Review

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A Comprehensive Systematic Pharmacological Review on *Harpagophytum procumbens* DC. (Devil's claw)

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Abstract. Popularly known as Devil's claw, *Harpagophytum procumbens* DC. (Pedaliaceae) is native to the Kalahari savannas of southern Africa and Namibia. It has been widely used to treat rheumatism. Its secondary tuberous roots contain iridoid glycosides (procumbide, procumboside, harpagoside) as the active principles. This species seems to stimulate migration of interleukins and leucocytes to painful and inflamed joint areas. The drug is indicated for osteoarthritis, degenerative disease of the joints and arthritic processes. Although, *in vivo* pharmacological studies have been carried out in different animal models, with different methodologies and different types of extracts, producing contradictory results, recent clinical studies have shown that *H. procumbens* could be a valid alternative to conventional drugs, especially in the treatment of lumbar pain.

Keywords: *Harpagophytum procumbens*, osteoarthritis, joint ailments, irridoid glycosides

Introduction

Harpagophytum procumbens DC. (Pedaliaceae), commonly known as Devil's claw, is a perennial herbaceous plant native to the arid steppes. It is virtually restricted to the southern part of the African continent, occurring mainly in South Africa, Namibia and Botswana, where it is known locally not only as Devil's claw, but also as grapple plant, wood spider and harpago.

H. procumbens occurs in areas with low annual rainfall (150-500 mm/year) on deep sandy soils of the Kalahari. It is found in savannah vegetation dominated by *Acacia* sp., but does not compete well with grasses. In fact, *H. procumbens* is most often found in areas where grass cover is less than 25% and where the herb cover is less than 20%. It is most abundant in open, trampled and overgrazed areas (Hachfeld, 2002), where it has clumped distribution (Raimondo and Donaldson, 2002).

In an area between the northern Cape and north west provinces of south Africa, densities were estimated at 50 plants/ha in the dense grasses of a well managed farm, 150 plants/ha on unharvested overgrazed communal land near the village of Madibeng and only 11 plants/ha on harvested communal land near Madibeng (Stewart and Cole, 2005).

H. procumbens is a weedy, tuberous plant with creeping annual stems up to 2 m long. The above-ground stems emerge after the first rains and die back in winter and during droughts. Stems grow from a persistent succulent primary tuber, called "mother tuber" by harvesters, the tap root of which can extend to a depth of 2 m. A number of secondary tubers, called "babies", emanate from the primary tuber via fleshy roots. The secondary tubers are up to 25 cm long and 6 cm thick (Schneider, 1997). The secondary tubers contain up to 46% stachyose, a photosynthetic storage product, which is thought to be an adaptation to drought conditions (Stewart and Cole, 2005).

The leaves are opposite, blue-green and usually have several lobes. The flowers are tubular and deep mauve-pink with yellow and white throats. They are open for one day and are pollinated by bees (Von Willert and Sanders, 2004). The flat woody capsules, which give the plant its scientific and common names, bear two rows of curved appendages studded with curved spines (*Harpagophytum* literally means grapple hook plant). The fruit is dispersed by animals (Ernst *et al*., 1988), as it attaches readily to fur and wool, and is also wind dispersed to some degree, as a breeze can carry a fruit some distance from the parent plant.

Seeds have a high degree of dormancy (Stewart and Cole, 2005; De Jong, 1985), which may be an adaptation to drought (Ernst *et al*., 1988). Ernst *et al*. (1988) estimated that only 20-25% of the seeds in a fruit establish soil contact in a given year, suggesting that this may be an adaptation to animal (or wind) dispersal. The same authors also estimated that seeds may remain viable in the seed bank for more than 20 years, by virtue of their low respiration rate.

The thick, fleshy, tuberous secondary tap roots of *H. procumbens* are usually dried and used in south African traditional medicine.

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Since its introduction to Europe from Africa in the early 1900s, dried tubers of the plant have been used to restore appetite, relieve heartburn and reduce pain and inflammation (Soulimani *et al.*, 1994; Costa De Pasquale *et al*., 1985; Occhiuto *et al*., 1985; Grahame and Robinson, 1981). There is increasing evidence to suggest that Devil's claw tubers may help relieve the pain and inflammation of arthritis and other painful disorders, though the mechanism of action is not yet well understood (Baghdikian *et al*., 1997; Lanhers *et al*., 1992; Whitehouse *et al*., 1983).

H. procumbens secondary root is used for an array of human ailments in the form of decoctions, infusions, tinctures and extracts. It has an ethnomedical reputation for efficacy in anorexia, indigestion, diabetes mellitus, hypertension, gout, fevers, skin cancer, infectious diseases, allergies, osteoarthritis, fibrositis and rheumatism, being particularly effective in small joint diseases.

