

HARPAGOPHYTUM RADIX

Definition

Harpagophytum Radix consists of the dried sliced secondary tubers of *Harpagophytum procumbens* D.C. ex Meissner subspecies *procumbens* and subspecies *transvaalense* Ihlenf. & H. Hartm. (Pedaliaceae).

Synonyms

Ssp. *procumbens*
Harpagophytum burchellii Decne.
Uncaria procumbens Burch.

Vernacular names

Beesdubbeltjie, duiwelsklou (A), devil's claw, grapple vine, kanako, legatapitse (Ts); khams, khuripe, xwate
Foreign names
Teufelskralle, trampelklette, racine de Windhoek, tubercule de griffe du diable

Description^{1,2}

Macroscopical



Figure 1a: dried sliced tuber



Figure 1b: fresh tuber

Prostrate, mat-forming perennial herb with several annual stems from a succulent taproot, with additional tubers on lateral roots, growing to 1,5m in length; **leaves** narrowly ovate to ovate, up to 65mm long × 40mm wide, petiole 30-45mm long, pinnately lobed, clothed with glandular hairs, the underside densely pubescent; **flowers** (Dec-Feb) borne singly in leaf axils, bright pink to magenta, tubular, with corolla limb purple or yellow, up to 7cm long; **fruit** a large, claw-like, dehiscent bilocular capsule, flattened at right angles to the septum, armed along the edges with four rows of woody arms up to 8cm long and bearing recurved spines.



Figure 2: colour plate of live plant

¹ Dyer, R.A. (1975). The genera of Southern African flowering plants. Vol 1. Dicotyledons. Botanical Research Institute, Pretoria.

² Ihlenfeldt, (1988). The genus *Harpagophytum*. Flora Zambesiaca **8(3)**: 109-113.

Note Illustration from: Jill Adams (1976), *Wild Flowers of the Northern Cape*. Department of Nature and Environmental Conservation of the Provincial Administration of the Cape of Good Hope, Cape Town.

Microscopical

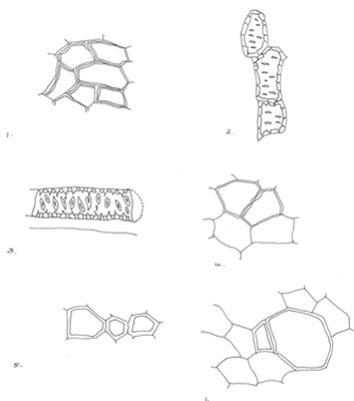


Figure 3: microscopical features

Characteristic features are: the very large vessels up to 160 μ in diameter with lignified pitted walls (3); the occasional sieve tubes and companion cells, staining light pink with phloroglucinol/HCl (6); the pale yellow-brown cork tissue (1); a matrix of thin-walled parenchyma with no intercellular spaces; the absence of starch, calcium oxalate crystals and fibres.

Crude drug

When fresh the tubers are light brown-buff in colour, with a slightly wrinkled appearance, up to 20cm long \times 6cm in diameter; the freshly cut surface is pale cream, darkening rapidly on exposure to air and showing a distinct cambial ring. When sliced and dried, the crude drug consists of discs up to 5mm thick and 4cm in diameter; these are light brown, often with a greenish tinge and somewhat shrivelled; a dark cambial zone and radial rows of xylem are visible. Odour faint, taste very bitter, fracture short.

Geographical distribution

Quite widespread on deep sand in open savannah of arid regions in South Africa: the Northern and North-West Provinces, Northern Cape Province and the western Free State Province; also in Namibia, Botswana and Zimbabwe.

Almost all the material used in commerce is obtained from natural stands in these countries and large quantities of tubers are exported annually. Despite concerns as to its conservation status, little cultivation of this species is currently undertaken.

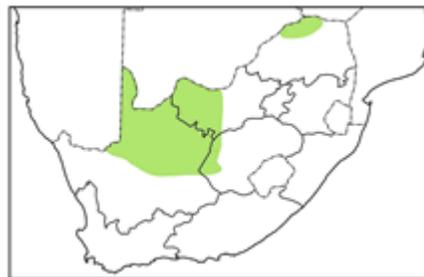


Figure 4: distribution map

Quality standards

Identity tests

Thin layer chromatography on silica gel using as solvent a mixture of toluene:diethyl ether:1.75M acetic acid (1:1:1). Reference compound cineole (0,1% in chloroform). Method according to Appendix 2a. R_f values of major compounds: 0,12 (purple); 0,33 (black); 0,42 (blue); 0,47 (blue-green); 0,64 (blue-green); rutin marker; 0,35 (orange) Plate viewed in UV light (wavelength 366nm)

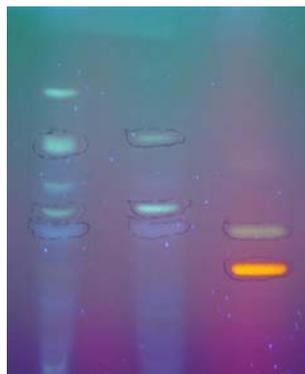


Figure 5: TLC plate

HPLC on C_{18} column, method according to Appendix 2b.

