Trop J Nat Prod Res, September 2024; 8(9):8418-8423 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Pro-fertility Effects of Gboma Eggplant (*Solanum macrocarpon*) Leaf Extract in Female Albino Rats

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ARTICLE INFO

Article history:
Received: 10 November 2024
Revised: 01 June 2024
Accepted: 04 September 2024
Published online: 01 October 2024

ABSTRACT

Fertility enhancement has been the subject of research for many years; more so due to the observed decline in fertility worldwide. *Solanum macrocarpon* has been widely acclaimed for its medicinal and antioxidant properties. However, its effects on fertility parameters have not been reported. This study evaluated the impact of ethanol leaf extract of *S. macrocarpon* (ELESM) on fertility parameters in female albino rats. Thirty (30) female rats of about 10 – 12 weeks of age were separated into six groups administered 0.5 ml of distilled water (placebo), 400mg/kg ELESM, 800mg/kg ELESM, 10 mg/kg cyclophosphamide (CP) + placebo, 10mg/kg CP + 400mg/kg ELESM, and 10mg/kg CP + 800mg/kg ELESM, respectively. After treatment (42 days), the females were mated with normal (untreated) adult male rats. The ELESM-treated rats exhibited significantly ($p < 0.05$) higher numbers of primary/secondary follicles, antral follicles and corpora lutea than the control groups. Cross-section of the ovaries of female rats showed normal histoarchitecture and healthy follicles at various developmental stages in the control and ELESM-treated rats, as well as improvement in histoarchitecture of CP + ELESM rats, compared with the CP + placebo group. Although the ELESM-treated animals had slightly higher fertility index, there was no statistical difference ($p > 0.05$) between their live foetal numbers, mean foetus weights, mean foetal crown-rump lengths, number of resorbed embryos, and fertility index compared with those of the normal control. The findings suggest the pro-fertility effects of the extract in female rats and the potential to ameliorate cyclophosphamide-induced gonadal toxicity.

***Keywords*:** *Solanum macrocarpon* , Eggplant, Fertility index, Ovarian follicles, Ovarian histology, Plant extract, Cyclophosphamide.

Introduction

The ability to reproduce is one of the most essential characteristics of living organisms as all forms of life can reproduce themselves from one generation to the next under appropriate conditions. Fertility refers to the ability to reproduce with pregnancy being the primary outcome parameter. Infertility, therefore, is defined as the inability to achieve pregnancy after a significant period of sexual intercourse without any form of contraceptive measure.[1] Fertility enhancement has been the subject of research over the years, especially due to the observed decline in fertility worldwide. The decline has been attributed to increasing industrialization and environmental exposures, both of which have negative impacts on fecundity and fertility.[2,3] In experimental animal models as well as clinical practice, parameters such as ovarian follicle counts,[4] sex hormone levels,[5,6] ovarian weight and histology,[7] and fertility index in pregnant rats[8,9] are commonly employed as markers of female fertility. Studies on fertility and reproductive physiology in animals commonly use certain drugs such as cyclophosphamide to model reproductive tissue dysfunction and damage.[10,11] Cyclophosphamide, which is an alkylating agent that is widely used in chemotherapy, produces several side effects including suppression of the immune system, oxidative stress and gonadal toxicity, which are exploited in experimental studies.[12–14]

Plant parts (e.g. roots, leaves, and fruits) have proved a useful and secure source of natural medicines for centuries throughout all known civilizations and diverse cultures.[15] It has been shown that the vast majority of plants contain biologically and pharmacologically potent ingredients, making them beneficial for treating a variety of illnesses.[16] To date, natural (plant) products as well as products/structures derived from them remain relevant, playing a major role in the process of finding and developing new drugs.[17] Numerous compounds originating from plants are at different phases of clinical development, demonstrating the practicality and importance of using natural products as sources and drivers of novel therapeutic possibilities.[17] Plants and their derivatives have long been used to aid fertility, employing their pro-fertility and aphrodisiacal qualities.[18–20] Moreover, in recent times, their application in the treatment of infertility has increased.[21]