When taken on a regular daily basis, it has a subtle laxative effect. Small doses of the plant's root extract are used for menstrual cramps, while higher doses help placental expulsion. Devil's claw is also used post partum as an analgesic and to keep the uterus contracted. The dry, powdered tuberous root of the plant is used directly as a wound dressing or mixed with animal fat or vaseline as a wound-healing and burn-healing ointment. Traditional ointments and creams of *H. procumbens* are applied topically for minor muscular aches and pains, and to painful joints. Traditional health practitioners of south Africa have also claimed that *H. procumbens* secondary root extract is useful for the treatment, management and/or control of epilepsy and childhood convulsions.

Extracts of *H. procumbens* are currently the focus of research as a potential therapeutic agent to treat rheumatoid arthritis and pain (Ernest and Chrubasik, 2000; Fox, 2000; Leblan *et al.*, 2000; Chrubasik *et al*., 1999).

There is increasing evidence to suggest that they may help relieve the pain and inflammation of arthritis and other painful disorders, although their mechanism of action (Baghdikian *et al*., 1997; Lanhers *et al*., 1992; Whitehouse *et al*., 1983) is not yet well understood and the active principles have not been identified unequivocally.

In this review we consider the botanical description, ethnopharmacology and phytochemistry of *H. procumbens*. Biological activity, pharmacology and toxicity are discussed and the results of recent clinical studies are presented as a basis for evaluating *H. procumbens* as an adjuvant in the treatment of pain and osteoarthritis.

Chemical constituents. The major class of compounds with therapeutic activity are iridoids, concentrations of which may vary from 0.5 to 3% in the dry tuber. Other parts of the plant (flowers, stems and ripe fruit) contain no iridoids or only traces (leaves) (Capasso *et al*., 2006). The main iridoids in *H. procumbens* are harpagoside, harpagide and procumbide. Harpagoside and its congeners occur as two isomers in mutual equilibrium: an open form with two free aldehyde groups and a cyclic form by virtue of an enol-ether bridge (Fig. 1). The cyclic configuration is stable when the molecule is gylcosylated (Van Haelen *et al.*, 1983). Hydrolysis of iridoids produces genins having a structure similar to that of certain prostaglandins.

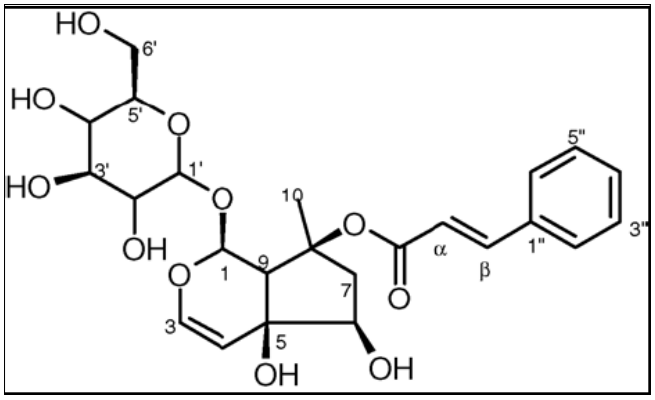

Fig. 1. Structure of harpagoside (8-O-E-cinnamoyl-harpagide).

The species *H. zeyehri*, the secondary roots of which are difficult to distinguish by microscope examination, has a different content and distribution of iridoids. Determination of the ratio of harpagoside and 8-*p*-coumaroyl-harpagide content has been proposed as a unequivocal chemotaxonomic method of differentiating *H. procumbens* from *H. zeyehri* (Baghdikian *et al.*, 1997).

In a recent study a thorough investigation of Devil's claw tubers led to the isolation of eleven iridoid glycosides, two of which were new (Qi *et al*., 2006).

Harpagoside and other iridoids are substances with a bitterness value of up to 120. Limits to bitterness value have not been imposed, but a minimum of 1.8% of amaroids is sufficiently high. Standardisation of extracts of the drug is based on harpagoside concentration (Bisset and Wichtl, 2001).

Besides iridoids, phytochemical studies on secondary roots of grapple plant have revealed a quinone (harpagoquinone), some aromatic acids (cinnamic acid and chlorogenic acid) and some flavonoids (kaempferol, kaempferide, fisetine and luteoline). Pentacyclic triterpenic acids (oleanolic acid and ursolic acid) and small quantities of a resin and an essential oil have also been found. Sterols, fats, hydrocarbons and

holosides have also been detected (Van Haelen, 1986). Two new phenolic glycosides (acteoside and isoacteoside) were identified by Burger *et al.* (1987). Major quantities of carbohydrates (stachyose) and several tetrahalosides bearing glucose and sucrose molecules have also been found. The presence of stachyose indicates a chemotaxonomic relationship of the Pedaliaceae family with the Lamiaceae and Verbenaceae (Van Haelen, 1986).

Pharmacology. Commercial preparations of Harpago contain 1.4-2.0% of harpagoside. The results of research into this species are difficult to compare and interpret, mainly because of the variety of extracts used. Methanolic extract and aqueous extract were the most common but differed in harpagoside content.

The World Health Organisation (WHO, 2007) lists Devil's claw for rheumatic pain, loss of appetite and dyspepsia and as adjuvant for degenerative disease of the locomotor system.