Major compounds:

Methanol extract: Retention times (mins): 8.42

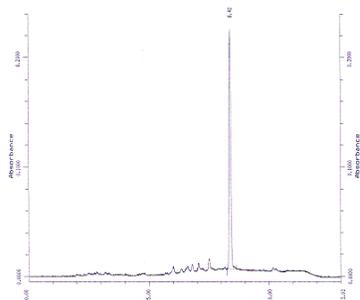


Figure 6: HPLC spectrum

Ethanol (70%) soluble extractive value: not less than 32% (range: 32.5 – 36.7%)

See current editions of European Pharmacopoeia (EP) and British Herbal Pharmacopoeia (BHP):

Total ash: not > 22% (BHP 1996); not > 8% (EP 1997)

Water soluble extractive (BHP 1996): not < 50%

Acid-insoluble ash (BHP 1996): not > 5%

Loss on drying (EP 1997): not > 0.5%, determined using 0.5g by drying in an oven at 100-105°C.

Purity tests

Assay

Harpagoside content (EP 1998): not < 1.2% (HPLC on reverse phase ODS column)

Other published assay methods (BHP 1996):

Total iridoid glycosides (UV spectrophotometry)

Harpagoside/harpagide content (GLC)

Major chemical constituents³

1. Iridoid glycosides 0.5-3.0%, principally harpagoside (cinnamyl ester of harpagide), harpagide and procumbide. Secondary tubers contain twice as much harpagoside as do primary tubers⁴.
2. Sugars: about 51%, principally the tetrasaccharide stachyose (up to 46%) together with smaller amounts

³ British Herbal Medicines Association (1992). British Herbal Compendium Vol. 1. Ed. Bradley, P.R., BHMA, Dorset.

⁴ Czygan, F-C. and Krüger, A. (1977). Pharmazeutisch-biologische untersuchungen der gattung *Harpagophytum*. 3. *Planta Medica* **31**: 305-307.

of the trisaccharide raffinose, sucrose and monosaccharides. These sugars replace starch or other high MM polysaccharides as reserve carbohydrates and account for the high water soluble extractive fraction (50-70%)

3. Triterpenoids: oleanolic acid, 3 β -acetyl oleanolic acid, ursolic acid
4. Phytosterols: mainly β -sitosterol, stigmasterol and their glucosides
5. Aromatic acids: caffeic, cinnamic, chlorogenic acids
6. Flavonoids: luteolin, kaempferol

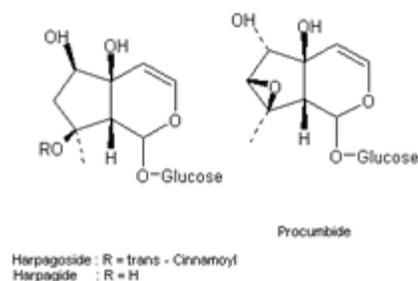


Figure 7: chemical constituents

Dosage forms

Traditional:

Aqueous infusions or decoctions are taken orally; an ointment prepared from fresh tuber is applied externally.

Patent medicines:

Tablets, tea, tincture, liquid extract, ointment

Medicinal uses

Traditional

A decoction of the rootstock is taken by the Topnaar people of Namibia and many ethnic groups in South Africa to treat stomach or post-natal pains, fever, lack of appetite, indigestion and diabetes. An ointment is applied to ulcers, boils and external cancerous growths.^{5, GR1} In Botswana, a decoction is taken to cure infectious

⁵ Van den Eynden, V., Vernemmen, P. and van Damme, P. (1992). The ethnobotany of the Topnaar. University of Ghent/EU.

diseases, to treat female infertility and for pains in the limbs.⁶

Non-traditional^{GR 7, 8, 10, 17} (See also ESCOP 1996; German Commission E monograph)

Preparations of the tuber are taken to treat painful arthroses, tendonitis, gout, lumbago, myalgia, dyspepsia and poor appetite and as supportive therapy for degenerative rheumatism.