The plant, *Solanum macrocarpon* Fam. Solanaceae (Figure 1), which is believed to have originated from West Africa is reportedly used in traditional medicine as an anthelminthic, and laxative to treat stomach, throat and cardiac ailments.[22,23] Some common names of the plant include Gboma eggplant, *Aubergine gboma*, African eggplant, and brinjal.[24] It serves as an important fruit and leaf vegetable in Nigeria and some other West African countries.[22] Parts of the plant, such as its fruits and leaves are edible - being used as vegetable to cook soups and sauces, and are known to give a characteristic bitter taste. Phytochemical constituents have been linked with playing a protective role and reducing attendant risks in several types of chronic diseases. This reputation is due, in part, to their antioxidant and free radical scavenging

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Citation: Ezechukwu CS, Mbegbu EC, Mgbenka BO, Nwani CD, Nnamonu EI, Orji EA. Pro-fertility Effects of Gboma Eggplant (*Solanum macrocarpon*) Leaf Extract in Female Albino Rats. Trop J Nat Prod Res. 2024; 8(9):8418-8423. https://doi.org/10.26538/tjnpr/v8i9.25

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

effects, since the pathogenesis of multiple chronic disorders affecting humans, including infertility, have been attributed to the effects of free radicals such as reactive oxygen and nitrogen species.[25] However, despite the many reported beneficial effects and uses of *S. macrocarpon* , there is a paucity of evidence regarding its effect on fertility. Hence, sequel to a comparative study of antioxidant potentials of fruits, leaves and roots of *S. macrocarpon* , in which the leaf extract showed the greatest antioxidant potential,[26] this study evaluated the effects of ethanol leaf extract of *Solanum macrocarpon* (ELESM) on fertility in albino rats, in view that its antioxidant properties could improve reproductive parameters.

Materials and Methods

Collection of plant material

A few mature fruits of *Solanum macrocarpon* were collected from a garden in the staff quarters of the University of Nigeria, Nsukka, from which the seeds of the plant were obtained, dried and cultivated in the agricultural farm of the university to obtain large quantities of the leaves for the study. Upon maturity, the leaves of the plant were harvested (in October 2018), washed, sliced into bits for easy drying at room temperature and ground into fine powder for use in preparing ethanol extract. A specimen of the plant material was deposited and assigned voucher number UNH 335 at the herbarium of the Department of Plant Science and Biotechnology, University of Nigeria, Nsukka.

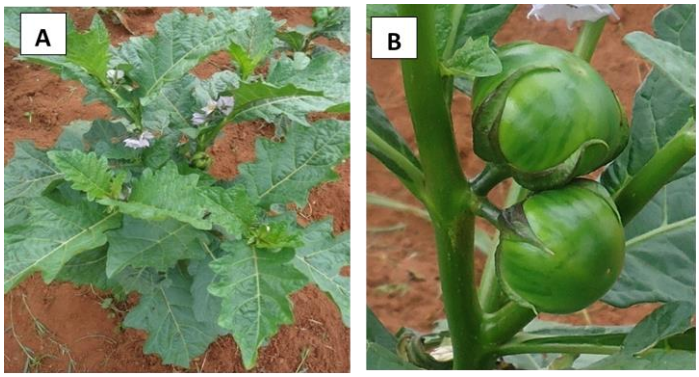

Figure 1: *Solanum macrocarpon* plant parts showing (A) leaves and (B) fruits

Preparation of extracts

The finely powdered leaf sample (500 g) was put into 1 L of 70% ethanol for 48 hours with occasional stirring. After the maceration, the mixture was filtered with the aid of a muslin cloth. This was then followed by evaporating the filtrate to dryness using a hot air oven set at 40ºC to obtain the extract. The extract was then preserved in a refrigerator at 4ºC before and throughout the experiment duration.

Experimental animals

The animals used in this study (30 female and 10 male Sprague Dawley rats of about 10 weeks of age) were procured from the Laboratory Animals Unit of the Department of Zoology and Environmental Biology, University of Nigeria, Nsukka. The animals were such as have not been used for any prior experiment. They were maintained on pelletized commercial rat feed and clean drinking water throughout the period of the experiment and were allowed seven days for acclimatization before the experiment.

