Uterolytic effect of *Hypoxis hemerocallidea* Fisch. & C.A. Mey. (Hypoxidaceae) corm ['African Potato'] aqueous extract

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Abstract

Extracts of *Hypoxis hemerocallidea* corm (African potato) are commonly used by some traditional health practitioners in KwaZulu-Natal Province of South Africa as natural antenatal remedy to prevent threatening or premature abortion and miscarriage, and to ensure successful confinement. In this study, we investigated the uterolytic activity of *H. hemerocallidea* corm aqueous extract on spontaneous, rhythmic contractions of uterine horns taken from pregnant rats and guinea-pigs, as well as on spasmogen-provoked contractions of stilboesterol-primed, oestrogen-dominated, non-pregnant rat and guinea-pig isolated uterine horns. Relatively low to high concentrations of *H. hemerocallidea* corm aqueous extract (APE, 25–400 mg/ml) inhibited the amplitude of the spontaneous, rhythmic contractions of, and relaxed, uterine horns isolated from pregnant rats and guinea-pigs in a concentration-related manner. Furthermore, relatively low to high concentrations of APE (25–400 mg/ml) relaxed basal tones of uterine horns taken from non-pregnant, oestrogen-dominated rats and guinea-pigs in a concentration-dependent manner. The same moderately low to high concentrations of APE (25–400 mg/ml) inhibited acetylcholine-, oxytocin-, bradykinin-, and potassium chloride (K⁺)-induced contractions of oestrogen-dominated rat and guinea-pig isolated uterine horns in a concentration-related manner. Although the mechanism of uterolytic action of APE could not be established, the results of the present study lend pharmacological credence to the folkloric, ethnomedical uses of APE as a natural antenatal remedy for threatening or premature abortion, and suggest that the uterolytic action of the corm’s extract is unlikely to be mediated via β₂-adrenoceptor stimulation, but probably mediated through a non-specific spasmolytic mechanism.

Key words: *Hypoxis hemerocallidea* corm, African Potato, aqueous extract (APE), natural antenatal remedy, threatening or premature abortion

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Introduction

Despite the remarkable advancement made in orthodox medicine within the last few decades, available biomedical evidence indicates that in South Africa, approximately 80% of the black Africans still rely on traditional health practitioners and medicinal plants for their daily healthcare needs. The use of traditional medicines during pregnancy still plays a crucial role in the lives of the people living in rural areas where modern healthcare facilities are often lacking. In many rural African communities, pregnancy is usually accompanied by many traditional taboos and ceremonies to ensure successful confinement and births of healthy children (Sewram et al. 1998; 2000). In the rural communities, various morphological parts of an array of plants from diverse families and species are usually consumed by pregnant women as antenatal remedies. Such antenatal remedies are traditionally formulated as powders, extracts, infusions, decoctions, concoctions, bath soaps, and so forth, to ensure successful confinement, and/or to induce or accelerate labour at full-term. Many known medicinal plants are used as natural remedies to induce or accelerate labour (Sewram et al. 1998; 2000), while a few others are used to prevent threatening or premature abortion, and ensure successful confinement. Unfortunately, however, the quality, safety and efficacy of most herbal medicines and plant products used as South African traditional antenatal remedies have not been subjected to scientific scrutiny. One of such frequently-used South African antenatal medicinal plants is Hypoxis hemerocallidea (Fisch. & C.A. Mey.; family, Hypoxidaceae). This ‘cure-all’ medicinal plant of South Africa is a tuberous, perennial herb with long, strap-shaped leaves and yellow, star-shaped flowers. The broad and slightly hairy leaves of H. hemerocallidea are arranged one above the other to form three distinct groups of leaves spreading outwards from the centre of the plant, while the bright yellow, star-shaped flowers are borne on long, slender stalks (Van Wyk et al., 2002). The tuberous rootstock (i.e., the ‘corm’) of the herb is popularly known as ‘African Potato’ in South Africa, and is widely used in South African traditional medicines as a remedy for a catalogue of human ailments. The traditional healers of South Africa have employed the corm of the plant as a “muthi” (isiZulu word for “medicine”) for centuries, and now, the humble African Potato has been claimed to be a ‘miracle plant medicine’ in the fight against various modern and 21st century diseases of mankind. This South African ‘cure-all miracle plant medicine’ has been claimed to be an effective remedy against HIV/AIDS-related diseases, arthritis, yuppie flu, hypertension, diabetes mellitus, cancer, psoriasis, gastric and duodenal ulcers, tuberculosis, urinary tract infections, asthma, and some central nervous system (CNS) disorders, especially epilepsy and childhood convulsions (Watt and Breyer-Brandwijk, 1962; Hutchings, 1989; Pujol, 1990; Hutchings et al. 1996; Albrecht, 1995; Albrecht et al., 1995; Van Wyk et al., 2002). The above pharmacotherapeutic effects of African Potato have been strongly ascribed to the sterols, stanols, sterolins and norlignan glycoside, hypoxoside, present in the corm (Drewes et al., 1984; Albrecht et al., 1995; Bouic et al., 1996; Nair et al., 2007). The best-known and fully-established chemical constituents of the plant’s corm are presented in Fig. 1.