Pharmacology/bioactivity^{GR14, 17}

Devil's Claw first came under scientific scrutiny during the 1950s when German scientists began investigating Namibian traditional medicines. Many *in vitro*, animal and clinical studies of its anti-inflammatory/analgesic activity have since been conducted, mainly in Germany, using the crude drug or extracts of various kinds. The following reports are not intended to be a comprehensive review, for which the reader should consult the scientific literature.

In vitro, animal and clinical studies of anti-inflammatory/analgesic activity have been conducted using the crude drug or extracts of various kinds.

In vitro studies have shown that a standardised 60% ethanolic extract containing 2.9% of harpagoside inhibited the release of tumour necrosis factor- α (TNF) induced by the treatment of human monocytes with lipopolysaccharide (LPS). Isolated harpagoside and harpagide were however ineffective in this assay. Harpagoside in the concentration range of 10-100 μ M has been shown to reduce thromboxane B2 synthesis in cells treated with calcium ionophore A23187⁷.

The anti-inflammatory and analgesic effects of a dried aqueous extract of *Harpagophytum procumbens* and of harpagoside have been evaluated in rats and mice⁸. The extract was found to exert significant and dose-dependent anti-inflammatory and analgesic effects in the carragenan-induced oedema and writhing tests respectively. Isolated harpagoside, assessed in the same two assays, did not appear to be involved in the anti-inflammatory activity, but did contribute to peripheral analgesia. The results of this study suggested that compounds other than harpagoside contributed to analgesic activity and also showed that the activity of *H. procumbens* extract was lost after acid treatment.

In a recent clinical study⁹ involving 122 patients with osteoarthritis of knee and hip, a four-month randomised, double blind trial was undertaken, comparing the effects of a *Harpagophytum* crude extract (6 \times 435mg capsules/day) with diacerhein 100mg/day). Assessment of pain and functional disability were made according to a visual analogue scale and severity of osteoarthritis evaluated by Lequesne's functional index. A reduction in spontaneous pain, as well as a progressive reduction in the Lequesne index was noted in both groups.

The results of a randomised double-blind trial¹⁰ to assess the safety and efficacy of *Harpagophytum* extract in the treatment of acute back pain (118 patients, given the equivalent of 6g crude drug = 50mg harpagoside daily, in divided doses, for four weeks), showed that concomitant use of a supplementary analgesic, Tramadol, did not differ significantly between the placebo and

⁶ Hedberg, I. and Staugard, F. (1989). Traditional medicine in Botswana. Ipeleng Publishers, Gaborone.

⁷ Tippler, B., Syrovets, T., Loew, D. *et al.* (1996). *Harpagophytum procumbens*: wirkung von extrakten auf die eicosanoidbiosynthese in Ionophor A23187-stimuliertem menschlichem Vollblut. Pp. 95-100 In: Loew, D. and Rietbrock, N. (eds.) *Phytopharmaka II: forschung und klinische Anwendung*. Steinkopff, Darmstadt.

⁸ Lanhers, M-C., Fleurentin, J., Mortier, F, Vinche, A. and Younos, C. (1992). Anti-inflammatory and analgesic effects of an aqueous extract of *Harpagophytum procumbens*. *Planta Medica* **58**: 117-123.

⁹ Chantre, P., Cappelaere, A. Leban, D. *et al.* (2000). Efficacy and tolerance of *Harpagophytum procumbens* versus diacerhein in the treatment of osteoarthritis. *Phytomedicine* **7**: 177-183.

¹⁰ Chrubasik, S. *et al.* (1996). Effectiveness of *Harpagophytum procumbens* in the treatment of acute low back pain. *Phytomedicine* **3**: 1-10.

treatment groups. However, 9/51 patients in the treatment group were pain free at the end of the treatment period as compared with 1/54 patients in the placebo group. A randomised double-blind trial (197 patients), conducted to assess the efficacy of a standardised extract (equivalent to 50-100mg harpagoside/day for 4 weeks) vs placebo in the treatment of low back pain¹¹, measured the number of patients who were pain free, without additional analgesic medication, for 5/7 days of the final week of the trial. The groups receiving placebo, 50mg and 100mg harpagoside/day had 3, 6 and 10 pain free patients respectively ($p=0.027$).

The efficacy as an analgesic of an aqueous ethanolic extract of *Harpagophytum procumbens* (standardised to contain 1.5% of iridoid glycosides) was assessed in 50 patients with arthroses of various kinds¹². Ten days after completing 1-3 three week courses of treatment, patients were assessed for pain severity. A significant decrease was noted in those with moderate pain who had received extract as compared to the placebo group.

Crude methanolic extracts of *H. procumbens* have demonstrated cardiovascular and anti-arrhythmic activity. The effects of isolated harpagoside and harpagide were also assessed in these studies^{13,14}.