Ethical approval

The ethical approval for this study was obtained from the Institutional Animal Care and Use Committee (IACUC), Faculty of Veterinary Medicine, University of Nigeria, Nsukka, with reference number FVM-UNN-IACUC-2019-042. The institutional guidelines for the use of experimental animals were carefully followed.

Determination of gonadosomatic index

The ovaries of all the rats were extracted, freed from adherent tissues and blood, and weighed. The gonadosomatic index was calculated as follows:[27]

$$\text{Gonadosomatic Index (GSI)} = \frac{\text{gonad weight}}{\text{body weight}} \times 100 \quad (1)$$

Histology of ovary and follicle count

This was carried out as described by Slaoui and Fiette.[28]The ovary samples from the various groups of rats were placed in Bouin's fluid for 24 hours for fixing and then transferred into 70% ethanol solution. After that, the tissues were soaked in chloroform for a whole night, and then penetrated and embedded in melted paraffin wax. Five to six microns were used to trim and section the blocks. The slices were then mounted on slides, put into xylene for 20 minutes to deparaffinize, washed and rehydrated in water, and then stained with hematoxylin and eosin (H and E). For the follicles count, every fifth section of each ovary was mounted, deparafinized, rehydrated and stained for 10 consecutive times. The ready-to-view slides were captured under the microscope using Motic camera 2.0 and the follicle numbers were visually counted.[28]

Determination of fertility parameters

The female rats were separated into six groups (A-F) comprising five rats per group, administered thus: Group A (control) – 0.5 mL of distilled water (placebo); Group B – 400 mg/kg ELESM; Group C – 800 mg/kg ELESM; Group D – 10 mg/kg cyclophosphamide (CP) + placebo; Group E – 10mg/kg CP + 400 mg/kg ELESM; Group F – 10 mg/kg CP + 800 mg/kg ELESM. The CP treatment was administered weekly while ELESM treatment was administered on alternate days. The treatment was maintained for 42 days after which, the treated females were mated with normal (untreated) adult male Sprague Dawley rats to assess their fertility parameters. For the mating phase, a mating cage was used with each female rat placed in a mating cage alone with a male. To confirm successful mating, the vaginal plug method or vaginal smear method was used.[29] After introducing the males, the cages were checked the following morning for signs of successful mating - the discovery of a vaginal (copulatory) plug on the cage floor and/or the detection of white flakes (which are the remains of the copulatory plug), in a freshly prepared vaginal smear on a grease-free microscope slide. The day of confirmation of mating was recorded for each female rat as its gestation day, and then the male rat was removed. Then, on gestation day 20 for each female rat, the rat was anaesthetized and laparotomized, drawing out the uterine horns and examining them for the fertility indices including numbers of implantation and resorption sites, live foetuses, and corpora lutea. The foetus weights were also taken and other fertility parameters were computed as follows:[29]

$$\text{Resorbed embryo number (REN)} = \text{Number of implantation sites} - \text{Number of live foetuses} \quad (2)$$

$$\text{Fertility Index (FI)} = \frac{\text{LFN} \times \text{FCRL} \times \text{PPF}}{\text{CLN}} \quad (3)$$

Where: PPF = Percentage of animals that achieved pregnancy in the group; LFN = number of live fetuses in each pregnant animal; FCRL = crown-rump length of each foetus; REN = number of resorbed embryos in each pregnant animal; CLN = number of corpora lutea in each pregnant animal

Statistical analysis

The IBM SPSS Statistics 20 software was used for the statistical analysis of all the data collected in the study. The statistical tools used were analysis of variance (ANOVA) and Duncan's multiple range test for analyzing the data and identifying homogenous means, respectively. All the statistical analyses were carried out at $p < 0.05$ significance level and the data are presented in the form mean ± standard error.

