Devil's Claw

Species (Family)

Harpagophytum procumbens DC. (Pedaliaceae)

Synonym(s)

Harpagophytum, Grapple Plant, Wood Spider

Part(s) Used

Secondary root tuber

Pharmacopoeial and Other Monographs

BHC 1992[G6]
BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
ESCOP 1996[G52]
Martindale 32nd edition[G43]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]

Legal Category (Licensed Products)

Devil's claw is not included in the GSL.[G37]

Constituents[G2,G6,G62]

Carbohydrates Fructose, galactose, glucose and *myo*-inositol (monosaccharides), raffinose, stachyose (46%) and sucrose (oligosaccharides).[1]

Iridoids Harpagide, 8-O-(*p*-coumaroyl)-harpagide, harpagoside, procumide, 6′-O-(*p*-coumaroyl)-procumbide, and procumboside (glucosides).[2] Pharmacopoeial standard: not less than 1.2% harpagoside, calculated with reference to the dried drug.[G15,G25]

Phenols Acetoside and isoacetoside (glycosides), and a bioside.[3]

Other constituents Amino acids and flavonoids (kaempferol, luteolin).

Other plant parts The flower, stem and ripe fruit are reported to be devoid of harpagoside; the leaf contains traces of iridoids.[4]

Food Use

Devil's claw is not used in foods.

Herbal Use

Devil's claw is stated to possess anti-inflammatory, antirheumatic, analgesic, sedative and diuretic properties. Traditionally, it has been used as a stomachic and a bitter tonic, and for arthritis, gout, myalgia, fibrositis, lumbago, pleurodynia and rheumatic disease.[G2,G6,G7,G8,G32,G64] Modern use of devil's claw is focused on its use in the treatment of rheumatic and arthritic conditions, and low back pain.

Dosage

Painful arthrosis and tendonitis

1.5–3 g dried tuber as a decoction, three times daily; 1–3 g drug or equivalent aqueous or hydroalcoholic extracts;[G52] liquid extract 1–3 mL (1 : 1, 25% ethanol) three times daily.[G6]

Loss of appetite or dyspepsia

Dried tuber 0.5 g as a decoction, three times daily.[G6]

Tincture 1 mL (1 : 5, 25% ethanol) three times daily.[G6]

Clinical trials of devil's claw root extracts for the treatment of low back pain have tested doses ranging from 600 to 2400 mg daily, orally, in two or three divided doses (equivalent to up to 100 mg harpagoside (depending on the concentration of the extract)).[5–7] In a clinical trial in osteoarthritis, participants received capsules containing powdered cryoground devil's claw root 2610 mg daily.[8] Other clinical trials in arthrosic conditions have used daily doses of devil's claw of 2.4 g dried tuber and 2.46 g hydroalcoholic extract.[9] Clinical trials in various rheumatic conditions have used daily doses of devil's claw of 0.75–2 g dried tuber and 1.23 g aqueous extract in two or three divided doses.[9]

Pharmacological Actions

The active constituents of devil's claw are widely held to be the iridoid glucosides although, of these, it has not been definitively established whether harpagoside is the most important pharmacologically active constituent of the whole extract. Other compounds present in the root may contribute to the pharmacological activities of devil's claw.[9,10] It has also been suggested that harpagogenin, formed by *in vivo* acid hydrolysis of harpagoside, may have biological activity.[11]

In vitro and animal studies

Animal studies using aqueous extracts of devil's claw have suggested that the extract may be inactivated by passage through the acid environment of the stomach.[10,12] One study compared the anti-inflammatory activities of aqueous devil's claw extract administered by different routes. Intraperitoneal and intraduodenal administration led to a significant reduction in the carrageenan-induced rat paw oedema test, but there was no effect following oral administration.[12] In another study, aqueous devil's claw extract pretreated with hydrochloric acid to mimic acid conditions in the stomach showed no activity in pharmacological models of pain and inflammation.[10]

Transformation of the iridoids harpagide, harpagoside and 8-*O*-(*p*-coumaroyl)-harpagide into the pyridine monoterpene alkaloid aucubinine B, chemically or by human intestinal bacteria *in vitro*, has been documented.[13,14] However, it is not known if aucubinine B is formed *in vivo* by intestinal bacteria and, therefore, whether it contributes to the pharmacological activity of devil's claw.[14]

Animal studies of the anti-inflammatory activity of devil's claw have reported conflicting results. Activity differs depending on the route of administration of devil's claw, and the model of inflammation, whether acute or subacute.