In vitro experiments. Recent *in vitro* studies, well listed in the review published by Grant *et al*. (2007), indicate that grapple plant preparations may interact with the inflammation cascade, including synthesis and activity of cytokines. Aqueous extract has been found to suppress expression of cyclooxygenase-2 (COX2), stimulated by lipopolysaccharides (LPS) and nitric oxide synthetase, in murine L929 fibroblasts. Lipopolysaccharides trigger a wide series of cell responses that play a major role in the pathogenesis of inflammatory reactions, including activation of inflammatory cells and production of cytokines and other mediators. Prostaglandin E2, synthesized by arachidonic acid via the cyclooxygenase enzyme complex, is a key mediator. The cyclooxygenase-1 (COX1) isoform is constitutional whereas COX2 is only expressed in response to proinflammatory signals, such as those of cytokines and bacterial endotoxin LPS. COX2 produces a large quantity of prostaglandin E2 which causes inflammation (Mitchell *et al*., 1995).

Nitric oxide (NO), synthesized from L-arginine by NO-synthetase (NOS), plays a major role in the regulation of many physiological processes. The various isoforms of NOS can be classified as inducible (iNOS), endothelial (eNOS) and neuronal NOS (nNOS). The first of the three is involved in inflammatory phenomena.

The anti-inflammatory and analgesic effect of aqueous extract of Devil's calw was recently confirmed (Jang *et al*., 2003) by assessing cell viability (MTT test) and expression of COX2 and iNOS (quantity of nitrite in cell supernatant) by reverse transcription polymerase chain reaction (RT-PCR) in L929 fibroblasts stimulated with LPS. The suppression of COX2 and iNOS expression found inhibited prostaglandin E2 synthesis.

Another study by Kaszkin *et al*. (2004) evaluated the utility of Harpago extract in the treatment of inflammatory kidney disease. Two extracts containing 8.9% (ex1) and 27% (ex2) harpagoside were tested for effects on IL-1-induced production of NO and on regulation of transcription of iNOS in rat renal cells. An 80% dose-dependent reduction in the formation of NO, due to inhibition of iNOS expression, was observed. A reduction in activity of the iNOS promotor of nuclear translocation of NF-kB was also found, indicating that the extracts impaired transcriptional activation of iNOS. This effect was confirmed by Huang *et al*. (2006) who demonstrated inhibition of mRNA levels induced by LPS and COX2 and iNOS expression in human hepatocarcinoma cells. Harpagoside also blocked activity of the NF-kB promoter stimulated by LPS in a dose-dependent manner in RAW264.7 cells. The results of the study show that inhibition of COX2 and iNOS expression by harpagoside involves suppression of NF-kP activation, resulting in inhibition of the inflammatory process and associated pain.

Other extracts containing lower concentrations of harpagoside did not cause this inhibition. Harpagoside alone only works at concentrations in the range 0.3-1.0 mg/ml which are much higher than those of total extracts, and a preparation completely devoid of the molecule strongly inhibited iNOS expression, indicating that other constituents are also involved in its activity. An extract also had a strong antioxidant effect which harpagoside does not have (Rindone, 2006).

A recent study investigated the mechanism of action of harpagoside, using human HepG2 hepatocarcinoma and RAW 264.7 macrophage cell lines. Harpagoside inhibited LPS-induced mRNA levels and protein expression of COX2 and inducible nitric oxide in HepG2 cells. These inhibitions appeared correlated with suppression of NF-kB activation by harpagoside, suggesting that inhibition of expression of COX2 and iNOS by harpagoside involves suppression of NF-kB activation, thereby inhibiting downstream inflammation and pain (Huang *et al*., 2006). These results show that certain extracts of Devil's claw could be an interesting source of drugs for treating glomerular and other inflammatory diseases.

Other *in vitro* studies have shown a significant decrease in synthesis of cell membrane degradation enzymes in isolated chondrocytes and dose-dependent inhibition of elastase. Inflammatory diseases of the joints, such as rheumatoid arthritis and osteoarthritis are characterised by loss of joint cartilage related to an imbalance between synthesis and breakdown of

the cartilagionous extracellular matrix. These diseases are accompanied by elevated induction of cytokines such as IL-1b and TNF-a. Increased release of cytokines leads to increased production of degradation enzymes, such as metalloproteases (MMPs). A significant reduction in MMP synthesis was recently demonstrated in human chondrocytes stimulated with IL-1b. Two extracts were used. The first contained 210 mg and the other 480 mg of dry extract; the latter was more effective (Schulze-Tanzil *et al*., 2004). The effect of Devil's claw on arthritis could be due to its capacity to suppress MMP production by inhibiting synthesis of proinflammatory cytokines.

As far as leucocyte elastase is concerned, aqueous extract showed rather weak, dose-dependent inhibitory activity (Boje *et al*., 2003).

A study by Fiebich *et al*. (2001) on *H. procumbens* extract SteiHap 69 (Steiner *Harpagophyton procumbens* extract 69) demonstrated its close-dependent anti-inflammatory effects by preventing the LPS-induced synthesis of tumour-necrosis factor α (TNF∗) by human monocytes. However, harpagide and harpagoside had no effect on LPS-induced TNF∗ release.

