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Safety profile in pregnant rats of a natural antidiabetic agent extracted from *Mormodica charantia*

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Abstract: We have examined the effects of an unripe fruit extract of *Mormodica charantia* Linn, on pregnancy outcome of rats when given during early- (days 1–7), mid- (days 8–16) and late- (days 15–21) gestation. The extract was administered orally in two different concentrations (1 ml/100 g/day or 2 ml/100 g/day). Several parameters of reproduction and neonatal development were determined and computed. The extract did not have deleterious effects on pregnancy outcome during early pregnancy (in terms of vaginal bleeding and pre- and post-implantation losses), late pregnancy (in terms of vaginal bleeding, number of pups born and day of partus) or neonatal development (in terms of body weight, time taken for the appearance of fur and opening eyes of pups). In contrast, during mid-pregnancy, the extract induced vaginal bleeding, resorption of fetuses, post-implantation losses, small for dates fetuses and retardation of fetal growth. However, the number of uterine implants remained unimpaired. Further, the extract had no effect on the duration or stage of the oestrous cycle in normally cycling rats. The fetal growth retardation is likely to have been mediated via the hypoglycaemic activity of the extract. We conclude that *M. charantia* should not be recommended as a natural antidiabetic drug in diabetes complicating pregnancy and that its heavy consumption is best avoided in normal pregnancy (especially during mid-gestation).

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Keywords: fetal growth, *Mormodica charantia*, oestrous, post-implantation loss, pregnancy, Sri Lanka, vaginal bleeding

Introduction: The fruit of *Mormodica charantia* Linn (Family: Cucurbitaceae, Gam Karavila in Sinhala and Packakkai in Tamil) is recommended by the Ayuvedic Physicians of Sri Lanka [1] as a food supplement in diabetes. The local population considers it to be a galactogague – (including milk secretion). The fruit extract of *M. charantia* has been scientifically evaluated and shown to have significant hypoglycaemic activity [2,3].

Allopathic drugs used in diabetes, (for example, sulfonylureas and biguanides) are contraindicated in pregnancy because of high perinatal morbidity and mortality [4]. Also, the seed extracts of *M. charantia* have abortifacent activity [5]. Since *M. charantia* is recommended as an antidiabetic food in Sri Lanka, we thought it important to determine the effects of this plant on reproductive outcome when consumed during pregnancy.

We have now investigated the effects of an extract of the fruits of *M. charantia* on pregnancy using the rat model, with a view to extrapolating the data to humans.

Materials and methods: Fresh unripe fruits of *M. charantia* were purchased from a vegetable store in Colombo, Sri Lanka. The identify of these was authenticated by Professor R.N. de Fonseka. Department of Botany, University of Colombo. The fruits were washed, deseeded and cut into thin slices. These were immediately minced using Kenwood mincer and the pulp squeezed through four layers of gauze.

The volume of the filtrate was measured and freeze-dried, using a freeze drier (Model LFD–600 EC, Laytant Life Science, Tokyo, Japan). When required the freeze-dried extracts were macerated in a porcelain mortar and reconstituted in distilled water (DW) to the original volume. 1 ml/100 g/body weight and 2 ml/100 g/body weight was orally administered to rats.

Healthy adult Sprague-Dawley rats (males weighing 200–250 g and females weighing 175–200 g) from our own colony were used as experimental animals. They were kept in a well-ventilated animal house under standardized conditions (temperature: 28–31 °C : photoperiod: approximately 12 h natural light and 12 h dark). The animal had free access to pelleted food (Oils and Fats Corp, Seeduwa, Sri Lanka) and tap water.

Pro-oestrous rats ($n = 62$) were selected by vaginal smearing and individually paired with a male rat of proven fertility (between 17.00 and 18.00 h). Successful matings were confirmed by the presence of sperm in vaginal smear the following morning (between 8.00 and 9.00 h), and this was designated as day 1 of presumed pregnancy.

30 day 1 (early-phase) pregnant rats were randomly divided into three groups and were orally treated (8.00–10.00 h) with DW (vehicle) or fruit extract daily for 7 consecutive days in the following manner: group 1 ($n = 10$), DW (1 ml/100 g/day); group 2 ($n = 10$) extract, (1 ml/100 g/day); group 3 ($n = 10$) extract, (2 ml/100 g/day).

20 day 8 mid-phase) pregnant rats were randomly divided into three groups and dosed orally (8.00–10.00 h) with DW or extract daily for eight consecutive days in the following manner: group 1 ($n = 6$), DW (1 ml/100 g/day); group 2 ($n = 6$) extract, (1 ml/100 g/day); group 3 ($n = 8$) extract, 2 ml/100 g/day).

12 day 15 late-phase) pregnant rats were randomly divided into two groups and treated orally (8.00–9.00 h) with DW ($n = 6$) (1 ml/100 g/day) or extract ($n = 6$) 1 ml/100 g/day daily for six consecutive days.

All these treated rats were observed daily during the treatment period and post-treatment period (either up to laparotomy or parturition) for survival, overt clinical signs of toxicity including vaginal bleeding and expulsion of products of conception, stress and changes in behaviour. Their body