



*Research Paper*

*Afr. J. Traditional,  
Complementary and  
Alternative Medicines*  
[www.africanethnomedicines.net](http://www.africanethnomedicines.net)

ISSN 0189-6016©2006

OXYTOCIN-LIKE EFFECT OF *HARPAGOPHYTUM PROCUMBENS* DC [PEDALIACEAE] SECONDARY ROOT AQUEOUS EXTRACT ON RAT ISOLATED UTERUS

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**Abstract**

*Harpagophytum procumbens* DC [family: Pedaliaceae] is widely used in South African traditional medicine for the treatment, management and/or control of a variety of human ailments. Some traditional health practitioners of South Africa have claimed that *H. procumbens* secondary root is a useful obstetric remedy for induction or acceleration of labour, as well as for expulsion of retained placentas in pregnant women. In the present study, we have, therefore, examined the effects of *Harpagophytum procumbens* secondary root aqueous extract (HPE) on isolated uterine muscle strips taken from pregnant and non-pregnant, young female rats. The plant's extract (HPE, 10–800 µg/ml) induced concentration-related, significant ( $P < 0.05$ – $0.001$ ) increases in the baseline tone (basal tension), and caused powerful spontaneous, rhythmic, myogenic contractions of the oestrogen-dominated uterine muscle strips taken from stilboesterol-pretreated, non-pregnant female rats. Relatively low to high concentrations of *H. procumbens* secondary root aqueous extract (HPE, 10–800 µg/ml) also provoked concentration-dependent, significant ( $P < 0.05$ – $0.001$ ) increases in the baseline tone (basal tension) and contracted uterine muscle strips taken from female rats in the early, middle and late stages of pregnancy. Moderate to high concentrations of the plant's extract (HPE, 200–1000 µg/ml) always provoked powerful contractions of isolated uterine muscle preparations of non-pregnant and pregnant rats. The results of this *in vitro* study indicate that *H. procumbens* secondary root aqueous extract (HPE) possesses significant contractile effect and/or uterotonic action on mammalian uterus. This finding probably suggests that the use of *Harpagophytum procumbens* secondary root preparations should be contra-indicated in pregnancy. The contractile effect and/or uterotonic action of the plant's extract may be due to release of uterotonic substances or mediators. However, the findings of the present laboratory animal study lend pharmacological credence to the suggested folkloric, obstetric

uses of the plant's secondary root for induction or acceleration of labour, as well as for expulsion of retained placentas in pregnant women in some communities of Southern Africa.

**Key words:** *Harpagophytum procumbens*, secondary root, aqueous extract, uterotonic action.

## Introduction

*Harpagophytum procumbens* DC [family: Pedaliaceae] is a weedy, perennial plant with annual creeping stems spreading from a central, thick, fleshy, tuberous tap root (Henderson and Anderson, 1966; Van Wyk *et al.*, 2002). The leaves are greyish-green and are usually irregularly divided into several lobes. The tubular flowers are either yellow and violet, or uniformly dark violet. The fruits have numerous characteristically long arms with sharp, grapple-like hooks (thorns), as well as two straight thorns on the upper surface (Watt and Breyer-Brandwijk, 1962; Van Wyk *et al.*, 2002). *H. procumbens* is virtually restricted to the southern part of Africa, occurring mainly in South Africa, Namibia, Botswana and Zimbabwe. The plant is commonly referred to as 'Devil's claw', a name derived from its claw-like fruits which may cling tenaciously to the foot and other parts of an animal's body and, is thus dispersed in this way (Watt and Breyer-Brandwijk, 1962; Van Wyk *et al.*, 2002).

The thick, fleshy, tuberous secondary tap roots of *Harpagophytum procumbens* are usually dried and used in South African traditional medicine. In the form of infusions, decoctions, tinctures, powders and extracts, *H. procumbens* secondary root is used for a variety of health conditions. It has an ethnomedical reputation for efficacy in anorexia, indigestion, diabetes mellitus, hypertension, gout, fevers, skin cancer, infectious diseases (including tuberculosis), allergies, osteoarthritis, fibrositis and rheumatism, being particularly effective in small joint diseases (Van Wyk and Gericke, 2000). 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 assist in expelling retained placentas (Watt and Breyer-Brandwijk, 1962; Van Wyk and Gericke, 2000; Van Wyk *et al.*, 2002). 'Devil's claw' is also used *post-partum* as an analgesic and to keep the uterus contracted (Watt and Breyer-Brandwijk, 1962; Van Wyk and Gericke, 2000; Van Wyk *et al.*, 2002). The dry, powdered tuberous root of the plant is used directly as a wound dressing, or it is mixed with animal fat or vaseline, to make a wound-healing or burn-healing ointment. Commercial ointments and creams of *H. procumbens* are applied topically for minor muscular aches and pains, and to painful joints (Watt and Breyer-Brandwijk, 1962; Van Wyk and Gericke, 2000; Van Wyk *et al.*, 2002). Serum cholesterol and uric acid levels are also reduced by *H. procumbens* products (Van Wyk and Gericke, 2000).

