Research article

Assessment of reproductive impact of the aerial parts of *Caralluma dalzielii* N. E. Br in female Wistar rats

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ABSTRACT

Caralluma dalzielii N. E. Brown belonging to family Asclepiadaceae, is a popular cactus-shaped plant native to East Africa. The aerial parts are used traditionally for treating various diseases including infertility. The present study evaluated the effects of the aqueous extract of the aerial parts of *Caralluma dalzielii* (AECD) on reproductive performance of female Wistar rats. Adult female virgin rats were allotted into four major groups namely pre-conception, post-conception, implantation site and ovariectomized rats' groups. Each group was subdivided into 4 groups and treated orally with 125, 250, 500 mg/kg of AECD or distilled water (vehicle). In the pre-conception and post-conception groups, litter sizes, pups' weights, deformities, gestation length and reproductive indices were determined. Number of implantation sites and weights of embryos were assessed in the implantation site group while in the ovariectomised rats' group, uterine weights were determined. AECD produced no difference in litter size and reproductive indices in pre-conception group while in post-conception group the litter size at 500 mg/kg was significantly ($p < 0.05$) reduced compared to the control. Post-implantation loss index was high, and the other reproductive indices were reduced at 500 mg/kg. Whereas at the dose of 125 mg/kg, post-implantation loss index was reduced, and litter size was increased when compared to the control group. At 500 mg/kg, AECD caused a significant ($p < 0.05$) decrease in the number of implantation sites and weight of embryos while at 125 mg/kg the implantation sites increased. A significant ($p < 0.05$) increase in the uterine weight in the ovariectomised rats' group was observed at all dose levels. Our study provides scientific evidence that supports the traditional use of AECD in the treatment of infertility. At a lower dose, AECD acts by increasing the number of implantation sites and litter size of animals but at a higher dose, it may be embryotoxic. AECD increases uterine wet weight in ovariectomised rats suggesting that the plant may be oestrogen-like.

1. Introduction

Caralluma dalzielii N.E. Brown (family: Asclepiadaceae) is a cactus-like shaped plant with 5-merous flowers that grows up to 1 m high mainly in West Africa and Sudan (de Kock and Meve, 2007). It is a perennial, erect and sparsely-branched plant with green stems (Burkill, 1985). In Africa, the species is distributed across the Sahel (Plowes, 2008) and in northern Nigeria it is usually found close to the prayer houses hence its Hausa name 'Karan Massallachi' meaning 'mosque stalk'. The plant is eaten raw by labourers as an appetite and thirst suppressant, and as an endurance enhancer (Adnan et al., 2014). It is used in folkloric medicine for the treatment of many diseases including infertility (Ugwah-Oguejiofor et al., 2019) and as aphrodisiac (Oyama et al., 2007; Ibrahim et al., 2010). The ethnomedicinal recipe of the plant for use in various disease conditions is as required. For the treatment of infertility, a decoction or maceration of the dried plant is made and taken as prescribed by the herbalist.

Scientific studies in male rats have demonstrated that oral administration of aqueous extract *Caralluma dalzielii* increase testosterone level with no distortion in the testicular tissues (Ugwah-Oguejiofor et al., 2018). The safety of this plant at LD_{50} greater than 2000 mg/kg has been documented (Ugwah-Oguejiofor et al., 2019). Saponins, flavonoids,

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alkaloids, volatile oil, steroids, glycosides, terpenoids, cardiac glycosides and saponins glycosides have been identified in the aqueous extract of the *C. dalzielii* (Ugwah-Oguejiofor et al., 2019). Isolation and characterisation of several compounds have been carried out on the plant extract (Oyama et al., 2007). Also, cytotoxic activities of the various pregnane glycosides fractions from the plant have been reported (De Leo et al., 2005). However, scientific evidence in literature about the effects of this native plant on female reproductive system is scarce.

The use of this plant has gained high popularity for the treatment of female infertility without scientific validation. The aim of the present study was therefore to investigate the effects of aqueous extract of the aerial parts of *Caralluma dalzielii* N. E. Br on reproductive performance of female Wistar rats.

