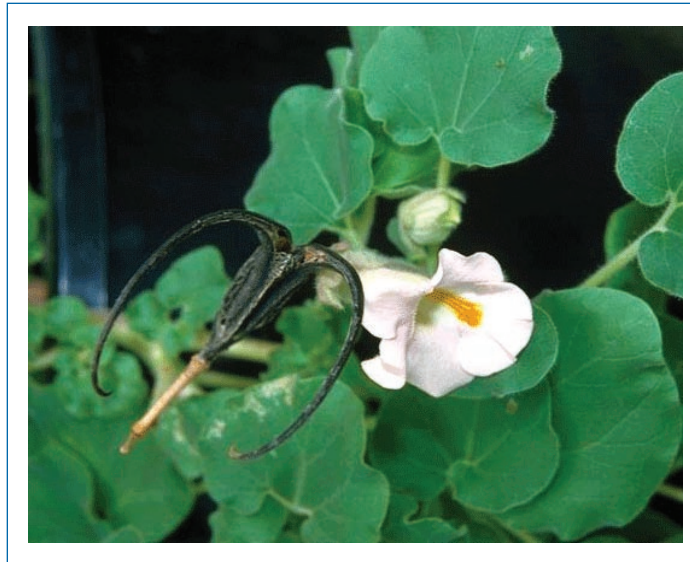


## *Harpagophytum procumbens* (Devil's Claw)

### Introduction

Historically, *Harpagophytum procumbens* (devil's claw) has been used as an analgesic, a remedy for fevers and allergies, and as a bitter by San bushmen in Africa to stimulate gastric enzymes and digestion. The *British Herbal Pharmacopoeia* recommends devil's claw as a diuretic and sedative,<sup>1</sup> and the German Commission E, the German counterpart to the U.S. Food and Drug Administration, approves devil's claw for dyspepsia, appetite stimulation, and degenerative disorders of the musculoskeletal system.<sup>2</sup> Devil's claw has also been used for liver and kidney disorders, as a purgative, an oxytocic, and as a topical agent to treat wounds and skin rashes.<sup>3,4</sup> Clinical research has shown it to be effective for arthritis and rheumatic disorders.<sup>2</sup>



### Description

Devil's claw belongs to the Pedaliaceae family and 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, Angola, Zambia, and Zimbabwe. Devil's claw is a ground trailing, weedy perennial about 18 inches long with a stout central taproot growing up to two meters deep. Secondary storage tubers, resembling elongated sweet potatoes, branch off horizontally. Leaves are large, have 3-5 lobes, and are covered in white mucilaginous cells, making them appear a grayish-green color. Flowers are trumpet shaped and pink, red, or purple with a yellowish center. The fruit grows from the flower and is woody, radiates numerous long, barbed spines, and gives the plant its commonly known names.<sup>3,5</sup>

### Active Constituents

The major chemical constituents of *Harpagophytum* are iridoid glycosides (primarily harpagoside, harpagide, and procumbide), sugars (mainly the tetrasaccharide, stachyose), triterpenoids (oleanolic and ursolic acid), phytosterols (primarily beta-sitosterol), aromatic acids (caffeic, cinnamic, and chlorogenic acids), and flavonoids such as luteolin and kaempferol.<sup>6</sup> Harpagoside, harpagide, and procumbide, found in the tubers of the plant, appear to be the most therapeutically important constituents. Secondary storage tubers contain twice as much harpagoside as the tap root.<sup>3</sup> All extracts are not equally effective; whole-plant extracts appear to have a better therapeutic effect than those prepared from isolated parts.<sup>7</sup> A review of clinical trials utilizing *H. procumbens* preparations for the treatment of joint and lower back pain found studies utilizing extracts containing 50-60 mg harpagoside daily gave more reliable data and were more effective at alleviating pain and improving mobility than extracts with lower amounts.<sup>8,9</sup>