In vivo experiments. *Anti-inflammatory and analgesic activity*. At first sight, the results of the few pharmacological studies conducted on *H. procumbens* seem contradictory, since they were based on different methods and on different animal models (acute and subacute inflammation) with different extracts administered by different routes (Bruneton, 2002). Recent results show that aqueous extract administered intraperitoneally at doses from 100 to 400 mg/kg is active in a dose-dependent manner on carrageenan-induced edema in rat paws. The same extract was inactive when administered orally, presumably due to gastric breakdown of the active principle. The extract was also inactive when given parenterally if previously treated with acids. It was active when administered intra-duodenally.

Under the same experimental conditions, harpagoside was inactive, but was found to promote peripheral analgesic activity of the aqueous extract (100 mg/kg i.p.). The authors suggested research into formulations that could improve the bioavailability of oral harpagoside. In a pilot study, plasma concentrations of 4 ng/ml and 15 ng/ml harpagoside were found 15 min and 2 h, respectively, after administration of 600 mg extract containing 50 mg harpagoside (Loew *et al*., 2001). However, the role of harpagoside remains controversial. Oral administration of aqueous extract of *Scrophularia frutescens* DC. (Scrophularieceae) to rats is reported to have antiinflammatory activity on carrageenan-induced edema that does not seem related to harpagoside (Garciá *et al*., 1996).

Adjuvant-induced arthritis is often used as a model of chronic and subchronic inflammation and is important in the study of pharmacological control of inflammatory proceses and in assessing the antiinflammatory and analgesic properties of drugs. One reason for the widespread use of this model has to do with the strong correlation between efficacy of drugs in this model and efficacy in humans (rheumatoid arthritis). In a study aimed at investigating the antiinflammatory effects of *H. procumbens*, Andersen *et al*. (2004) induced arthritis by acute and chronic treatment. A single administration of three doses of extract (25, 50 and 100 mg/kg) had some analgesic effect, measured on the basis of response to thermal stimuli (hot plate test). The same effect was observed after chronic administration.

Kundu *et al*. (2005) reported a study of the antiinflammatory mechanism of Devil's claw. Methanol extract was tested for effects on expression and COX2 induced by TPA (a phorbol ester) in mouse skin. Topical application of the extract inhibited directly-induced COX2 expression, decreasing the catalytic activity of extracellular signal-regulated protein kinase (ERK), which regulates activation of transcription factors that mediate COX2 induction. The extract inhibited activation of activator protein-1 (AP1) and attenuated expression of its key component c-Fos, while nuclear factor NFB was unaffected (Kundu *et al*., 2005).

Another mechanism of action study (Na *et al*., 2004) assessed inhibition of COX2 expression induced by TPA in human mammary epithelial cells MCF10A and on mouse skin *in vivo*. Methanol extract of devil's claw inhibited binding of NFB transcription factor to DNA in MCF10A cells in a dose-dependent way. Suppression of DNA binding suggests a chemopreventive effect.

In a study, Mahomed and Ojewole (2004) evaluated the analgesic effect (hot plate and acetic acid test), antiinflammatory effect (albumin-induced edema) and antidiabetic effect (streptozotocine-induced diabetes) of aqueous extract in rats. Diclofenac (100 mg/kg i.p.) and clorpropamide were used as reference drugs. Aqueous extract (50-800 mg/kg i.p.) had a significant analgesic effect on nociceptive thermal and chemical stimulation in mice and a significant dose-dependent reduction in albumin-induced edema. The extract also caused a reduction in plasma levels of glucose in normal rats and rats with streptozotocin-induced edema. These results seem to explain popular use of this plant as an analgesic and to alleviate inflammation and diabetes in south Africa.

Clinical studies. There have not been many clinical tests on humans and their heterogeneity makes it difficult to draw conclusions. It has been demonstrated that grapple plant

alleviates pain in chronic inflammation of the joints but its efficacy seems less than that of aspirin and indomethacin (Newall *et al*., 1996). However, certain preparations of the drug and special physical exercises can be a valid alternative to synthetic drugs, especially in the treatment of lumbago.

The results of studies on *H. procumbens* are not easy to compare and interpret, mainly because of the variety of extracts used. Methanol and aqueous extracts are, however, the most widely used in these studies. In Europe, Doloteffin, extract WS 1531® and extract LI174® are used. The preparations differ in their harpagoside content.

Since *H. procumbens* has a broader mechanism of action that conventional NSAIDs, inhibiting both cyclooxygenases and lipooxygenases involved in the metabolic pathway of arachidonic acid, it has been tested clinically in certain rheumatic inflammatory diseases.

The primary end-points of the clinical trials conducted on *H. procumbens* were a reduction of inflammation and pain, as well as improved movement and mobility of patients with rheumatism. As shown by the examples that follow, the plant proved to be just as effective in reducing these parameters as certain conventional treatments with which it was compared. To assess the efficacy of *H. procumbens* in the treatment of lumbago and osteoarthritis, it is worth considering the systematic review of clinical studies by Grant *et al*. (2007), by Setty and Sigal (2005), and by Gagnier *et al*. (2004).