2. Materials and methods

2.1. Collection and preparation of aqueous extract of Caralluma dalzielii

The aerial parts of *C. dalzielii* was collected from Sokoto North local government area in Sokoto state in the month of December (2016) after the flowering season. Taxonomic identification and authentication were carried out in the Department of Pharmacognosy and Ethnopharmacy, Usmanu Danfodiyo University, Sokoto by Dr. Halilu Mshelia. A voucher specimen (Pcg/UDUS/Asdy/001) of the plant was deposited in the herbarium of the same department. The plant was air dried at room temperature to a constant weight and pulverised with pestle and mortar. Five hundred grams of the dried powdered material was macerated in 5 L of distilled water for 48 h. The aqueous extract was filtered through a Whatman filter paper and the resulting filtrate evaporated to dryness over a regulated hot water bath maintained at 60–70 °C to obtain a 9.12 % (w/w) residue.

2.2. Experimental animals

One hundred and fifty female virgin Wistar rats (*Rattus norvergicus*) weighing about 180–200 g (10 weeks old) were obtained from Mike Ugwah animal house in Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. The animals were allowed to acclimatise for 2 weeks before the commencement of the study. Standard commercial chow and water were provided *ad libitium* for the animals. Housing conditions were maintained at 25 ± 2 °C at 12 h day/night cycles. The study was approved by the Animal Research Ethical Committee of the Department of Pharmacology and Toxicology, Usmanu Danfodiyo University, Sokoto (PTAC/Cd/MT/002-17). Procedures for the study complied with EC Directives 86/609/EEC and the established public health guidelines in Guide for Care and Use of Laboratory Animals (2011).

Virgin rats with at least two consecutive regular 4–5 days oestrus cycles were randomly allotted into four main groups: i) The first group was to assess reproductive indices in pre-conception treatment with the extract; ii) the second was to assess reproductive indices in continuous treatment with the extract till delivery (post-conception); iii) the third group was aimed to study implantation sites and iv) the fourth group was to evaluate the effect of the extract on uterine weight in ovariectomised rats. Each of the four main groups was divided into 4 subgroups: 3 treated groups which received 125, 250 or 500 mg/kg/day of the aqueous extract of *Caralluma dalzielii* (AECD) and the control group which received 5 ml/kg/day of distilled water (vehicle) orally.

2.3. Evaluation of reproductive performance in rats

2.3.1. Assessment of reproductive indices in pre-conception treatment group

Twenty-four female rats were divided into 4 groups of 6 animals each. Group I was the control and received distilled water (5 ml/kg/day). Groups II-IV were the treatment groups and received 125, 250 and 500 mg/kg/day of AECD. Oral treatment to all experimental groups were carried out daily by gastric feeding for a period of 10 days prior to mating. The animals were paired with the males when they were at proestrus phase from day 11. Majority of the rats were pregnant within 1–2 days. The few animals that were not pregnant were left with the male for not more than 5 days. Vaginal smears were examined every morning for detection of spermatozoa using a light microscope. Day 1 of the pregnancy was taken as the day on which spermatozoa was detected in the vaginal smear (Mello et al., 2005; Ruiz-Luna et al., 2005). All the animals were daily observed for signs of illness, abortion and prolong duration of pregnancy. Inspection for births in all the animals' cages commenced from pregnancy day 19. Immediately after birth the numbers of alive and dead pups were recorded, the pups were weighed and generally inspected for any deformity up to day 21 after birth.

2.3.2. Assessment of reproductive indices in post-conception treatment group

Forty female rats were divided into 4 groups (I-IV) of 10 animals each. Group I was the control and received distilled water (5 ml/kg/day). Groups II-IV were the treatment groups and received 125, 250 and 500 mg/kg/day of AECD. All experimental groups were treated orally as before for a period of 10 days prior to mating and continuously during mating until delivery (Ugwah-Oguejiofor et al., 2011). On day 11, all the animals were housed two female rats per male animal in a cage following the previous method of mating. The animals were inspected as before and the numbers of alive and dead pups were recorded, the pups were weighed and generally inspected for any deformity up to day 21 after birth.

2.3.3. Assessment of implantation sites

Twenty-four female rats were divided into 4 groups (I-IV) of 6 animals each. Group I was the control and received distilled water (5 ml/kg/day). Groups II-IV were the treatment groups and received 125, 250 and 500 mg/kg/day of AECD. All experimental groups were treated orally by gastric feeding daily for a period of 10 days prior to mating, during mating and up till 10 days of gestational age. On day 11, all the animals were sacrificed by cervical dislocation. Hysterotomy was performed, implantation sites were checked, and the embryos counted and weighed.