## Mechanisms of Action

### Anti-inflammatory

A dried aqueous extract of devil's claw has been shown to exert a significant dose-dependent analgesic and anti-inflammatory effect in rats at 5 and 10 mg/kg. However, carrageenan-induced paw edema was not affected by the isolated harpagoside constituent, suggesting harpagoside may not have an anti-inflammatory effect, at least in the doses used in this animal model of inflammation. This suggests that other devil's claw constituents may be responsible for the anti-inflammatory effect.<sup>10</sup>

An *in vitro* study using two rat cell lines found harpagoside inhibited lipopolysaccharide-induced inducible nitric oxide (iNOS) and cyclooxygenase-2 (COX-2) expression via nuclear factor kappaB (NF- $\kappa$ B) suppression, thereby inhibiting inflammation.<sup>11</sup> Another similar *in vitro* study compared two devil's claw root extracts for their effect on iNOS expression in rat mesangial cells. One extract contained naturally present root constituents and 8.9-percent harpagoside, and the second extract contained naturally present root extracts and 27-percent harpagoside. A significant (80%) suppression of nitrite formation was observed for both extracts and was attributed to reduced iNOS promoter activity and suppression of NF- $\kappa$ B translocation. Interestingly, a harpagoside-free extract also inhibited iNOS expression to a significant degree, indicating extract constituents other than harpagoside are in part responsible for the anti-inflammatory effect.<sup>12</sup>

### Analgesic

Harpagoside appears to exert a peripheral analgesic effect. Human research has demonstrated decreased pain in knee and hip osteoarthritis and non-specific low-back pain after ingestion of devil's claw extracts containing harpagoside.<sup>13,14</sup> Although the mechanism behind this effect has not yet been determined, it is thought to be closely connected to its anti-inflammatory properties.

### Antioxidant

Animal research has demonstrated a significant antioxidant effect for devil's claw extract when administered intra-peritoneally to rats. Dose-dependent increases in superoxide dismutase, catalase, and

glutathione peroxidase were observed in rat brain tissue and a reduction in lipid peroxidation was also noted. The antioxidant properties may be partially responsible for the anti-inflammatory effect of devil's claw extracts.<sup>15</sup> The flavonoids (proven scavengers of free radicals)<sup>16</sup> and plant phenols (hydrogen donors and oxygen radical neutralizers)<sup>17</sup> present in devil's claw extracts may be the constituents responsible for the observed antioxidant activity.

### Digestive Aid

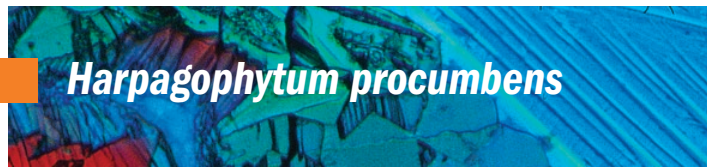
The "bitter" action of devil's claw provided by the iridoid glycosides increases gastric acid production and stimulates digestion.<sup>18</sup>

### Chondroprotective

Harpagophytum is chondroprotective, possibly due to inhibition of inflammatory mediators, including COX-2, leukotrienes, nitric oxide, tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 $\beta$ . In addition, matrix metalloproteinases and elastase that play key roles in cartilage degradation are inhibited.<sup>11,19</sup>

### Clinical Indications

Numerous trials have been conducted using devil's claw extracts of various types for osteoarthritis, rheumatism, or low-back pain. Unfortunately, the results of many of the studies are of questionable value because of methodological flaws. Early uncontrolled trials did provide valuable information on appropriate dosing and adverse effects, but most of the trials comparing devil's claw with other medications for arthritis and back pain were potentially biased due to lack of blinding and randomization. Several randomized, placebo-controlled studies (RCTs) were also flawed due to poor or absent baseline data, while others lacked transparency of data. In addition, a few of the studies used special extracts of devil's claw not available clinically, so results are of limited clinical value. Studies yielding the best results utilized devil's claw extracts containing 50-100 mg harpagoside daily.<sup>20</sup>