Results and Discussion

Effect of ELESM on gonadosomatic index of female albino rats

The results on the effect of ELESM treatment on the gonadosomatic index (GSI) of female albino rats (Table 1) showed no significant differences ($p > 0.05$) in the ovary weights and gonadosomatic index among all the experimental groups including the normal control (placebo) and the CP + placebo positive control. This suggests that the treatments did not significantly affect the gonad-to-body weight ratio. The gonadosomatic index is usually employed as a measure of possible toxicity to the gonads. A decrease in the rate of folliculogenesis or a rise in the rate of follicular atresia might lead to decreased GSI and vice versa.[27,30] Thus, the findings indicate the absence of gross adverse changes that could impact the gonad weights, and rule out the possibility of a gonadotoxic effect of ELESM, thereby alluding to its safety in this regard.

Table 1: Effect of ethanol leaf extract of *Solanum macrocarpon* (ELESM) on gonadosomatic index of female albino rats

Group	Body Weight (g)	Ovary Weight (g)	Gonadosomatic Index
Control (Placebo)	184.10 ± 5.25^{a}	0.076 ± 0.011^{a}	0.041 ± 0.005^{a}
400 mg/kg ELESM	188.78 ± 7.47^{a}	0.076 ± 0.011^{a}	0.040 ± 0.004^{a}
800 mg/kg ELESM	183.86 ± 6.01^{a}	0.090 ± 0.011^{a}	0.049 ± 0.006^{a}
CP + placebo	178.04 ± 6.98^{a}	0.074 ± 0.017^{a}	0.041 ± 0.009^{a}
CP + 400 mg/kg ELESM	191.30 ± 4.27^{a}	0.072 ± 0.009^{a}	0.038 ± 0.005^{a}
CP + 800 mg/kg ELESM	181.02 ± 4.24^{a}	0.088 ± 0.012^{a}	0.048 ± 0.006^{a}

Note: Values in a column with one or more identical letter superscripts are not significantly different ($p > 0.05$).

Effect of ELESM on follicle counts of female albino rats

The ELESM-treated rats had significantly ($p < 0.05$) higher primary/secondary follicles (PSF), antral follicles (AF) and corpora lutea (CL) counts than the control (placebo) group (Table 2). In addition, the CP + 400mg/kg ELESM and CP + 800 mg/kg ELESM groups had significantly higher PSF, AF and CL than the positive control (CP + placebo) group, but comparable to that of the normal control (placebo) group. The mammalian ovary produces oocytes within primordial/immature follicles, which are known to be of a definite number/quantity at birth.[31] The growing follicles are recruited from the primordial follicle pool into growing follicles – the primary, secondary, antral and preovulatory follicles.[31] The numbers of growing ovarian follicles, especially the antral follicle count, are widely recognized and employed as an indicator of folliculogenesis, female fertility and ovarian function.[4,32]. The observed higher follicle counts in ELESM-treated rats, thus, suggest an increase in follicle recruitment and development in these animals, with the resultant being an increase in the numbers of follicles reaching maturity and subsequently ovulating. This has a direct relevance on the fecundity and fertility of the animals,[4] as an increase in the rate of folliculogenesis is associated with an increase in fertility rate.[30]

Table 2: Effect of ethanol leaf extract of *Solanum macrocarpon* (ELESM) on ovarian follicle counts of female albino rats

Group	Primary/Secondary Follicles	Antral Follicles	Corpora Lutea
Control (Placebo)	88.96 ± 4.71^{b}	33.80 ± 1.79^{b}	9.47 ± 0.50^{b}
400 mg/kg ELESM	106.08 ± 5.61^{c}	39.70 ± 2.10^{c}	13.80 ± 0.73^{c}
800 mg/kg ELESM	114.80 ± 6.08^{c}	47.42 ± 2.51^{d}	14.87 ± 0.79^{c}
CP + placebo	40.28 ± 2.13^{a}	13.85 ± 0.73^{a}	3.80 ± 0.20^{a}
CP + 400 mg/kg ELESM	78.55 ± 4.16^{b}	29.95 ± 1.58^{b}	8.80 ± 0.46^{b}
CP + 800 mg/kg ELESM	86.27 ± 4.57^{b}	30.18 ± 1.60^{b}	9.00 ± 0.48^{b}

Note: Values with different letter superscripts in a column are significantly different ($p < 0.05$).