2.3.4. Calculation of reproductive indices

The following reproductive indices were calculated (Mello et al., 2005): Mating index defined as number of sperm positive females/number of mated females × 100; Pregnancy index defined as number of pregnant females/number of sperm positive females × 100; Delivery index defined as number of females delivering/number of pregnant females × 100; Birth live index defined as number of live offspring/number of offspring delivered × 100; Post-implantation loss index defined as number of implantation sites – number of live foetuses/number of implantation sites × 100.

2.3.5. Assessment of uterine weight in ovariectomised rats

In order to assess a possible estrogenic role of AECD on uterine weight, female rats were ovariectomised. Animals were shaved in the surgery area and anaesthetised with a combination of intraperitoneal doses of ketamine (80 mg/kg) and xylazine (10 mg/kg). A transverse peritoneal incision was made on the middle part of the abdomen, and the ovaries were exposed and removed. Two weeks after recovery from surgery, a smear was performed on all rats for 10 days before treatment commenced to confirm that all ovariectomised animal smears showed no cornification. Twenty rats were exposed orally by gavage to distilled water (5 ml/kg distilled water), 125, 250 or 500 mg/kg of AECD for a period of 7 days. At the end of the treatment, rats were sacrificed by cervical dislocation. Body and uterine wet weights were recorded. Uterine index was calculated as:

Uterine index = Weight of the uterus/Body weight of the rat X100

2.4. Statistical analysis

The results were expressed as Mean ± SEM or Mean ± SD. Comparison of means were performed by One-Way Analysis of Variance

(ANOVA) followed by Dunnett's post- hoc test. Reproductive indexes were analysed using the paired proportion test (Chi square). Statistical evaluations were performed using GraphPad prism 6 and a difference was considered significant at $p < 0.05$.

3. Results

3.1. Effect of AECD on reproductive indices in pre-conception treatment group

The number of pups of animal treated with 500 mg/kg/day of the extract was higher than the control although this was not statistically significant (Table 1). There was a significant ($p < 0.05$) increase in pup's body weight in the group treated with 250 mg/kg/day of the extract but not in other doses when compared with the control (Table 1). Other fertility indices like sperm positive females, pregnant females, mating index (%), pregnant Index (%), delivery index (%) and birth live index (%) were similar to that of the control group (Table 1).

3.2. Effect of AECD on reproductive indices in post-conception treatment group

The number of pups per litter increased as the dose of the extract decreased. The highest dose of AECD, 500 mg/kg/day, produced the least number of pups per litter which was significantly ($p < 0.05$) lower than that of the control. The extract at 125 mg/kg/day produced more pups than the control. Also, the pups body weight was significantly ($p < 0.05$) higher at 125 mg/kg/day than the control. The period of gestation was not different from any of the groups and control. No external deformity

was noticed in any of the groups (Table 2). In the fertility indices assessment, the number of sperm positive animals was highest in the extract group that received 500 mg/kg/day and higher than the control group (Table 2). Pregnancy and delivery indices at the dose of 500 mg/kg/day were significantly ($p < 0.05$) lower while mating index was significantly ($p < 0.05$) higher than that of the control group. The post-implantation loss index at 500 mg/kg/day was more than the control and the other treated groups. At the extract doses of 125 and 250 mg/kg/day, the post-implantation loss indices were lower than that of the control group. The extract at 125 mg/kg/day showed the least post-implantation loss index (Table 2).

3.3. Effects of C. dalzielii on implantation sites of rats

The number of implantation sites in the lowest dose 125 mg/kg/day, was significantly ($p < 0.05$) more than that of the control group and all the other treated groups. AECD at the dose of 500 mg/kg/day produced the least number of implantation sites which was significantly ($p < 0.05$) lower than that of the control group (Figure 1).

The mean weight of the embryos at the extract dose of 250 mg/kg/day was significantly ($p < 0.05$) higher than those of the control group. The highest dose at 500 mg/kg/day produced mean weight of embryos that was significantly ($p < 0.05$) lower than that of the control group (Figure 2). The embryos of the rats that received 500 mg/kg/day of the extract were highly resorbed at 10 days' gestational age (Figure 3) compared with all the other groups.

A = implantation sites of rats treated with 125 mg/kg/day aqueous extract; B = implantation sites of rats treated with 250 mg/kg/day

Table 1. Reproductive outcome of pre-conception treatment with *C. dalzielii* on the rats.