A study of the pharmacokinetic properties in humans of *Harpagophytum* extracts (80% ethanol) and their effects on eicosanoid

biosynthesis *in vitro* and *ex vivo*¹⁵ demonstrated a close relationship between harpagoside levels and leukotriene biosynthesis inhibition (dose range 400-1800mg, given orally) in adult males. An clinical assessment (randomised, placebo-controlled, double-blind) of the efficacy of a 60% ethanolic *Harpagophytum* extract (LI 174 = Rivoltan) in the treatment of low back pain¹⁶ found significant clinical efficacy in patients receiving 480mg of extract orally twice daily for 4 weeks. The product (a film-coated tablet) was well tolerated and no serious adverse drug reactions were reported.

A further recent clinical study (250 patients) assessed the efficacy of *Harpagophytum* extract in the treatment of non-specific lower back pain as well as osteoarthritic knee or hip pain¹⁷. Patients were given the equivalent of 60mg harpagoside daily for 8 weeks and benefits (assessed using various disease-specific and generic measures of efficacy) were achieved in 50-70% of cases, with few adverse effects. About 10% of patients reported minor adverse events that could possibly have been attributed to Doloteffin but the conclusion of the investigators was that the preparation was worth considering for all 3 types of pain.

Contraindications

Gastric and duodenal ulcers^{GR 7}, diabetes, cardiac disorders, patients receiving

¹¹ Chrubasik, S. *et al.* (1999). Effectiveness of *Harpagophytum* extract WS 1531 in the treatment of exacerbation of low back pain: a randomised, placebo-controlled, double-blind study. *European Journal of Anaesthesiology* **196**: 118-129.

¹² Lecomte, A and Costa, J.P. (1992). *Harpagophytum* dans l'arthrose. *Le Magazine* **15**: 37.

¹³ Circosta, C. *et al.* (1984). A drug used in traditional medicine: *Harpagophytum procumbens* DC. II Cardiovascular activity. *Journal of Ethnopharmacology* **11**: 259-274.

¹⁴ Costa de Pasquale, R. *et al.* (1985). A drug used in traditional medicine: *Harpagophytum procumbens* DC. III. Effects on hyperkinetic ventricular arrhythmias by reperfusion. *Journal of Ethnopharmacology* **13**: 193-199.

¹⁵ Loew, D., Mollerfeld, J., Schrodter, A. and Puttkammer, S. (2001). Investigations on the pharmacokinetic properties in humans of *Harpagophytum* extracts and their effects on eicosanoid biosynthesis *in vitro* and *ex vivo*. *Clinical Pharmacology and Therapeutics* **69(5)**: 356-364.

¹⁶ Gobel, H, Heinze, A., Ingwerson, M., Niederberger, U. and Gerber, D. (2001). *Harpagophytum* extract LI 174 (Devil's Claw) for the treatment of non-specific back pain. *Schmerz* **15**: 10-18.

¹⁷ Chrubasik, S., Thanner, J., Kunzel, O., Conradt, C., Black, A. and Pollak, S. (2002). Comparison of outcome measures during treatment with the proprietary *Harpagophytum* extract Doloteffin in patients with pain in the lower back, knee or hip. *Phytomedicine* **9(3)**: 181-194.

hypo/hypertensive therapy,
pregnancy/lactation^{GR 17}.

Adverse reactions

A single report of headache, tinnitus, severe anorexia and loss of taste has been noted. Toxicity is stated to be minimal, with oral LD₀ and LD₅₀ in mice reported to be >13.5g/kg body weight. Clinical, haematological and gross pathological findings have been described as unremarkable in rats given 7.5g/kg by mouth for 7 days. Hepatic changes could not be demonstrated. No chronic toxicity studies have been located. Harpagoside is reported to be highly toxic following IV administration^{GR 17}. Mild and infrequent gastro-intestinal symptoms have been reported in clinical trials^{9, 10}.

Precautions

The German Commission E monograph recommends that patients suffering from gallstones consult a physician prior to using preparations of *H. procumbens*.

Dosage

1. See^{GR17}

Dried tuber: 0.1- 0.25g three times daily.

Liquid extract (1:1 in 25% ethanol): 0.1-0.25ml three times daily.

Tincture (1:5 in 25% ethanol): 0.5-1.0ml three times daily.

2. See^{GR 7}

To be taken three times daily, unless otherwise prescribed:

For dyspepsia or lack of appetite: dried tuber, 0.5g in decoction; tincture (1:5 in 25% ethanol) :1ml

For other indications: dried tuber (1.5-2.5g in decoction; liquid extract (1:1 in 25% ethanol): 1-2ml.