Effect of ELESM on Ovarian Histology in Female Albino Rats

Histological sections of the ovaries of female rats after 42 days of treatment (Figure 2) showed normal histoarchitecture and healthy follicles at various stages of development with normal features in the control and ELESM-treated rats. However, consistent with CP-induced gonadal toxicity, increased vacuolar degeneration of the ovarian medullary cells was observed in the CP + placebo group, which seemed to be ameliorated in the CP + 400 mg/kg ELESM and CP + 800 mg/kg ELESM groups in which only mild tissue damage was observed. Ovarian histology has been a useful tool for assessing ovarian tissues to determine the presence or otherwise of pathological conditions in both experimental and clinical scenarios.[33] The normal histoarchitecture observed in the ELESM-treated rats suggests that the extract administration did not result in toxicity to the ovaries of the animals. Thus, increasing the extract dosage could yield better outcomes regarding ameliorating CP-induced ovarian tissue damage.

Effect of Ethanol Leaf Extract of Solanum macrocarpon (ELESM) on Fertility Parameters in Female Albino Rats

The observed corpora lutea number (CLN), implantation number (IM) and resorbed embryo number (REN) were not significantly different ($p > 0.05$) between any of the treatment groups, although the CP-treated groups generally had lower CLN and IM but higher REN (Table 3). The CP-treated groups had significantly lower live foetal number (LFN) than the control but there was no significant difference between the LFN of the 400 mg/kg ELESM and 800 mg/kg ELESM in comparison with the control group. While the CP + placebo group recorded no live foetus, the CP + 400 mg/kg ELESM and CP + 800mg/kg had LFN of 2.00 ± 1.53 and 1.00 ± 1.00 respectively (Table 3). The mean foetal weights (MFW) and mean foetal crown-rump lengths (MFCRL) of the 400 mg/kg ELESM and 800 mg/kg ELESM treatment groups were not statistically different ($p > 0.05$) from that of the control (placebo) group. However, the CP-treated animals had significantly lower MFW and MFCRL compared with those that did not receive CP. The percentage of pregnant females (PPF) in all the groups was 100% except the CP + placebo and CP + 800 mg/kg ELESM which both recorded 33.33%. Finally, although the 400 mg/kg and 800 mg/kg ELESM-treated rats recorded higher fertility index (FI), they were not

statistically different from that of the control ($p > 0.05$). Similarly, the FI of the CP + 400 mg/kg ELESM and CP + 800 mg/kg ELESM groups were higher than that of the CP + placebo (0.00 ± 0.00), but not statistically different ($p > 0.05$).

Pregnancy parameters such as corpora lutea number (CLN), implantation number (IM), live foetal number (LFN), mean foetal weight (MFW), mean foetal crown-rump length (MFCRL) and fertility index (FI) have been widely used as indicators of fertility status in experimental rodent models.[29,34–36] Although the 400 mg/kg and 800 mg/kg ELESM-treated rats had slightly higher FI than the control group, the difference was not significant ($p > 0.05$). similarly, the CLN, IM, LFN, MFW, and MFCRL of the 400 mg/kg and 800 mg/kg ELESM-treated animals were comparable with those of the control group ($p > 0.05$). The CP-treated rats recorded significantly lower LFN, MFW, MFCRL as well as FI, which seemed to be slightly improved in the CP + 400 mg/kg ELESM rats. Thus, the observed significantly higher PSF, AF and CL counts in the ELESM-treated female rats did not translate to significantly higher pregnancy outcomes.