Weak anti-inflammatory activity has been reported in rats following intravenous administration of devil's claw extract.[15] Anti-inflammatory activity of harpagoside has been demonstrated in experimental models, including the croton oil-induced granuloma pouch test, and for harpagogenin, the aglucone of harpagoside, in the croton oil-induced granuloma pouch test and in formalin-induced arthritis in rats.[16] Dried aqueous extract of devil's claw administered by intraperitoneal injection demonstrated significant activity in the carrageenan-induced oedema test in rats, an acute model of inflammation.[10] The effect on oedema was dose dependent for doses of devil's claw extract 100–400 mg/kg, and reached a maximum 3 hours after carrageenan injection. Other studies in rats have reported significant reductions in oedema using the same model following pretreatment with intraperitoneal[12,17] and intraduodenal, but not oral, dried aqueous extract of devil's claw.[12] Other studies have reported that dried aqueous extract of devil's claw administered orally had no effect on carrageenan- or *Mycobacterium butyricum*-induced oedema in rat paw.[18,19] In addition, oral dried aqueous extract of devil's claw had no significant effect in adjuvant-induced arthritis in rats.[18] By contrast, in these studies, both indomethacin and aspirin displayed significant anti-inflammatory activity.[18,19]

Analgesic activity has also been documented for devil's claw in animal studies. Pretreatment with dried aqueous devil's claw extract at doses of 100 mg/kg and above, administered intraperitoneally, resulted in peripheral analgesic activity demonstrated by a significant reduction in the number of writhings induced by acetic acid in mice.[10] However, no effect was observed in the hotplate test, indicating a lack of central analgesic activity with devil's claw extract. The peripheral analgesic properties of intraperitoneal dried aqueous extract of devil's claw have been confirmed in other studies for doses of 400 mg/kg and above.[17] These studies also reported peripheral analgesic and anti-inflammatory properties for the related species *Harpogophytum zeyheri*.[17]

A clear mechanism of action for the purported anti-inflammatory effects of devil's claw has yet to be established. *In vitro*, devil's claw (100 mg/mL) had no significant effect on prostaglandin (PG) synthetase activity, whereas indomethacin (316 μg/mL) and aspirin (437 μg/mL) caused 50% inhibition of this enzyme.[19] In other *in vitro* studies in human whole blood samples, devil's claw extracts and fractions of extracts were tested for their effects on thromboxane B_2 (TXB_2) and leukotriene (LT) biosynthesis.[20] TXB_2 is an end-product of arachidonic acid metabolism by the cyclooxygenase 1 (COX-1) pathway. Inhibition appeared to be dependent on the harpagoside content of the extracts or fractions.[20] Harpagoside (100 μmol/L), but not harpagide (100 μmol/L), inhibited calcium ionophore A23187-stimulated release of TXB_2 from human platelets.[21] However, harpagoside and harpagide had no significant inhibitory effect on calcium ionophore A23187-stimulated release of PGE_2 and LTC_4 from mouse peritoneal macrophages.[21] *In vitro* inhibition of tumour-necrosis-factor-α (TNF-α) synthesis in lipopolysaccharide-stimulated human monocytes by a hydroalcoholic

extract of devil's claw (SteiHap 69) has also been documented.[22]

Crude methanolic extracts of devil's claw have been shown to be cardioactive *in vitro* and *in vivo* in animals. A protective action against ventricular arrhythmias induced by aconitine, calcium chloride, epinephrine (adrenaline)/chloroform and reperfusion has been reported for devil's claw given intraperitoneally or added to the reperfusion medium.[23,24] The crude extract was found to exhibit greater activity than pure harpagoside.[24] In isolated rabbit heart, low concentrations of a crude methanolic extract had mild negative chronotropic and positive inotropic effects,[23] whereas high concentrations caused a marked negative inotropic effect with reduction in coronary blood flow.[23] In anaesthetised dogs, harpagoside administered orally by gavage caused a decrease in mean aortic pressure and arterial and pulmonary capillary pressure.[25]

In vitro, harpagoside has been shown to decrease the contractile response of smooth muscle to acetylcholine and barium chloride on guinea-pig ileum and rabbit jejunum.[26] Harpagide was found to increase this response at lower concentrations, but antagonised it at higher concentrations.[26] On the basis of these studies in isolated smooth muscle, it was suggested that the constituents of devil's claw may influence mechanisms regulating calcium influx.[26]