Previous studies in our laboratories indicate that *Harpagophytum procumbens* secondary root aqueous extract stimulates and contracts the gastro-intestinal tract and vascular smooth muscle preparations of certain experimental animals (Mohamed and Ojewole, 2004; Mahomed *et al.*, 2005). Moreover, there are some anecdotal reports that *H.*

*procumbens* secondary root extracts and/or preparations possess uterotonic actions in human subjects. In order to scientifically confirm or deny the possible oxytocic effect of *H. procumbens* secondary root extracts on mammalian uterus, the present study was undertaken to examine the plausible oxytocin-like effect of the plant's root aqueous extract on isolated uterine muscle strips of pregnant and non-pregnant rats.

## **Materials and Methods**

The experimental protocol used in this study was approved by the Ethics Committee of the University of Durban-Westville, Durban 4000, South Africa; and conforms with the "Guide to the care and use of animals in research and teaching" [published by the University of Durban-Westville, Durban 4000, South Africa].

### **Plant Material**

Fresh pieces of *Harpagophytum procumbens* DC secondary roots were purchased from Upington "Muthi" Market in the Northern Cape Province of South Africa (between November, 2002 and March, 2003). The roots were identified by the staff of the North-West University's Botany Department as the secondary roots of *Harpagophytum procumbens* DC [family: Pedaliaceae]. Voucher specimen of the plant's secondary roots have been deposited in the University's Herbarium.

### **Preparation of *Harpagophytum procumbens* Root Aqueous Extract**

One kilogramme (1 kg) of fresh secondary roots of *H. procumbens* were sliced and air-dried at room temperature. The sliced, air-dried roots of the plant were milled into fine powder in a Waring commercial blender. The powder was Soxhlet extracted twice, on each occasion with 2.5 litres of distilled water at room temperature for 24 hours with shaking. The combined aqueous extracts were filtered and concentrated to dryness under reduced pressure at  $30\pm 1^{\circ}\text{C}$ . The resulting aqueous extract was freeze-dried, finally giving 15.56 g [i. e., 1.556% yield] of a light-brown, powdery crude aqueous root extract of *Harpagophytum procumbens*. Aliquot portions of the crude root aqueous extract residue were weighed and dissolved in distilled water for use on each day of our experiment.

### **Animal Material**

Young adult, female Wistar rats (*Rattus norvegicus*) weighing 250–300 g were used. The animals were kept and maintained under laboratory conditions of temperature, humidity, and light; and were allowed free access to food (standard pellet diet) and water *ad libitum*. The animals were divided into two categories as follows:

## **Oestrogen-dominated, non-pregnant rats**

All the rats in this group were pretreated with stilboesterol (0.1 mg/kg s. c.) for 20–24 hours before use (in order to induce oestrus state). Vaginal smears were taken immediately before the animals were sacrificed in order to ascertain that the animals were in oestrus state. Female rats in oestrus state were used in this study.

## **Pregnant Rats**

Mated female rats were examined daily for the presence of cervical plug. The day on which cervical plug was first observed was taken as ‘day one’ of pregnancy of the female rat. Early pregnancy was regarded as day 1 to day 8, while late pregnancy was taken to be from day 16 to day 20 following cervical plug detection.