Outcome/Dose (mg/kg)	125	250	500	Control
No of (dams) pups	(5)31	(5)27	(5)39	(5)37
No of pups per litter	6.2 ± 1.3	5.4 ± 2.51	7.8 ± 2.15	7.4 ± 0.55
Pups body weight (g)	5.9 ± 0.04	6.8 ± 0.15*	6.2 ± 0.29	5.9 ± 0.01
Mated females	6	6	6	6
Sperm positive females	6	6	6	6
Pregnant females	5	5	5	5
Mating index (%)	100	100	100	100
Pregnant Index (%)	83	83	83	83
Delivery Index (%)	100	100	100	100
Birth live Index (%)	100	100	100	100

Values presented as Mean ± SD for no of pups; Mean ± S.E. M for weight of pups.
*p < 0.05 compared to control.

Table 2. Reproductive outcome of post-conception treatment with *C. dalzielii* on the rats.

Outcome/Dose (mg/kg)	125	250	500	Control
No of (dams) pups	38 (5)	20 (4)	2 (2)*	28 (5)
No of pups per litter	7.4 ± 0.55	5.2 ± 0.82	1.0 ± 1.41*	6.2 ± 1.92
Pups body weight (g)	6.46 ± 0.18*	5.64 ± 0.14	5.85 ± 0.04	5.77 ± 0.10
Mated females	10	10	10	10
Sperm-positive Females	7	7	10*	6
No. of ext. deformity	0	0	0	0
Gestation period	21.88 ± 0.33	22.08 ± 0.02	22.04 ± 0.08	22.08 ± 0.22
Mating Index (%)	70	70	100*	60
Pregnancy Index (%)	71.43	57.14	20*	83.33
Delivery Index (%)	71.43	57.14	20*	83.33
Birth live Index (%)	100	100	100	100
Post-implant. loss Index (%)	9.52*	13.79	78.26*	24.32

Implant. = Implantation; ext. = external; Values presented as Mean ± SD for no of pups.
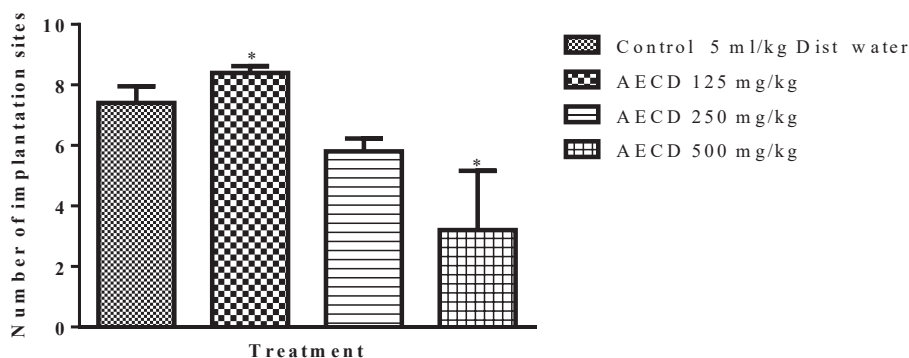*p < 0.05 compared to control.

Figure 1. Effects of *C. dalzielii* on the number of implantation sites of rats. n = 6; *$p < 0.05$ compared to control; AECD = Aqueous extract of *Caralluma dalzielii*; Values are expressed as Mean ± S.E.M.
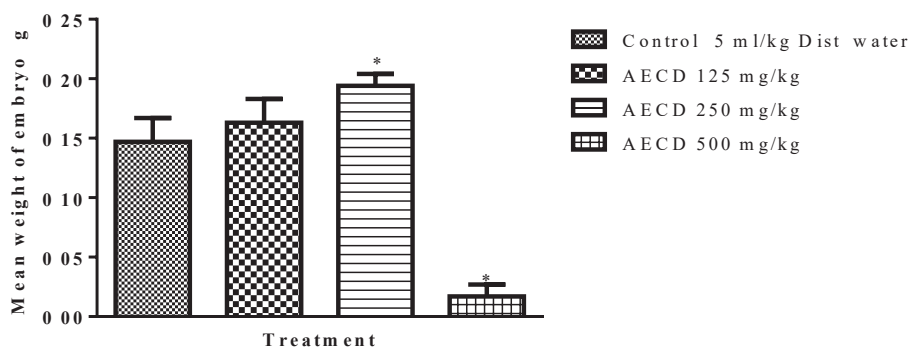

Figure 2. Effects of *C. dalzielii* on mean weight of embryos in the implantation site experiment. n = 6; *$p < 0.05$ compared to control; AECD = Aqueous extract of *Caralluma dalzielii*; Values are expressed as Mean ± S.D.

aqueous extract; C = implantation sites of rats treated with 500 mg/kg/day aqueous extract; D = implantation sites of Control rats.