Table 3: Effect of ethanol leaf extract of *Solanum macrocarpon* (ELESM) on fertility parameters in female albino rats

Group	CLN	IM	LFN	REN	MFW (g)	MFCRL (cm)	PPF (%)	FI
Control (Placebo)	9.33 ± 0.88^{a}	9.33 ± 0.88^{a}	7.33 ± 0.88^{b}	2.00 ± 1.16^{a}	2.38 ± 0.03^{c}	4.23 ± 0.08^{b}	100.00	337.97 ± 52.40^{b}
400 mg/kg ELESM	7.33 ± 0.33^{a}	7.00 ± 0.58^{a}	6.00 ± 0.58^{b}	1.00 ± 0.00^{a}	2.74 ± 0.24^{c}	4.42 ± 0.09^{b}	100.00	359.53 ± 15.64^{b}
800 mg/kg ELESM	9.00 ± 0.00^{a}	9.00 ± 0.00^{a}	8.33 ± 0.33^{b}	0.67 ± 0.33^{a}	$1.96 \pm 0.04^{b,c}$	4.13 ± 0.06^{b}	100.00	382.41 ± 11.93^{b}
CP + placebo	3.67 ± 3.67^{a}	3.67 ± 3.67^{a}	0.00 ± 0.00^{a}	3.67 ± 3.67^{a}	0.00 ± 0.00^{a}	0.00 ± 0.00^{a}	33.33	0.00 ± 0.00^{a}
CP + 400 mg/kg ELESM	6.67 ± 1.45^{a}	7.00 ± 1.53^{a}	2.00 ± 1.53^{a}	5.00 ± 2.00^{a}	$0.85 \pm 0.43^{a,b}$	$2.29 \pm 1.15^{a,b}$	100.00	110.95 ± 72.72^{a}
CP + 800 mg/kg ELESM	2.67 ± 2.67^{a}	2.67 ± 2.67^{a}	1.00 ± 1.00^{a}	1.67 ± 1.67^{a}	$0.81 \pm 0.81^{a,b}$	1.38 ± 1.38^{a}	33.33	17.21 ± 17.21^{a}

Note: Values in a column with one or more identical letter superscripts are not significantly different ($p > 0.05$). CLN = corpora lutea number, IM = implantation number, LFN = live foetal number, REN = resorption number, MFW = mean foetal weight, MFCRL = mean foetal crown-rump length, PPF = percentage of pregnant females, FI = fertility index