The effects of some cations, anions and certain drugs on spontaneous activities of uterine smooth muscle strips taken from non-pregnant and pregnant mammals have been investigated and reported by a number of workers (Kuriyama and Suzuki, 1976; Osa and Kawarabayashi,
Uterolytic effects of African Potato (1977; Kuriyama et al., 1998). According to Kuriyama et al. (1998), visceral smooth muscle cells play a critical role, through changes in their contraction-relaxation cycle, in the maintenance of homeostasis in biological systems. The investigators further observed that features of the cells differed markedly from one tissue to the other, and from one species to another. The workers also noted that often, there were regional differences within a given tissue.

Using micro-electrode techniques, Kuriyama and Suzuki (1976) investigated the changes in membrane electrical properties of rat myometrium during gestation and following ovarian hormone treatments. The investigators recorded spontaneously-generated bursts of electrical activity, alternating with silent periods, from non-pregnant, pregnant and post-partum myometria, and found that membrane potential was highest during the middle stage of gestation, although the spike amplitude within a burst was not uniform. The investigators further observed that in the final stage of gestation and during parturition, the membrane potential was low, and that the spikes within a burst were of low frequency and uniform amplitude. Kuriyama and Suzuki (1976) further observed that the resting and active membrane properties of progesterone-treated myometria were similar to those seen during the middle stages of gestation.

Osa and Kawarabayashi (1977), using the double sucrose gap method, investigated the

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Fig. 1. Structures of hypoxoside, rooperol and \(\beta\)-sitosterol. The biologically-inactive norlignan diglucoside, hypoxoside, is deconjugated and converted by \(\beta\) glucosidase enzyme to form the biologically-active aglycone, rooperol.
effects of Na⁺, Ca²⁺, anions and isoprenaline on the plateau potential in circular muscles of pregnant rat myometrium, and observed that the amplitude and duration of the plateau potential increased by raising the concentration of the external Ca²⁺ to between 0.3 and 3 mM, and that the plateau potential decreased when the external Ca²⁺ concentration was further increased. The investigators also observed that the plateau potential was prolonged in low Na⁺ solution, and that isoprenaline increased membrane conductance and depressed the plateau.

However, the present study was prompted by the claim of some traditional health practitioners in KwaZulu-Natal Province of South Africa that decoctions, infusions and extracts of *Hypoxis hemerocallidea* corm are effective antenatal remedies for the treatment, management and/or control of threatening or premature abortions. The aim of this study was, therefore, to investigate the uterolytic action of African Potato aqueous extract in mammalian experimental animal paradigms *in vitro*.

**Materials and methods**

**Ethical considerations**

The experimental protocols and procedures used in this study were approved by the Animal Ethics Committee of the University of KwaZulu-Natal, Durban 4000, South Africa; and conform to the “Guide to the Care and Use of Animals in Research and Teaching” [published by the Ethics Committee of the University of KwaZulu-Natal, Durban 4000, South Africa].