3.4. Effect of aqueous extract of Caralluma dalzielii on uterine weight in ovariectomised rats

Treatment of the ovariectomised rats with AECD for 7 days caused a significant increase in the uterine wet weight of the rats. The uterine indices as calculated in all the treated groups were significantly (p < 0.05) more than that of the control (Figure 4).

4. Discussion

The present study evaluated the effects of administration of aqueous extract of *Caralluma dalzielii* on reproductive performance in female Wistar rats. When the extract was administered to the rats before mating commenced, the litter size, pups' weight and all fertility indices were similar to that of the control group. However, when the extract was administered to pregnant rats, the litter size, pups' weight and all fertility indices decreased as the dose of the extract increased. The post-implantation loss index was higher than that of the control group at the highest dose group and lower than the that of the control group at the lowest dose group.

Assessment of the effect of AECD administered to the rats prior to mating produced no significant advantage on the rats as the fertility indices were similar to that of the control group. There may be other possible effects which this pre-conception treatment may confer to the rats, but our study has not shown that. However, on continuous administration, AECD at a higher dose increased the mating index of the rats. Spermatozoa were found in the vaginal smear of all the rats that were mated (100% mating index), this feature suggests that the extract may have no contraceptive effects (da Rocha et al., 2018). Furthermore, assessment of the effect of AECD on pregnant rats showed an increase in

both litter size and pups body weight at a low dose. This suggests that at a lower dose, AECD may cause multiple pregnancies. Our study showed that at a higher dose level, AECD produced a lower litter size of the animals suggesting that the extract may contain compounds that are inimical to the development and growth of embryos. Hence our need to determine the effect of the extract on embryo implantation sites.

When implantation takes place, the embryo can either continue its normal development or be resorbed (Mourik et al., 2009; Yakubu and Bukoye, 2009). There are certain substances that interfere with the process of implantation. Some of such substances include steroidal hormones (Chen et al., 2013) and alkaloids (Morris et al., 1967; Poole and Poole, 2019). These substances can either cause increased delay in development and/or resorption of the embryo (Goonasekera et al., 1995; Almeida and Lemonica, 2000; Leite et al., 2004). In this study, administration of AECD on sperm positive rats for ten consecutive days increased the number of implantation sites at a lower dose and caused a decrease in the number of implantation sites at a higher dose. The decrease in the number of implantation sites may be an evidence that AECD at a high dose may have a toxic effect on embryo development. The post-implantation loss index is an essential parameter for assessing the number of embryos implanted in the uterus (Chang et al., 2002; da Rocha et al., 2018). The post-implantation loss index was higher at the highest dose. At a lower dose, AECD may support implantation and possibly have a protective effect on the number of resorptions whereas, at a higher dose, it may promote activities that are not favourable for embryo implantation and growth. This result explains possibly why the number of pups produced by the dams at the lower dose group was significantly higher than that produced at the highest dose group. The increase in post-implantation loss index with the corresponding decrease in the litter size of the rats receiving high dose of the extract could also be attributed to possible disturbance in the equilibrium level of reproductive hormones in the animals (Ding et al., 1994; Hiremath et al., 1999). This is because embryo implantation is being regulated by a time-dependent interplay of

Figure 3. Implantation sites of rats showing resorption in rats treated with 500 mg/kg of aqueous extract of *Caralluma dalzielii*. A= implantation sites of rats treated with 125 mg/kg/day aqueous extract; B= implantation sites of rats treated with 250 mg/kg/day aqueous extract; C=implantation sites of rats treated with 500 mg/kg/day aqueous extract; D= implantation sites of Control rats

the ovarian hormones (oestrogens and progesterone). Loss of implantation may occur if there is a disruption in these hormone interplay (Ding et al., 1994). Oestrogenic activity of the plant was therefore evaluated in ovariectomised rats.