Searches in PubMed, Embase, Cochrane Controlled Trials Registry, Cochrane Musculoskeletal Specialized Register, Dissertation Abstracts, BIDS ISI and Cochrane Complementary Medicine Fields Specialized Register brought to light 130 references to clinical studies on *H. procumbens*. After exclusion of duplicates and articles based on inadequate qualitative criteria, 12 randomized studies were selected, four on the treatment of lumbar pain (Chrubasik *et al*., 2003, 1999, 1996), five on the treatment of osteoarthritis (Biller, 2002; Frerik *et al*., 2001; Chantre *et al*., 2000; Lecomte and Costa, 1992; Schruffler, 1980) and three on the treatment of various other forms of pain involving muscles and bones (Pugno, 2006).

Of the four studies on treatment of lumbago (total number of patients 505), two compare *H. procumbens* with placebo, one with various conventional therapies (e.g., antiinflammatory drugs, massage, physical exercise) and one with COX2 inhibitor, rofecoxib. Of the five studies on treatment of osteoarthritis (total number of patients 385), three compare the plant with placebo and two with standard drugs. All three studies on treatment of other forms of muscle and bone pain compared *H. procumbens* with placebo.

A recent study examined, whether the anti-inflammatory response to whole extract of *H. procumbens* in rats was a consequence of adrenal corticosteroid release. Carrageenan-induced inflammatory response in the hindpaws was evaluated in control, sham-operated and adrenalectomized rats. The extract was administered orally (by gavage) or intraperitoneally, 30 min prior to nociceptive stimulus. Blood samples were then collected, and the number of circulating leukocytes was estimated. The results showed that whole extract of *H. procumbens* administered intraperitoneally had an inhibitory effect on acute inflammatory response, irrespective of the participation of adrenal corticosteroids. When administered orally, the extract was ineffective (Catelan *et al*., 2006).

Lumbar pain. Chrubasik *et al*. (1997) treated 102 lumbago patients with 4500 mg/day of aqueous extract of *H. procumbens* (30 mg/day harpagoside) or with conventional NSAIDs or with physical manipulation, for 6 weeks. No significant differences in pain-free time and change in Arthus index were found between patients undergoing the three treatments.

Chrubasik *et al*. (1999) subsequently treated 197 patients with pseudoradiating and non radiating lumbago with 4500 mg/day of aqueous extract of dried tubers of *H. procumbens* (50 mg/day harpagoside), with 9000 mg/day of the same extract (100 mg/day harpagoside) or with placebo. Patients treated with either dose of extract showed an improvement in pain with respect to patients treated with placebo.

The next prospective, randomized, double-blind study by Chrubasik *et al*. (2003) was particularly interesting, because it compared the effects of commercial aqueous extract of dessicated, pulverized tubers with that of the latest generation synthetic antiinflammatory agent, rofecoxib, a selective COX2 inhibitor. The subjects were 88 patients, age 45-75 years, with at least a six-month history of rheumatic back pain, worsening in the 8 weeks prior to the study, divided into two groups of 44 patients. The first group received 2400 mg/day of extract (60 mg/day harpagoside) for 6 weeks plus one tablet/day of placebo. The second group received a tablet per day of rofecoxib (12.5 mg) and two tablets of placebo three times a day. Patients of both groups could also take up to 400 mg/day tramadol drops (2.5 mg/ml), a synthetic opioid receptor agonist.

During treatment, patients kept a diary in which they scored pain intensity on a 5 point scale (no pain, slight, moderate, strong and acute pain) and the daily dose of tramadol taken. Patients also answered a standardised questionnaire on general health, daily activities and type of pain, a questionnaire on depression (Beck Depression Inventory BDI) and a health assessment questionnaire (HAQ).

Forty-three patients in the *H. procumbens* group and 36 in the rofecoxib group completed treatment. The number of patients responding completely to therapy increased up to the fifth week, more or less in the same manner in both groups. At week 6, the total number of responses reached 17% of patients (10 patients in the *H. procumbens* group and five patients in the rofecoxib group). Comparison of the weekly mean pain scores between weeks four and six did not show significant differences in the number of patients showing 20-50% improvement in the two groups. The Arthus pain index decreased by about 10% during treatment. The greatest reduction was recorded in week 2.

Thirty-four of the 88 patients (38.6%) resorted to tramadol, 21 in the *H. procumbens* group and 13 in the rofecoxib group. Mean consumption of tramadol over 6 weeks was 230 mg in the first and 133 mg in the second group.

Fourteen patients reported side-effects on 39 occasions, 28 of which (13 in the *H. procumbens* group) could be ascribed to treatment. Gastrointestinal disorders were reported by 8 patients in the *H. procumbens* group and 9 in the rofecoxib group; in the latter, gastrointestinal effects were more severe, causing 5 patients to drop out.