Methanolic extracts have also exhibited hypotensive properties in normotensive rats, causing a decrease in arterial blood pressure following oral doses of 300 mg/kg and 400 mg/kg body weight.[23]

Devil's claw extracts possess weak antifungal activity against *Penicillium digitatum* and *Botrytis cinerea*.[27]

Clinical studies

Pharmacokinetics There is little published information on the pharmacokinetics of devil's claw extract in humans. A pharmacokinetic study involving a small number of healthy male volunteers ($n = 3$) measured plasma harpagoside concentrations after oral administration of devil's claw extract (WS1531 containing 9% harpagoside) 600, 1200 and 1800 mg as film-coated tablets.[20] Maximal plasma concentrations of harpagoside were reached after 1.3–1.8 hours, and were 8.2 ng/mL and 27.8 ng/mL for doses of harpagoside of 108 and 162 mg, respectively (corresponding to 1200 and 1800 mg devil's claw extract, respectively). Other studies involving small numbers of healthy male volunteers indicated that the half-life ranged between 3.7 and 6.4 hours. Other results suggested that there may be low oral absorption or a considerable first-pass effect with devil's claw extract, although this needs further investigation.[20]

Pharmacodynamics A study involving healthy volunteers investigated the effects on eicosanoid production of orally administered devil's claw (four 500-mg capsules of powder, containing 3% glucoiridoids, daily for 21 days).[28] No statistically significant differences on PGE_2, TXB_2, 6-keto-$PGF_{1\alpha}$ and LTB_4 were observed following the period of devil's claw administration, compared with baseline values. By contrast, in a subsequent study involving whole blood samples taken from healthy male volunteers, a biphasic decrease in basal cysteinyl-leukotriene (Cys-LT) biosynthesis, compared with baseline values, was observed following oral administration of devil's claw extract (WS1531 containing 9% harpagoside) 600, 1200 and 1800 mg as film-coated tablets.[20]

Therapeutic activity The efficacy and effectiveness of devil's claw has been investigated in more than 10 clinical studies involving patients with rheumatic and arthritic conditions, and low back pain.[9,29] These studies have involved different methodological designs, including several uncontrolled studies, and different preparations of devil's claw, including crude drug and aqueous extracts. These studies have been summarised elsewhere,[9,29,G56] and several are discussed in detail below.

A randomised, double-blind, placebo-controlled study involving 118 patients with acute exacerbations of chronic low back pain investigated the effects of devil's claw extract 800 mg three times daily (equivalent to 50 mg harpagoside daily) for four weeks.[7] There was no statistically significant difference between the devil's claw and placebo groups in the primary outcome measure – consumption of the opioid analgesic tramadol over weeks 2–4 of the study – among the 109 patients who completed the study. This was an unusual choice of primary outcome measure as it gives no direct indication of the degree of pain experienced by participants. There was a trend towards improvement in a modified version of the Arhus Low Back Pain Index (a measure of pain, disability and physical impairment) for devil's claw recipients compared with placebo recipients, although this did not reach statistical significance. A greater proportion of patients in the devil's claw group were pain-free at the end of the study, although this was only a secondary outcome measure.

On the basis of these findings, a subsequent randomised, double-blind, placebo-controlled trial involving 197 patients with exacerbations of low back pain tested the effects of two doses of devil's

claw (WS1531) extract against placebo.[6] Participants received devil's claw extract 600 mg or 1200 mg daily (equivalent to 50 mg and 100 mg harpagoside daily, respectively), or placebo, for four weeks. There was a statistically significant difference ($p = 0.027$) between devil's claw and placebo with respect to the primary outcome measure – the number of patients who were pain-free without tramadol for at least five days during the last week of the study. However, numbers of patients who were pain-free were low (3, 6 and 10 for placebo, devil's claw 600 mg daily and devil's claw 1200 mg daily, respectively). Furthermore, this is a non-standard outcome measure. Arhus Low Back Pain Index scores improved significantly in all three groups, compared with baseline values, although there was no statistically significant difference between groups.