**Animals**

Healthy, young adult, pregnant and non-pregnant (normal) female Wistar rats (250–350 g) and Dunkin-Hartley guinea-pigs (300–400 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 drinking tap water *ad libitum*. Some of the non-pregnant (normal) rats and guinea-pigs were pre-treated with stilboesterol (0.2 mg/kg s.c.) 20–24 hours before use. Vaginal smears were taken immediately before sacrifice in order to ascertain that the animals were in oestrus. Pregnancy was established in mated rats and guinea-pigs by examining the animals daily for the presence of cervical plugs. The day on which cervical plug was first found was taken as ‘day one’ of pregnancy. Early pregnancy was regarded as days 1–8, middle gestation period was taken as days 10–14, and late pregnancy was taken to be days 16–20. All the animals were fasted for 16 hours, but still allowed free access to drinking tap water, before the commencement of our experiments.

**Plant material**

Fresh corms of *Hypoxis hemerocallidea* (African Potato) were purchased from a fruit kiosk along West Street in Durban, KwaZulu-Natal Province of South Africa, between June and November, 2007. The corms were identified and authenticated by the staff of Botany Department, University of KwaZulu-Natal (where a voucher specimen of the plant has been deposited). One kg of the fresh corms were washed with distilled water, cleaned, cut into smaller pieces and milled in a waring commercial blender. The milled corm was macerated in
distilled water and extracted twice, on each occasion with 2.5 l of distilled water at room temperature (26 ± 1°C) with occasional shaking for 48 hours. The combined distilled water solubles obtained were concentrated to dryness under reduced pressure in a rotary evaporator at 60 ± 1°C. Freeze-drying and solvent elimination of the crude aqueous extract gave 78 g (i.e., 7.8% yield) of a dark-brown, powdery, ‘African Potato’ aqueous extract (APE). Without any further purification, aliquot portions of the crude extract residue (APE) thus obtained were weighed and dissolved in distilled water (at room temperature) for use on each day of our experiments.

**Acute toxicity testing**

The median lethal dose (LD₅₀) of APE was determined in mice by a modified method of Lorke (1983), using intraperitoneal and oral (intragastric) routes. Mice fasted for 16 hours were randomly divided into groups of 10 mice per group. The procedure described in detail earlier by Ojewole (2006) was used for the determination of the acute toxicity of the plant’s extract in the mice, following intrapritoneal and oral routes.

**Evaluation of uterolytic activity of APE**

Each non-pregnant (normal) or pregnant animal was euthanized with halothane inhalation and bled out. Its two uterine horns were carefully cleaned free from extraneous and connective tissues, trimmed and quickly removed. Tubular segments of approximately equal lengths (2–3 cm long) were removed from the uterine horns by cutting off both ends. The two uterine horn segments thus obtained were separately suspended in 30-ml Ugo Basile’s two-chambered organ-baths (model 4050) containing de Jalon’s physiological solution (DJS, of composition, in g/l: NaCl, 9.0; KCl, 0.42; NaHCO₃, 0.5; CaCl₂·2H₂O, 0.06; and glucose, 0.5) maintained at 32 ± 1°C and continuously aerated with carbogen (i.e., 95% O₂ + 5% CO₂ gas mixture). Each uterine horn strip was subjected to an applied resting tension of 1 g, and allowed to equilibrate for 45–60 min, during which time the bathing de Jalon’s physiological solution (DJS) was changed every 15 min before it was challenged with stepwise, escalated concentrations of APE (25–400 mg/ml) alone, or sequential doses of acetylcholine (ACh), oxytocin, bradykinin or potassium chloride. Two uterine horn strips from the same animal, one used as extract- or drug-treated ‘test’, and the other one used as distilled water-treated ‘control’ preparation, were always set up at a time (in order to make allowance for changes in tissue sensitivity). The ‘control’ uterine horn strips were always treated with distilled water (0.1–0.5 ml) only. Sub-maximal contractions (i.e., 70–80% of the maximum contractions) of the drug-treated ‘test’ preparations were elicited by sequential, exogenous additions of either ACh (1 µg/ml), oxytocin (0.5 µU), bradykinin (5 ng/ml), or potassium (K⁺, 30 mM) to the bath fluid. Sub-maximal muscle tensions developed by the spasmogens used were similar, and approximately equal to 1.5 g. APE-induced decreases in the spasmogen-provoked muscle tensions were considered as inhibitory effects of APE. The inhibitory effects of APE on the sub-maximal muscle tensions developed by each of the spasmogens used were investigated by sequential additions of stepwise, graded concentrations of APE (25–400 mg/ml) to the bath-fluid, followed, 2–3 min later, by subsequent additions of any of the spasmogens used to the bath fluid.