Analysis of the results did not reveal any statistically significant differences in effect on lumbar pain between the two therapies. The study was completed with follow-up one year later (Chrubasik *et al*., 2005). Thirty-eight patients previously in the *H. procumbens* group and 35 in the rofecoxib group were treated daily up to 54 weeks with a dose of extract containing 60 mg harpagoside. Fifty-three patients completed 24 weeks of follow-up and 43 completed 54 weeks. No significant difference in daily pain score, resort to other analgesics, Arthus index and HAQ score was found between patients previously in the two groups. Apart from individual fluctuations, follow-up showed a slight improvement in Arthus index and HAQ with respect to the initial study. On the basis of 21,761 patient days, the percentages of patients who were pain-free, or with slight, moderate, strong or acute pain were 28, 39, 22, 8.5 and 1.5%, respectively. Three patients reported minor side-effects.

The authors concluded that maintenance therapy with *H. procumbens* in patients previously treated with the same extract or with rofecoxib produced similar effects and that long-term treatment with the extract was well tolerated.

Osteoarthritis. In 1980, Schrulffer treated 50 osteoarthritis patients with 2500 mg/day of aqueous extract of *H. procumbens* (less than 30 mg/day harpagoside) or with phenylbutazone for 30 days. Grapple plant was found to attenuate pain and improve physical condition better than phenylbutazone.

Lecomte and Costa (1992) treated 89 patients with arthritis of different joints (spine, neck, hip, knee) with powdered secondary root of *H. procumbens* (200 mg/day equivalent to 60 mg/day harpagoside) or placebo for 60 days. The Schober test showed that pain improved more in patients receiving *H. procumbens* than in those receiving placebo.

Chantre *et al*. (2000) treated 122 osteoarthritis patients with hip or knee pain with 4500 mg/day of powder of cold-dried secondary roots of grapple (equivalent to 57 mg/day harpagoside) or with the NSAID diacerein, also known as diacetylrhein, for 16 weeks. Intent-to-treat analysis showed that the plant was not less effective than the drug.

In 2001, Frerik *et al*., treated 46 osteoarthritis patients with 4500 mg/day hydroethanolic extract (Teufelskrallenextrakt LoHar 45) (60% ethanol) of *H. procumbens* (equivalent to less than 30 mg/day harpagoside) or placebo for 20 weeks. Following a specific phytotherapeutic sheme, patients also took ibuprofen; among aims of the study, there was to know the percentage of patients responding to therapy: 71% of patient taking *H. procumbens* responded to therapy compared to 41% of those on placebo. The difference was statistically significant (p=0.041) (method of statistical analysis not indicated).

In 2002, Biller, treated 78 osteoarthritis patients with knee pain with 4500 mg/day of hydroalcoholic extract of *H. procumbens* (60% alcohol; less than 30 mg/day harpagoside) or placebo for 20 weeks. Patients also took 800 mg/day ibuprofen from week 1 to week 8, and 400 mg/day from week 9 to week 16. From week 17 to week 20 they took Grapple plant alone or placebo. The end-points of the study were the percentage of patients responding to therapy, variations in the WOMAC index of pain and non-recourse to ibuprofen in weeks 17-20. Ninety percent of patients in the grapple group responded to therapy compared to 80% in the placebo group. Mean use of ibuprofen in weeks 17-20 was one tablet/day in the *H. procumbens* group and 5 tablets in the placebo group. The plant was therefore more effective than placebo.

In 2007, Chrubasik *et al*., recruited 114 patients (56 with chronic nonspecific lower back pain, 37 with osteoarthritic knee and 21 with osteoarthritic hip pain) into a survey of the effects of Doloteffins at a dose providing 60 mg harpagoside per day for up to 54 weeks. Their symptoms and well-being were monitored at 4-6 week intervals by disease-specific and generic outcome measures, and patients also kept a diary of their pain and need for rescue medication. The principal analyses were based on Intention to Treat (ITT) with Last Value Carried Forward (LOCF). Multivariate Analysis of Variance (MANOVA) indicated appreciable overall improvement during the survey,

similar in the back, knee and hip groups. In separate ANOVAs, most of individual outcome scores decreased significantly over time. Multiple regression analysis indicated that changes from baseline were independent of patient characteristics. Additional analgesic requirements (which were very modest) declined during the year of the survey. "Response during treatment" was achieved in 75% of patients, and was reflected in the percentages of those who rated the treatment "good" or "very good". Side-effects were few and minor.

In 2007 Warnock and coworkers, published a 8-week open label clinical trial to examine the effectiveness of a Devil's claw preparation (Bioforce, Scotland, United Kingdom) in the treatment of arthritis and other rheumatic conditions, such as arthritic dominant hands. A particular form of osteoarthritis is hand osteoarthritis; this form of arthritis does not seem to depend on any evident cause and mainly affects certain joints of the hand, especially the distal interphalangeal joints, which gradually develop hard swellings known as Heberden nodules, the proximal interphalangeal joints, the tumefactions of which are known as Bouchard nodules, and the metacarpal trapezium, which often becomes partly dislocated. The structural changes (reduced thickness of joint cartilage, sclerosis, subchondrial geodes and osteophyte formation) cause chronic pain and dysfunction with relapsing-remitting acute phases related to joint misalignment (distress of compartmental capsule and ligaments) and secondary synovitis.