In a randomised, double-blind, placebo-controlled study involving patients with non-specific low back pain, 65 participants received devil's claw extract (LI-174, Rivoltan), or placebo, 480 mg twice daily (equivalent to 24 mg harpagoside daily) for four weeks.[5] There was a significant improvement ($p < 0.001$) in visual analogue scale (VAS) scores for muscle pain in the devil's claw group, but not the placebo group, compared with baseline values, after two and four weeks' treatment. Differences in VAS scores between the two groups were statistically significant after four weeks' treatment ($p < 0.001$). Significant differences between the two groups in favour of devil's claw after four weeks' treatment were also observed with several other parameters, including muscle stiffness and muscular ischaemic pain.

A randomised, double-blind trial has compared the efficacy of devil's claw extract with that of diacerein in 122 patients with osteoarthritis of the knee and hip.[8] Participants received powdered cryo-ground devil's claw (Harpadol) 2.61 g daily, or diacerein 100 mg daily, for four months.

VAS scores for spontaneous pains improved significantly in both groups, compared with baseline values, and there were no differences between devil's claw and diacerein with respect to VAS scores.

In a placebo-controlled study involving 89 patients with rheumatic complaints, devil's claw recipients (who received powdered crude drug 2 g daily for two months) showed significant improvements in sensitivity to pain and in motility (as measured by the finger-to-floor distance), compared with placebo recipients.[30]

Open, uncontrolled studies involving patients with rheumatic and arthritic disorders report conflicting results for the effectiveness of devil's claw. One study involved 13 patients with arthritis, rheumatoid arthritis or psoriatic arthropathy who received tablets of devil's claw aqueous extract 1.23 g daily for six weeks in addition to their conventional drug treatment. There were no significant changes after 6 and 12 weeks in pain, early morning stiffness, and the Ritchie Articular Index (a method of assessing joint tenderness), compared with baseline values.[31] By contrast, other open uncontrolled studies of devil's claw involving patients with rheumatic disorders (who received devil's claw powder 1.5 g daily for 60 days)[32] or arthrosis (who received devil's claw aqueous extract, containing 2.5% iridoid glycosides, 3–9 g daily for 6 months)[33] reported improvements in pain and 'complaints' at the end of the treatment period compared with baseline values.

Another study involved 45 patients with osteo- or rheumatoid arthritis who received devil's claw root extract 2.46 g daily for two weeks in addition to non-steroidal anti-inflammatory drug (NSAID) treatment, followed by devil's claw extract alone, for four weeks.[34] It was reported that there were no statistically significant changes in pain intensity and duration of morning stiffness during the period of treatment with devil's claw extract alone. In subgroups of patients with rheumatoid arthritis and those with osteoarthritis, small decreases were observed in concentrations of C-reactive protein and creatinine, respectively. The design of this study in terms of the treatment regimen (NSAID followed by devil's claw extract without a washout period), however, renders the results difficult to interpret.

Side-effects, Toxicity

Randomised, placebo-controlled trials involving patients with rheumatic and arthritic conditions who have received devil's claw extracts or powdered drug at approximately recommended doses for four weeks have reported mild, transient gastrointestinal symptoms (such as diarrhoea, flatulence) in a small proportion (less than 10%) of devil's claw recipients.[5–7] No serious adverse events were reported, although one patient withdrew from one study because of tachycardia.[7] In an open, uncontrolled study, one patient withdrew after four days' treatment with devil's claw aqueous extract 1.23 g daily because of several symptoms, including frontal headache, tinnitus, anorexia and loss of taste.[31]

In a randomised, controlled trial comparing devil's claw extract with diacerein in patients with osteoarthritis, numbers of patients ending the study prematurely because of suspected adverse drug reactions were 8 and 14 for devil's claw and diacerein recipients, respectively.[8] In total, 26 diacerein

recipients and 16 devil's claw recipients reported one or more adverse events ($p = 0.042$). The numbers of adverse events attributed to the treatment was significantly lower for devil's claw than for diacerein (10 versus 21; $p = 0.017$). The most frequently reported adverse event, diarrhoea, occurred in 8.1% and 26.7% of devil's claw and diacerein recipients, respectively.