In ovariectomised rats, circulating level of oestrogen is very low because of the removal of the ovary, which is the primary source of oestrogen in females (Ateba et al., 2013). The increase in weight of the uterus after administration of the extract for 3–7 days depicts estrogenic effect (Hewitt et al., 2003). Oestrogen causes uterine growth response in a non-genomic mechanism which involves a combination of hypertrophic responses inducing changes such as increase in vascular permeability, water imbibition, and cellular infiltration (Rockwell et al., 2002; Hewitt et al., 2003; Jablonski et al., 2003). This sequence of events subsequently leads to an increase in uterine weight. In our study, the extract increased uterine wet weights in the rats which indicated oestrogen-like activity. Following this result, the decrease in implantation site and the number of pups in the rats receiving the highest dose of the extract could be linked to the possible reduction in the ovulation rate of the rats resulting from the negative feed-back mechanism as a result of high oestrogenic activity induced by high dose of the extract (Skibola, 2004). It may also be linked to possible contraction in the uterine smooth muscle caused by oestrogen-like compounds which could lead to the resorption of the embryos after its implantation (Ford, 1982). Even though oestrogen is necessary for implantation and

maintenance of pregnancy (Huet and Dey, 1987; Hamilton and Kennedy, 1993) high level of it are known to disrupt fertility (Jefferson et al., 2002; Ashworth et al., 2006; Ross et al., 2007). Previous studies have collaborated with this report where phytoestrogens have been shown to cause loss of pregnancies and infertility (Burton and Wells, 2002).

In both the pre-conception and post-conception treatment groups, there was no external malformations observed in the pups at all dose levels. This implies that the extract of AECD may not be teratogenic however, more studies are needed to confirm this. There was also no effect on the gestation length. Also, the plant has shown in our previous studies to contain alkaloids, flavonoids, saponins and steroids (Ugwah-Oguejiofor et al., 2019). These phytoconstituents interact with the reproductive system in several ways. Alkaloids have been shown to decrease plasma concentrations of hormones that encourage fertility (Lauritzen et al., 1997; Browning et al., 1998; Bianco et al., 2006) and cause embryotoxicity (Kumar and Sachin, 2013). Some flavonoids possess antioxidant properties therefore they can scavenge reactive species or influence the intracellular redox status (Thirupathy et al., 2011). Thus, some have been shown to be protective against oxidative stress that could cause implantation loss of embryos (Yu et al., 2014). Some saponins are known to improve oocyte quality by decreasing the proportion of abnormal oocytes which may be present in the animal (Yu et al., 2003). These compounds may thus be responsible for the activities observed in the plant extract. However, further studies are needed to isolate and characterise the active compound in the plant.

5. Conclusion

In conclusion, administration of high dose of the aqueous extract of *Caralluma dalzielii* to adult female rats increases post-implantation loss and decreases the litter size. At a high dose, it may be embryotoxic. However, at a lower dose, it increases the litter size and reduces the post-implantation loss. The extract also increases uterine weight in ovariectomised rats. Our study provides scientific evidence for the traditional use of the *C. dalzielii* extract to enhance female fertility.

Declarations

Author contribution statement

C.J. Ugwah-Oguejiofor: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

C.O. Okoli: Conceived and designed the experiments.

M.O. Ugwah: Performed the experiments; Contributed reagents, materials, analysis tools or data.
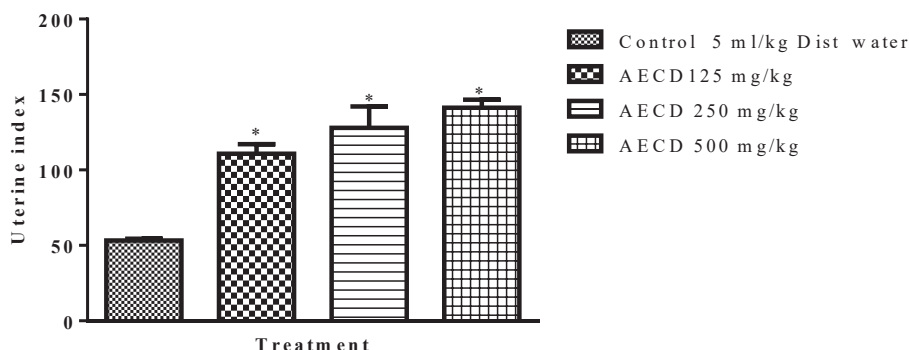
R.U. Okolo: Analyzed and interpreted the data.

Figure 4. Effect of aqueous extract of *Caralluma dalzielii* on uterine weight in ovariectomised rats. n = 6; *$p < 0.05$; Values presented as Mean ± S.E.M.

S.O. Bello: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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