Radiologically, the disease is characterised by restriction of the joint line, small pseudocysts and marginal osteophytes. Subluxation can occur with time. The disease is not accompanied by changes in humoral parameters. It mainly affects women over 40 years of age and is progressive, though the speed of progression varies from person to person.

No drugs have yet been demonstrated to slow or arrest progression of joint damage, though cartilage protectors such as diacerein and glycosaminoglycans are widely used. NSAIDs are usually used to control pain and have the advantage of also controlling secondary inflammatory reactions. However, NSAIDs are contraindicated in cases of gastritis, gastric ulcer, kidney failure, heart failure and hypertension and cannot be taken with other drugs such as oral anticoagulants. They have frequent gastrointestinal, renal and cardiovascular side-effects.

In the study of Warnock *et al*. (2007) patients aged 18-75 years with mild to moderate rheumatic disorders were enrolled. The patients received a daily dose of 2 Devil's claw tablets containing a total daily dose of 960 mg Devil's claw dry extract made with 60% ethanol (DER 1.5-3:1). Effectiveness was measured using a global assessment of pain function and stiffness in the effected area with a numerical rating scale (NRS), as well as joint-specific assessments. The WOMAC scale was used to assess effects on arthritic dominant hands. In addition, a general assessment of perceived effectiveness on a 6-point scale, onset of action, the SF-12 Quality of Life Questionnaire, and daily patient diaries were used to assess effectiveness.

A total of 222 patients were included in the Intention to Treat (ITT) analysis. Compliance at week 8 was 75-100% for 140 patients. The average global scores for pain, stiffness, and function were significantly improved from baseline to weeks 4 and 8 ($P<0.0001$ for both). The average scores for pain in the hand, wrist, elbow, shoulder, hip, knee and back were significantly improved from baseline to week 8 ($P<0.05$) and week 4 ($P<0.01$) (except for right elbow). In addition, the average WOMAC subscale scores (knee: n=114, hip: n=68) were significantly improved from baseline to weeks 4 and 8 ($P<0.0001$ for both). The average Algofunctional Hand Osteoarthritis Index (n=113) scores were also significantly improved from baseline to week 8 ($P<0.0001$). Average finger floor distances of patients with back pain (n=81) were significantly improved from baseline to week 8 ($P<0.0001$).

In addition, more than half of the patients rated the Devil's claw treatment as "excellent" or "good"; and investigators rated the Devil's claw extract's effectiveness as "excellent" or "good" in more than half of the patients. A total of 171 out of 222 patients (77%) reported a beneficial effect due to the devil's claw tablets. Of these patients, 104 reported feeling an effect between 1 and 4 weeks from baseline. Average scores for pain, daily function, and stiffness in the patient's daily diaries were significantly improved from week 1 to weeks 2 and 8 ($P<0.0001$) for both). In addition, the average SF-12 scores on the physical and emotional subscales were significantly improved from baseline to weeks 4 and 8 (n=207, $P<0.0001$ for both). Almost half (44.8%) of patients taking analgesics for rheumatic disorders at baseline had reduced their dosage at week 8; and 26% had completely stopped taking analgesics at week 8. There were no significant changes in blood parameters, liver function, or vital signs during the study. A total of 49 possibly or probably drug-related adverse events were reported, none considered serious. The majority of the adverse events reported were mild to moderate gastrointestinal complaints. The tolerability of the devil's claw tablets was rated as "good" by the majority (87.4%) of patients. In addition, 74.3% of the patients stated that they would take the devil's claw tablets again.

Effect on smooth muscle contraction. A number of studies have shown that dry extract of Devil's claw, up to 40 µg/ml, slightly increases the amplitude and tone of contractions of isolated jejunum. At higher doses tone decreases and the

amplitude of contractions declines sharply. The same biphasic effect on contractions has also been observed in isolated rabbit uterus (Occhiuto *et al*., 1985).

***Effect on cardiovascular system*.** Intragastric administration of 100 mg/kg body weight of an aqueous or methanol extract of *H. procumbens* root protected rats against ventricular arrhythmias induced by epinephrine-chloroform and calcium chloride (Circosta *et al*., 1984). Intraperitoneal administration of 25 mg/kg bw of a methanol extract of *H. procumbens* roots inhibited cardiac arrhythmias induced by aconitine, epinephrine-chloroform and calcium chloride in fasted rats. Intragastric administration of 300-400 mg/kg bw of a methanol extract of *H. procumbens* root to normotensive rats reduced heart rate and arterial blood pressure (Circosta *et al*., 1984). Another studies have demonstrated that lower doses of the extract have slight negative chronotropic and positive inotropic effects (Occhiuto *et al*., 1985), whereas larger doses have a marked inotropic effect, with reduction in coronary blood flow. The inotropic effect is attributed to harpagide (Costa *et al*., 1985).