## **Experimental Procedure**

Each of the pregnant and stilboesterol-pretreated non-pregnant female rats was killed by applying a sharp blow to the back of its head and bled out. The two uterine horns of the animal were cleaned free from fatty and connective tissues and trimmed. Tubular segments of approximately equal lengths (2–3 cm) were removed from the uterine horns by cutting off both ends. The two tubular uterine-horn segments (2–3 cm long) were set-up under physiological conditions as described in detail earlier by (Ojewole, 1977). Each isolated uterine muscle strip was separately suspended in 30-ml Ugo Basile Two-Chambered Organ Baths (model 4050) containing de Jalon’s physiological solution (of composition, in g/litre: NaCl, 9.0; KCl, 0.42, CaCl<sub>2</sub>, 0.06; MgCl<sub>2</sub>, 0.005; NaHCO<sub>3</sub>, 0.5; and glucose, 0.5) maintained at 32±1°C and continuously aerated with carbogen (i. e., 5% carbon-dioxide + 95% oxygen gas mixture). Two uterine muscle preparations (one used as ‘control’ and the other one used as HPE- (or other drug-) treated ‘test’ preparation) were always set-up to allow for changes in the uterine muscle sensitivity. Each preparation was subjected to a resting tension of 1.0 g, and allowed to equilibrate for 30–45 minutes before it was challenged with HPE (and other drugs used). Doses of HPE (and other drugs used) were added to the bath-fluid either cumulatively or sequentially, and washed out three-to-five times after the maximum responses of the tissues were attained. Distilled water (i. e., the vehicle in which HPE and other drugs used in this study were dissolved) was used as the ‘control’ fluid for HPE and other drugs tested. Concentrations of bath-applied HPE (and other drugs used) were repeated where appropriate and/or possible, at regular intervals of 3–20 minutes after the last washing. HPE- (and other drug-) induced responses of the uterine muscle preparations were recorded isometrically by means of Ugo Basile force-displacement transducers, Ugo Basile’s 2-Channel “Gemini” Recorder, and pen-writing microdynamometers (model 7070).

## Data Analysis

Data obtained were pooled and presented as means ( $\pm$ SEM). Data from distilled water-treated 'control' preparations were used as baseline values. The differences between the plant's extract (HPE)- (and other drug-) treated 'test' preparations, and distilled water-treated 'control' preparations, were analysed statistically by using "Paired Student's t-test". The level of significance of the differences between the 'test' and 'control' group data means was determined. Values of  $P \leq 0.05$  were taken to imply statistical significance.

## Results

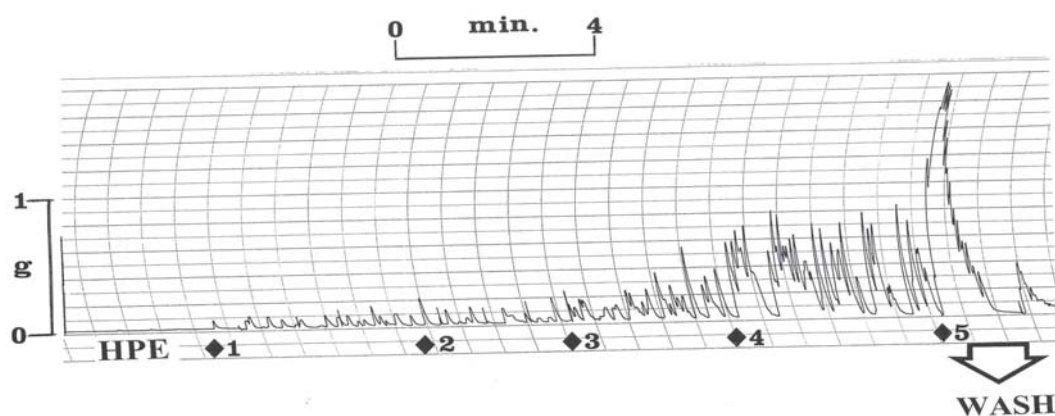
### Oestrogen-dominated, non-pregnant uterine strips

Uterine muscle strips taken from stilboesterol-pretreated, non-pregnant female rats were found to be quiescent and devoid of spontaneous, myogenic, rhythmic activity. However, relatively low to high concentrations of *H. procumbens* secondary root aqueous extract (HPE, 10–800  $\mu$ g/ml) cumulatively applied to the bath-fluid caused concentration-related, significant ( $P < 0.05 - 0.001$ ) increases in the baseline tone (basal tension), and induced powerful spontaneous, rhythmic, myogenic contractions of the oestrogen-dominated uterine muscle strips taken from stilboesterol-pretreated, non-pregnant female rats. Figure 1 illustrates a typical trace obtained. Moderate to high concentrations of the plant's extract (HPE, 200–1000  $\mu$ g/ml) sequentially added to the bath-fluid, always provoked powerful contractions of the uterine muscle preparations (data not shown). Sequentially applied acetylcholine (ACh, 0.1–2.0  $\mu$ g/ml), physostigmine (PHY, 2.5–10.0  $\mu$ g/ml), bradykinin (BKN, 1.0–10.0 ng/ml) and oxytocin (OTC, 0.05–0.5 unit/ml) also induced concentration-dependent, significant ( $P < 0.05 - 0.001$ ) contractions of the oestrogen-dominated uterine muscle preparations taken from the non-pregnant rats (data not shown). The spontaneous, rhythmic, myogenic contractions of the quiescent, oestrogen-dominated uterine muscle strips of the non-pregnant rats induced by relatively low to high concentrations of *Harpagophytum procumbens* secondary root aqueous extract (HPE, 10–1000  $\mu$ g/ml) were inhibited or abolished in a concentration-dependent manner by bath-applied indomethacin (IDM, 0.1–5.0  $\mu$ g/ml) or atropine (ATR, 0.1–5.0  $\mu$ g/ml). Relatively low to moderate concentrations of the plant's extract (HPE, 10–800  $\mu$ g/ml) potentiated ACh-, PHY-, BKN- and OTC-induced contractions of the oestrogen-dominated isolated uterine muscle strips in a concentration-related manner (data not shown).