In all cases, after the maximal relaxation to each of the graded concentrations of APE had
been achieved, the uterine horn muscle preparation was washed out 3–5 times with fresh de Jalon's physiological solution, and then left to recover (for 10–20 min) and return to pre-drug treatment baseline level before it was contracted again with any of the standard spasmogens. Changes in tension developed by the uterine horn preparations (contractions and/or relaxations) were recorded isometrically by means of Ugo Basile's force-displacement transducers and pen-writing 'Gemini' recorders (model 7070).

**Drugs**

The following reference drugs were used: acetylcholine chloride, potassium chloride (Sigma Chemical Co.), oxytocin (Parke-Davis), and bradykinin (Sandoz). All drugs were dissolved and/or diluted in distilled water on each day of our experiments. Drug concentrations quoted in the text refer to final organ-bath concentrations.

**Data analysis**

Experimental data obtained are presented as means (± SEM). Data obtained from distilled water-treated 'control' uterine horn muscle strips were used as baseline values. The differences between the data obtained with the plant's extract- and reference drug-treated 'test' uterine horn muscle preparations, and the data obtained with distilled water-treated 'control' uterine horn muscle strips, were subjected to one-way analysis of variance (ANOVA; 95% confidence interval, GraphPad Prism 5), followed by Dunnett's post-hoc test (Dunnett and Goldsmith, 1993). In all cases, values of $P \leq 0.05$ were taken to imply statistical significance.

**Results**

**Acute toxicity study**

The LD$_{50}$ value for intraperitoneally-administered APE was found to be $1,785 \pm 116$ mg/kg, while the LD$_{50}$ value for orally-administered APE was $3.72 \pm 0.45$ g/kg. Oral administration of APE up to 2.5 g/kg did not produce any visible toxic manifestations (e.g., respiratory distress, uncoordinated muscle movements, etc) or mortalities in mice.

**Effects of APE on uterine horns isolated from pregnant rats and guinea-pigs**

Uterine horns taken from pregnant rats and guinea-pigs exhibited spontaneous, rhythmic, pendular contractions. Relatively low to high concentrations of APE (25–400 mg/ml) inhibited the amplitude, and sometimes the frequency, of the spontaneous, rhythmic contractions, and relaxed the uterine muscle preparations in a concentration-related manner. Figure 2 shows a typical trace obtained with a pregnant guinea-pig isolated uterine horn, while Fig. 3 summarizes results obtained with rat and guinea-pig uterine horns. In all cases, moderate to high concentrations of APE (200–400) always caused profound relaxations of uterine horns taken from pregnant rats and guinea-pigs in a concentration-dependent fashion (Fig. 4).

**Effects of APE on uterine horns isolated from oestrogen-dominated, non-pregnant rats and guinea-pigs**

Uterine horns taken from stilboesterol-primed, and oestrogen-dominated, non-pregnant
(normal) rats and guinea-pigs were always quiescent and devoid of spontaneous, rhythmic contractions (unlike uterine horns isolated from pregnant rats and guinea-pigs). Relatively low to high concentrations of APE (25–400 mg/ml) always relaxed the basal tones of the uterine horn muscle preparations in a concentration-dependent manner. The same low to high concentrations of APE (25–400 mg/ml) always inhibited ACh-, oxytocin-, bradykinin- or
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potassium chloride-induced contractions of the oestrogen-dominated uterine horns in a concentration-related manner (data not shown).

Discussion

The LD$_{50}$ value for intraperitoneally-administered APE was found to be 1,785 ± 116 mg/kg, while the LD$_{50}$ value for orally-administered APE was 3.72 ± 0.45 g/kg. The gut wall and hepatic ‘first pass’ metabolic and elimination processes, coupled with the slow and variable degree of absorption following oral administration of APE would result in low blood (systemic) levels of the extract that would be non-toxic and non-lethal to the animals. On the contrary, the relatively rapid absorption following intraperitoneal administration of APE would result in high systemic levels of the extract, leading to toxic effects in the animals. The differences in blood concentrations of the extract following oral and intraperitoneal routes of administration would, therefore, seem to account for the differences obtained for the LD$_{50}$ values of APE in the acute toxicity studies.