***Antidyspeptic activity*.** As bitter tonic *H. procumbens* has similar effects to gentian with prokinetic effects on gastrointestinal smooth muscle and is indicated in cases of hyposecretory dyspepsia with loss of appetite (WHO, 2007).

A decoction of *Radix Harpagophyti* is one of the strongest bitter tonics known (Weiss and Fintelmann, 2000). Ingestion of an infusion prepared from the root (dose not specified) over a period of several days led to an improvement in the symptoms of disorders of the upper part of the small intestine, which were accompanied by disturbances of choleresis and bile kinesis (Weiss and Fintelmann, 2000). It has been proposed that, because the root is very bitter, is a good stomachic and stimulates the appetite, it may also be useful for the treatment of dyspeptic complaints (Jaspersen-Schib, 1989; Czygan and Krüger, 1977).

Pharmacokinetics. Commercial extract of *H. procumbens* taken orally has been shown to produce a plasma peak of harpagoside in humans within 1.3-2.5 h (Loew *et al*., 2001). Iridoid glycosides are metabolised by human intestinal flora to aucubin B, a pyridine alkaloid. The reaction seems to be catalyzed by the enzyme α-glycosidase in the presence of ammonium ions (Baghdikian *et al*., 1999a, 1999b).

A special role is certainly played by gastric acid which may activate or inactivate iridoid glycosides. It has been suggested that the products of acid hydrolysis have antiinflammatory and antirheumatic activity and that contact with gastric secretions is important. Others sustain that glycosides are more active than the corresponding genines and that gastric acid disactivates the active principle. Indeed, aqueous extract reduces carrageenan-induced edema in rats if administered intraperitoneally or intraduodenally, but not when taken orally (Soulimani *et al*., 1994).

Toxicity. Long-term toxicity does not seem to have been studied. Certain authors underline the need for such studies, particularly in view of the widespread use of the plant in phytotherapy and as complementary therapy, especially in cases in which prescription of anti-inflammatory drugs is unjustified, at least in the early stages of disease. Pharmacological studies with experimental animals have shown that *H. procumbens* is well tolerated: the i.p. DL_{50} of harpagoside and harpagide in mice is 1 and 3.2 g/kg, respectively (Cardini, 2006).

Side-effects. Mild infrequent gastrointestinal symptoms were reported in clinical trials (Chrubasik *et a*l., 1999; Belaiche, 1982) and in cases of known hypersensitivity. Digestive side-effects include diarrhoea (Chantre *et al*., 2000), dyspepsia and sense of satiety (Wegener and Lupke, 2003), though the risk of side-effects is much less than that with synthetic analgesics (Chrubasik, 2004) and the plant is very well tolerated (Chrubasik, 2004).

Contraindications. *Radix Harpagophyti* is contraindicated in cases of gastric and duodenal ulcer and known hypersensitivity to the roots, because the bitter taste stimulates peptic acid (Blumenthal, 1998; Hänsel *et al*., 1993). Owing to a lack of safety data, *Radix Harpagophyti* should not be used during pregnancy and nursing, due to possible oxytocic effects (Mabey *et al*., 1988).

Since *H. procumbens* has antiarrhythmic activity (Circosta *et al*., 1984), it should not be taken in association with antiarrhythmic drugs. A possible interaction with anticoagulants such as Warfarin, that could promote bleeding, has been reported (Heck *et al*., 2000; Shaw *et al*., 1997). It is well known that a number of herbs and foods alter the metabolism of Warfarin by acting on cytochrome P450. Budzinski *et al*. (2000) demonstrated that Devil's claw did not inhibit the activity of cytochrome P450 isoenzymes *in vitro*. On the other hand, Unger and Frank (2004) described a liquid chromatography/mass spectrometry method with automated online extraction to simultaneously determine the *in vitro* inhibitory potency of herbal extracts on six major human drug-metabolising cytochrome P450 enzymes. The authors concluded that popular herbal remedies, including Devil's claw root, could be identified as inhibitors of the applied CYP enzymes with IC(50) values between 20 and 1000 µg/ml. Unger and Frank (2004)

showed that this inhibition could be the reason for drug interactions of clinical significance.

These controversial results are not easy to compare; more studies are needed. However, on the basis of pharmacological considerations, ESCOP (2003) does not exclude interaction with antiarrhythmics and warns against possible interaction with Warfarin.

Other precautions. No information is available on precautions concerning drug and laboratory test interactions, carcinogenesis, mutagenesis, impairment of fertility, teratogenic effects during pregnancy or paediatric use.

Preparations. Dried root for decoctions and infusions, powdered root or extract in capsules, tablets, tinctures and ointments (Bisset, 1994; Iwu, 1993).

Store in the dark in a sealed container.

Posology. (Unless otherwise indicated). Daily dose for loss of appetite: 1.5 g of root in decoction, 3 ml of tincture (1:10, 25% ethanol); for painful arthritis or tendonitis 1.5-3.0 g of root in decoction, three times a day, 1-3 g of root or equivalent (WHO, 2007).

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