### Pregnant uterine strips

Uterine muscle strips taken from pregnant rats were found to be spontaneously active, producing rhythmic contractions on their own accord. The effects of HPE on isolated uterine muscle strips taken from pregnant rats were found to be qualitatively and quantitatively similar to those produced by the plant's extract on isolated uterine muscle strips taken from stilboesterol-pretreated, non-pregnant female rats.

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**Figure 1:** Effects of graded concentrations of *Harpagophytum procumbens* secondary root aqueous extract (HPE) on oestrogen-dominated rat isolated uterine muscle strip. HPE 1, 2, 3, 4 and 5 represent 25, 50, 100, 200 and 400  $\mu\text{g/ml}$  of *Harpagophytum procumbens* secondary root aqueous extract cumulatively added to the bath fluid at the solid points ( $\blacklozenge$ ) respectively. HPE was washed out at the open, downward-pointing, right-hand-side arrow.

Relatively low to high concentrations of *Harpagophytum procumbens* secondary root aqueous extract (HPE, 10–1000  $\mu\text{g/ml}$ ) provoked concentration-related, significant ( $P < 0.05$ – $0.001$ ) increases in the baseline tone (basal tension), and contracted uterine muscle strips taken from rats in the early, middle or late stages of pregnancy (data not shown).

## Discussion

The findings of the present *in vitro*, uterine muscle strip study are similar to those obtained on the chick isolated, parasympathetically-innervated oesophageal muscle preparations (Mahomed, 2004), and on some mammalian isolated gastro-intestinal tract smooth muscles (Mahomed *et al.*, 2005). Relatively low to high concentrations of *Harpagophytum procumbens* secondary root aqueous extract (HPE) always induced concentration-related, significant ( $P < 0.05$ – $0.001$ ), persistent and profound spontaneous, rhythmic, myogenic contractions of, and contracted, uterine muscle strips taken from stilboesterol-pretreated female rats. The plant's extract produced similar contractile effects on uterine muscle strips taken from pregnant rats. The precise mechanism of this stimulant action of the plant's extract on uterine muscle strips is not fully understood at the moment. The ability of indomethacin and/or atropine to reduce or abolish HPE-induced contractions of the uterine muscle preparations used in this study would appear to suggest possible release of prostaglandins and/or other uterotonic substances or mediators, including acetylcholine, by the plant's extract. The observation that *H. procumbens* secondary root aqueous extract (HPE) possesses anticholinesterase activity (Mahomed, 2004) would also

appear to buttress the possible involvement of cholinergic muscarinic receptor stimulation in the uterine stimulant, uterotonic action of HPE.

*Harpagophytum procumbens* root has been reported to contain sugars, flavonoids, iridoid glycosides, phenolic acids, quinones, phytosterols, triterpenoids, acetoside esters and minerals (Watt and Breyer-Brandwijk, 1962; Van Wyk and Gericke, 2000; Van Wyk *et al.*, 2002). Although the exact chemical constituent/s of *H. procumbens* secondary root that is/are responsible for the observed uterine contractile effect of the plant's aqueous extract still remains speculative, the iridoids harpagoside (a cinnamic acid ester), harpagide and procumbide, are speculated to probably account, at least in part, for the uterotonic action of HPE. However, the experimental evidence obtained in the present *in vitro* study indicates that aqueous secondary root extract of *H. procumbens* possesses contractile, uterotonic action on mammalian uterus. This finding also suggests that the use of *Harpagophytum procumbens* root should be contra-indicated in pregnancy. The contractile effect and/or uterotonic action of the plant's extract (HPE) may be due to release of uterotonic substance/s or mediator/s. However, the findings of the present laboratory animal study lend pharmacological credence to the suggested folkloric, obstetric uses of the plant's secondary root extract for induction or acceleration of labour, as well as for expulsion of retained placentas in pregnant women in some communities of Southern Africa.

## Acknowledgements

The authors are grateful to Mrs. Nirasha Nundkumar for her assistance in the extraction of *Harpagophytum procumbens* secondary roots, and to Miss Kogi Moodley for her technical assistance. Financial support from South African National Research Foundation (NRF) to one of us (IM Mahomed) is thankfully acknowledged.

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