## Osteoarthritis

In a multicenter, uncontrolled trial, a tableted medication, Doloteffin® (2,400 mg aqueous extract of devil's claw tubers equivalent to 50 mg harpagoside daily) was given to 75 patients with osteoarthritis-induced knee and hip pain daily for 12 weeks. Pain was assessed via the Western Ontario and McMaster Universities (WOMAC) questionnaire, a visual analog scale (VAS), and physician exam at baseline, six, and 12 weeks. At 12 weeks the WOMAC total pain score was reduced by 22.9 percent and the VAS pain score decreased by 24.5 percent compared to baseline. Physician assessment of pain reported a 46-percent improvement in pain on palpation, 35-percent improvement in movement limitation, and 25.4-percent improvement in joint crepitus at 12 weeks.<sup>13</sup>

A larger study of Doloteffin involved 250 patients with osteoarthritis of the knee (n=85) or hip (n=61), or nonspecific low-back pain (n=104) over eight weeks. Doloteffin dosage was 60 mg harpagoside daily. After eight weeks, patients in the hip-pain and knee-pain groups demonstrated 35- and 37-percent improvement in WOMAC scores compared to baseline, respectively. When averaging all pain indices measured, patients with hip pain experienced a 54-percent improvement, while those with knee pain demonstrated 38-percent improvement compared to baseline. Similar results were observed for patients in the back-pain group.<sup>21</sup> Despite limitations to this study, including lack of a control group and the variety of pain assessments with poor correlation among them, this surveillance study indicates a significant benefit of Doloteffin for osteoarthritic pain.

The efficacy and safety of Harpadol®, a devil's claw powdered extract administered at 2,610 mg daily (435 mg per capsule; containing a total daily dosage of 57 mg harpagoside) was studied for four months in 122 patients suffering from knee and hip osteoarthritis and compared to 100 mg daily diacerhein, an anthraquinone derivative (plant source not identified) with proven osteoarthritis ameliorating properties. Severity of arthritis was assessed via the Luquesne Index, a reliable tool used to rate pain. Harpadol administration resulted in a significant and progressive reduction in the index values, equal to that of diacerhein. Patients taking devil's claw also used significantly fewer non-steroidal anti-

inflammatory drugs (NSAIDS) or other pain-relieving medications than patients taking diacerhein, and the frequency of adverse events was significantly lower in the Harpadol group than in the diacerhein group. Harpadol was shown to be at least as effective as diacerhein and resulted in fewer side effects.<sup>14</sup>

In an RCT, 89 subjects with osteoarthritis were given 2,000 mg (60 mg harpagoside) devil's claw extract (n=45) or placebo (n=44) daily for eight weeks. Subjects in the devil's claw group experienced significant decrease in pain measured on the VAS scale compared to placebo; significant improvement in mobility was also reported.<sup>22</sup>

## Rheumatism/Low-Back Pain

A review of published literature conducted in 2007 found 10 randomized, controlled trials utilizing *H. procumbens* for relief of low-back pain.<sup>23</sup> Although many were methodologically flawed, three RCTs by Chrubasik et al were of moderate-to-high scientific quality and demonstrated benefit. In the earliest trial, 118 patients (59 in each group; 51 in treatment group and 54 in placebo group completed study) ages 18-75 with a six-month history of nonspecific low-back pain were given 6 g Harpagophytum (containing 50 mg harpagoside) or placebo for four weeks. After four weeks 9/51 in the treatment group and 1/54 in the placebo group were pain free.<sup>24</sup>