There is an isolated report of conjunctivitis, rhinitis and respiratory symptoms in a 50-year-old woman who had experienced chronic occupational exposure to devil's claw.[35]

The mechanism of action of devil's claw remains unclear, in particular, whether it has significant effects on the mediators of acute inflammation. Data from *in vitro* and clinical studies in this regard do not yet give a clear picture (*see In vitro* and animal studies and Clinical studies, Pharmacodynamics). It has been stated that adverse effects associated with the use of NSAIDs are unlikely to occur with devil's claw, even during long-term treatment.[G50,G52] While there are no documented reports of gastrointestinal bleeding or peptic ulcer associated with the use of devil's claw, the latter statement requires confirmation. Use of devil's claw in gastric and duodenal ulcer is contraindicated, although this appears to be because of the drug's bitter properties.[G50]

Acute and subacute toxicity tests in rodents have demonstrated low toxicity of devil's claw extracts. In a study in mice, the acute oral lethal dose (LD) LD_0 and LD_{50} were greater than 13.5 g/kg body weight.[19] In rats, clinical, haematological and gross pathological findings were unremarkable following administration of devil's claw extract 7.5 g/kg by mouth for seven days. Hepatic effects (liver weight, and concentrations of microsomal protein and several liver enzymes) were not observed following oral treatment with devil's claw extract 2 g/kg for seven days.[19] Other studies in mice have reported acute oral acute intravenous LD_0 values of greater than 4.64 g/kg and greater than 1 g/kg, respectively.[15] For an extract containing harpagoside 85%, acute oral LD_0, acute intravenous LD_0 and acute intravenous LD_{50} values were greater than 4.64 g/kg, 395 mg/kg and 511 mg/kg, respectively.[15]

Contra-indications, Warnings

Devil's claw is stated to be contra-indicated in gastric and duodenal ulcers,[G3,G52] and in gallstones should be used only after consultation with a physician.[G3] On the basis of pharmacological evidence of devil's claw's cardioactivity, the possibility of excessive doses interfering with existing treatment for cardiac disorders or with hypo/hypertensive therapy should be considered.

Pregnancy and lactation It has been stated that devil's claw has oxytocic properties,[36] although the reference gives no further details and the basis for this statement is not known. In addition, there is no further evidence to substantiate the statement. However, given the lack of data on the effects of devil's claw taken during pregnancy and lactation, its use should be avoided during these periods.

Pharmaceutical Comment

The chemistry of devil's claw has been well documented. The iridoid constituents are thought to be responsible for the reputed anti-inflammatory activity of devil's claw, although it is not known precisely which of these are the most important for pharmacological activity, and the importance of other compounds. There is conflicting evidence from *in vitro*, animal and human studies regarding the anti-inflammatory activity of devil's claw and possible mechanisms of action. Several randomised trials using devil's claw extracts standardised on harpagoside content have reported superiority over placebo for some aspects of low back pain and rheumatic complaints. However, some studies used non-standard outcome measures and carried out several post-hoc analyses. Further studies have used recognised, predefined outcome measures to establish the therapeutic value of standardised devil's claw extracts in patients with arthritic and rheumatic conditions.

On the basis of randomised controlled trials involving patients with arthritic and rheumatic disorders, devil's claw extracts appear to have a favourable short-term adverse effect profile when taken in recommended doses. Mild, transient gastrointestinal effects, such as diarrhoea and flatulence, may occur. Chronic toxicity studies and clinical experience with prolonged use are lacking, so the effects of long-term use are not known. On this basis, and in view of the possible cardioactivity of devil's claw, devil's claw should not be used for long periods of time at doses higher than recommended. Further studies involving large numbers of patients are required.

Some commercial extracts of devil's claw root may have been prepared not only from the roots of *H. procumbens*, but also from the roots of *H. zeyheri*, which are similar macroscopically.[17] However, the two species differ in the concentration of the constituents harpagoside and 8-*O*-*p*-coumaroyl-harpagide. On this basis it has been stated that the species can be distinguished chemically by determining the ratio harpagoside:8-*O*-*p*-coumaroyl-harpagide. The ratio

is stated to be near one for *H. zeyheri* and between 20 and 38 for *H. procumbens* which has a low 8-*O*-*p*-coumaroyl-harpagide content.[17] While this ratio may be sufficient for chemotaxonomic differentiation, it may not be adequate for quality control.[37] Other studies have demonstrated that the harpagoside content of several powdered dry extracts of devil's claw from different manufacturers varies, and that each extract has a unique profile of other constituents.[38]

References

See also General References G2, G3, G5, G6, G9, G15, G25, G31, G32, G36, G43, G49, G50, G52, G56, G62 and G64.

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