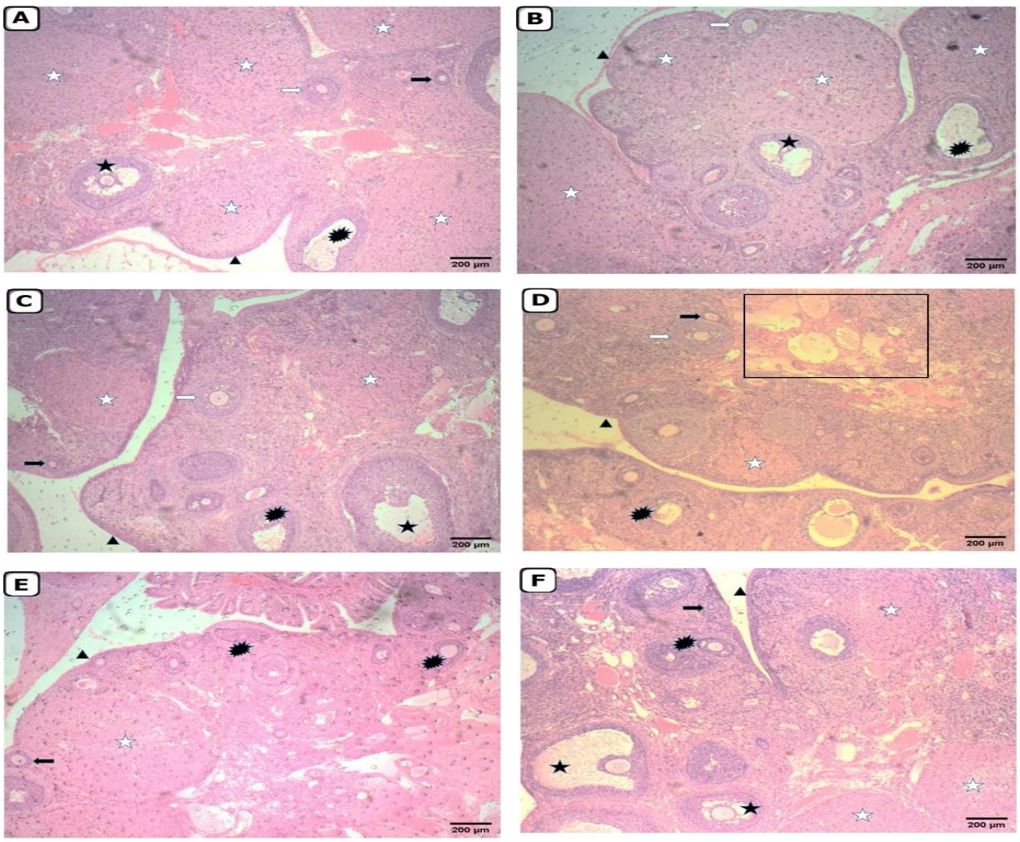

Figure 2: Photomicrographs of ovarian histological sections of albino rats (x100) showing ovarian surface epithelium (▲), primary follicles (➡), secondary follicles (⇨), antral follicles (★), corpora lutea (☆), degenerating follicles (✹), and area of vacuolar degeneration of the ovarian medullary cells (□ only in Group D). Treatment groups A = control (Placebo), B = 400 mg/kg ELESM, C = 800 mg/kg ELESM, D = CP + placebo, E = CP + 400 mg/kg ELESM, F = CP + 800 mg/kg ELESM

This could be due to the limited sample size (number of animals) or extract dose used. Notwithstanding, there are indications of potential fertility-enhancing effects in the female rats considering the slight increase in the fertility index of the ELESM-only animals compared with the normal control as well as the CP + 400 mg/kg ELESM group compared with the CP + placebo (positive control) group. IM normally

correlates with the CLN indicating blastocyst implantation in the endometrium and normal reproductive capacity.[37] Reduced litter size (i.e. low LFN), reduced implantation and increased embryo resorption are classical antifertility effects, which may occur due to inadequacy of the endometrial environment for implantation or hypermotility of the myometrium.[34,38]Atoe et al.[9] reported foetal mortality in pregnant rats exposed to *Alchornea cordifolia* and *Secamone afzelii* leaf extracts. In the same vein, Chang and colleagues[37] reported foetal toxicity in rats administered *Solanum lycocarpum* powder in terms of increased resorption, reduced number of live foetuses and reduced foetal weights. A similar study by Schwarz et al.[39] using *S. lycocarpum* fruit reported the absence of any impairment to the animals' gestation, but evidence of mild toxicity to the animals and their foetuses. FW and FCRL, are parameters of foetal growth and development. Reduced FW and FCRL, which indicate impaired foetal development might be caused by placental inadequacy or defective placental formation.[39] Summarily, although ELESM failed to significantly improve the FI and pregnancy outcomes of the CP-treated rats, we infer that the extract might possess pro-fertility effects given the observation of a slight rise in the FI of the ELESM-treated animals, as well as the improved histoarchitecture of the CP-treated rats. The choice of extract doses used in this study was based on the conventional practice of using doses between 100 mg/kg and 800 mg/kg for extracts with acute toxicity (LD_{50}) doses greater than 5000 mg/kg.[40–42] However, given that the LD_{50} of ELESM is greater than 5000 mg/kg as published elsewhere,[26] we speculate that the extract might significantly improve the fertility index at higher doses and longer duration than those used in this study.

Conclusion

The study sought to evaluate the effect of the ethanol leaf extract of *Solanum macrocarpon* (Gboma eggplant) on fertility parameters using female albino rats. Taken together, the findings indicate the pro-fertility potential of *S. macrocarpon* leaf extract in female albino rats in terms of increase in numbers of primary/secondary follicles, antral follicles and corpora lutea in addition to a marginal increase in fertility index. Furthermore, the extract showed the potential ability to ameliorate cyclophosphamide-induced gonadal toxicity based on improved ovarian histoarchitecture in cyclophosphamide-treated rats.

Conflict of Interest

The authors have no conflict of interest to declare

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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