Effectiveness of Harpagophytum extract WS 1531 (50 mg or 100 mg harpagoside daily) was evaluated in 197 subjects with low-back pain. Patients were randomly assigned to 50 mg harpagoside (n=65), 100 mg harpagoside (n=66), or placebo (n=66) for four weeks. The principal outcome measure was the number of pain-free subjects assessed by the Arhus low-back pain index. After four weeks, 10, six, and three subjects were pain free in the 100-mg, 50-mg, and placebo groups, respectively. Based on the Arhus index, however, the greatest symptomatic benefit was observed in the 50-mg harpagoside group, with no additional benefit in terms of decreased pain intensity with the higher dose of harpagoside.<sup>25</sup>

An RCT compared Doloteffin and Vioxx® for the treatment of low-back pain in 88 patients (44 in each group) for six weeks. Patients received either 2,400 mg Doloteffin (60 mg harpagoside) or 12 mg



## Monograph

Vioxx daily. Ten patients in the devil's claw group reported no pain without rescue medication during the sixth week of the trial, compared to five patients in the Vioxx group. Eighteen Dolotefin patients and 12 Vioxx patients reported greater than 50-percent reduction in average pain scores over the course of the trial. In terms of overall Arhus index pain scores, patients in the Dolotefin group reported an average score decrease of 23 percent compared to 26 percent in the Vioxx group. Adverse events were also comparable in both groups.<sup>26</sup> A one-year follow-up of this trial revealed a slight increase in improvement on the Arhus scores achieved in the pilot study.<sup>27</sup>

### Botanical-Drug Interactions

Devil's claw extract has been shown to inhibit certain cytochrome P450 enzymes; therefore, may have an impact on numerous pharmaceutical drugs also metabolized via these enzymes, including Coumadin, antihypertensives, statin drugs, anti-epileptic and antidiabetic agents, antidepressants, and proton pump inhibitors. Devil's claw extract moderately inhibited CYP2C8/9/19 and CYP3A4 with IC<sub>50</sub> values between 100-350 µg/mL. The root extract also minimally inhibited CYP1A2 and CYP2D6 with IC<sub>50</sub> values >900 µg/mL.<sup>28</sup>

Because devil's claw has been shown to lower blood sugar in animals, caution is advised when giving devil's claw extracts to diabetic patients taking other blood-sugar-lowering medications,<sup>29</sup> as it could potentiate their effects. *H. procumbens* also has been shown to cause a significant dose-dependent reduction of arterial blood pressure and heart rate in animals. A protective effect against arrhythmias was also observed.<sup>30</sup> Therefore, devil's claw extracts administered in conjunction with other medications that affect heart rhythm, blood pressure, or heart rate may have an additive effect and dosages may need to be adjusted. Devil's claw extracts also appear to have some degree of blood thinning activity,<sup>30</sup> so caution should be used when prescribing it with blood-thinning agents.



### Side Effects and Toxicity

Extracts of *H. procumbens* appear to be safe when used in appropriate dosages. Side effects are few and usually limited to gastrointestinal upset.

Harpagoside has been found to be of low toxicity with an LD<sub>50</sub> >13.5 g/kg in mice.<sup>31</sup> In a review of 28 clinical trials of devil's claw extracts, adverse events occurred at a rate of about three percent and did not exceed the rate of those experienced with placebo. Long-term use appears to be safe and without toxicity.<sup>32</sup>

### Warnings/Contraindications

Patients with duodenal ulcers should probably avoid using devil's claw due to its effect on gastric pH.<sup>18</sup> Because of reported oxytocic properties, devil's claw extracts are contraindicated during pregnancy.<sup>18</sup>

### Dosage

Devil's claw extracts can be administered in several forms; dosage varies with each, depending on concentration of active constituents present. The following are typical dosages used historically and clinically.<sup>33</sup>

Dried Root: 0.5-1.0 g dissolved in water given orally three times daily for appetite stimulation and stomach upset.

Dried root powder (tablet or capsule): 1,800-2,400 mg (50-100 mg harpagoside) daily for arthritis and musculoskeletal pain and inflammation.

Crude aqueous root extract: 2-9 g daily for low-back pain and osteoarthritis.

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