The effects of some cations, anions and certain drugs on spontaneous activities of uterine smooth muscle strips taken from non-pregnant and pregnant mammals have been investigated by a number of workers (Kuriyama and Suzuki, 1976; Osa and Kawarabayashi, 1977; Kuriyama et al., 1998). Pharmacologically, relaxations of uterine smooth muscle strips taken from non-pregnant and pregnant mammals are believed to be mediated via $\beta_2$-adrenoceptor stimulation. However, the results of the present study indicate that APE possesses uterolytic activity in the mammalian experimental animals used. To the best of our knowledge, this is the first report on uterine activity of H. hemerocallidea corm in biomedical literature. The findings of our study are in agreement with the observations reported by Kuriyama and Suzuki (1976), Osa and Kawarabayashi (1977) and Kuriyama et al. (1998).

However, previous studies in our laboratories and elsewhere have reported antidiabetic, hypoglycaemic, anti-inflammatory and analgesic (Ojewole, 2002; 2006; Mahomed and Ojewole, 2003); antibacterial, anti-inflammatory and antioxidant (Steenkamp et al., 2006); anti-cancer (Albrecht et al., 1995); and renal (Musabayane et al., 2005) effects of APE in various experimental animal paradigms. The above pharmacotherapeutic effects of ‘African Potato’ have been ascribed to the sterols, stanols, sterolins and norlignan glycoside, hypoxoside, present in the corm (Drewes et al., 1984; Albrecht et al., 1995; Bouic et al., 1996; Nair et al., 2007).
known and fully-established chemical constituents of the plant’s corm are presented in Fig. 1.

APE (25–400 mg/kg p.o.) dose-dependently and significantly \( (P<0.05–0.01) \) inhibited the amplitude (and in some cases, the frequency) of the spontaneous, rhythmic contractions of, and relaxed, pregnant rat and guinea-pig uterine horn preparations in a concentration-dependent manner. The same low to high concentrations of APE (25–400 mg/ml) also inhibited ACh-, oxytocin-, bradykinin-, or potassium chloride-induced contractions of oestrogen-dominated, non-pregnant rat and guinea-pig uterine horn preparations in a concentration-related manner (data not shown), suggesting that APE-induced uterine horn relaxations are unlikely to be mediated through \( \beta_2 \)-adrenoceptor stimulation. Recent studies in our laboratories (Nyinawumuntu and Ojewole, 2008 - unpublished observation) have shown that APE provoked concentration-related inhibitions of the spontaneous, rhythmic, peristaltic contractions of the rabbit isolated duodenum, and relaxed the muscle. Moreover, it has been observed that APE relaxed guinea-pig isolated ileum in a concentration-related manner, and antagonized ACh-, histamine-, serotonin-, and potassium chloride \( (K^+) \)-induced contractions of the guinea-pig ileum in a concentration-dependent manner (Nyinawumuntu and Ojewole, 2008 - unpublished observation). The above observations are in consonance with the findings of the present study which suggest that APE possesses antimotility and non-specific spasmolytic effects. However, the spasmolytic effects of APE on spasmogen-induced contractions of uterine horn muscle strips taken from stilboesterol-primed, oestrogen-dominated, non-pregnant rats and guinea-pigs, like the spasmolytic effects of the plant’s extract on rabbit and guinea-pig intestinal smooth muscles, would appear to be mediated through a non-specific spasmolytic mechanism. The sterols, stanols and sterolins present in \( \text{H. hemerocallidea} \) corm, especially rooperol and \( \beta \)-sitosterol (see Fig. 1), are speculated to account for the uterolytic and spasmolytic activities of APE. Further studies are, however, required to clarify this speculation. In conclusion, experimental evidence obtained in the present laboratory animal study indicates that \( \text{Hypoxis hemerocallidea} \) corm aqueous extract possesses uterolytic activity. This finding lends pharmacological support to the anecdotal, ethnomedical uses of ‘African Potato’ as a natural supplementary antenatal remedy for the management and/or control of threatening or premature abortion in some rural communities of South Africa.

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