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Effect of Azanza Garckeana on Sexual Behaviour and Fertility Potential in Alloxan Induced Diabetic Female Wistar Rats

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ABSTRACT

The use of medicinal plants to enhance sexual function has gained increasing attention due to their accessibility, cultural acceptance, and fewer side effects compared to conventional drugs. This study evaluated effect of Azanza garckeana on sexual behaviour and fertility potential in alloxan induced diabetic female wistar rats. sixty adult female rats were randomly divided into six groups of ten animals each: negative control, positive control, standard drug, Azanza garckeana (250 mg/kg) , Azanza garckeana (500 mg/kg) and Azanza garckeana (1000 mg/kg). A 30 minute observation of sexual behavior of rats in the respective groups was made on 14th day of the treatment using an infrared camera. The female rats were mated at a 1:2 ratio with male rats for the fertility research and a vaginal plug was used to identify the first successful conception. Sexual behaviors, including darting frequency and latency, hopping frequency and latency, and lordosis frequency and latency, were assessed following oral administration of the treatments. The results revealed that alloxan decreased sexual behaviour in the induced group, but the extract improved it by reducing latency and increasing frequencies. The plant's high levels of alkaloids and steroids/triterpenes may contribute to its aphrodisiac properties. Fertility indices in the respective alloxan induced groups were elevated in the AGF treated groups with the low dose having 100 per cent fertility index. These findings suggest potential therapeutic applications of these plants in managing female sexual dysfunction.

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INTRODUCTION

The efficient functionality of the reproductive system hugely depends on the neuroendocrine axis (commonly called 'hypothalamo-pituitary-gonadotropin—HPG axis') (Amah-Tariah et al., 2016; Köves et al., 2020). Via this axis, these central neural networks regulate pituitary and gonadal functions to ensure the initiation of reproductive cycles, fertility, and sexual behavior (Silva et al., 2023). Distortion of the normal physiology of this axis by underlying diseases such as diabetes mellitus could bring about sexual dysfunctions and low preganancy outcomes in women of reproductive age .

Several scientific reports have indicated that dysfunctions in sexual desire, arousal, lubrication, orgasm and satisfaction have become prevalent in women of reproductive age suffering from either Type 1 or 2 diabetes mellitus (Doruk et al.,2005; Degirmenci et al, 2017; Enzlin et al 2019). This could be due to vascular and neurological impairments caused by hyperglycemia. Microvascular damage and neuropathy could reduce blood flow to the genital areas, interfere with vaginal lubrication and diminish genital sensory responses, thereby impairing sexual arousal and satisfaction (Doruk et al., 2005).

Cases of infertility, amenorrhea and hypogonadism have also been reported in women with either Type 1 and 2 diabetes. This could be due to hypoinsulinemia or hyperinsulinemia. As several studies have shown that insulin and insulin like growth factor pathway seems to influence ovarian function. (Morariu et al.,2015; Codner et al., 2012; Thong et al.,2019; Nandi et al.,2013; Livshits & Seidman, 2009).

Insulin binds to its own receptors in the ovaries to stimulate steroidogenesis. It interacts with gonadotropins in an additive

manner especially Luteinizing Hormone (LH) by amplifying LH-induced production of androgens by theca cells (Franks et al., 1999; Nandi & Poretsky, 2013). Therefore hyperinsulemia as in Type 2 diabetes could lead hyper androgenism as in the case in Polysystic Ovarian Syndrome (PCOS) (Thong et al., 2020; Codner et al., 2012).

At the ovarian level insulin enhances amino acid transport into granulosa cells, stimulates glucose uptake and utilization and low-density lipoprotein metabolism and regulates growth and development of granulosa cells (Booth, 1990) . Consequently, patients with Type 1 Diabetes Mellitus could exhibit insufficient metabolic control due to hypoinsulinaemia leading to a high prevalence of amenorrhea, hypogonadism and infertility (Codner et al., 2012). This could drastically affect the fertility potential (pregnancy outcomes) of the individual.

Studies have reported that diagnosis of diabetes earlier in life especially before ten years of age could lead to delayed menarche (Yeshaya et al., 1995). It was found that better glycemic control and prevention of diabetic complications improves these irregularities and increases fertility rates.

An estimated one in six individuals of reproductive age suffer from low libido, which continues to be a significant global reproductive health concern (WHO, 2023). In sub- saharan Africa, including Nigeria, where prevalence rates are high and access to traditional medical treatment is restricted by infrastructure and financial constraints, the burden of this ailment is especially severe (Odeigah et al., 2020).

Over a long period of time, people have devised ways to increase sexual urge and improve fertility. This has led to the discovery and use of substances called aphrodisiacs (Gundiza et al., 2009). The term aphrodisiac has been used for substances that enhance sexual activity and are helpful in treating sexual disorders. (Retendara &deep 2013)

Due to the high cost of synthethic drugs and its side effects, the use of plants or their products to treat sexual disorders or to improve sexual performance has a long history in most countries, and their investigation in animals have proven that they are effective in improving sexual desire and sexual behavior in animals.

Among the tula people of the north eastern Nigeria, ripened fruits of Azanza garckeana commonly known as Gorontula are consumed as aphrodisiac and for treatment of infertility. (Onwa et al., 2009). This fruit is potentially therapeutic for addressing female sexual dysfunction (FSD), which encompasses problems with desire, arousal, lubrication, orgasm, and sexual satisfaction (Dikko et al., 2016). They can be soaked in a small amount of water to form jelly or boiled and made into porridge. The leaves are also eaten as vegetable (Ochokwu et al., 2015;Maroyi, 2017)). The various portions of the plant is known to possess medicinal attributes and are used to manage conditions in areas where the plant is found (Adamu et al., 2013).

Although, traditional practitioners have continued use of the fruits of this plant as therapies for low libido and infertility, there are no substantial scientific proofs to back these claims. Therefore this research is aimed at ascertaining the therapeutic effect of the hydroethanolic extract of this fruit Azanza garckeana as an aphrodisiac and in pregnancy outcomes.

2. METHOD

Experimental design

The present study was a laboratory-based experimental study using Wistar rat models. The work was carried out in the Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt.

Ethical consideration

Prior to commencement of the work, ethical approval was obtained from the University of Port Harcourt Ethics Committee on the 1st of June 2023 with reference number: UPH/CEREMAD/REC/MM89/231. All experimental procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (U.S. National Research Council, 2019). Appropriate measures were taken to ensure the safety and well-being of animal handlers in line with the Animal Handling Safety and Health Procedures (UWA S & H, 2021).

Preparation of Azanza garckeana Extract

Fruits of Azanza garckeana were collected from Tula Town, Kaltungo Local Government Area, Gombe State, Nigeria, where the plant is widely cultivated. The plant material was identified and authenticated by Dr Ekeke Chemezie, a plant taxonomist at the University of Port Harcourt Herbarium, Nigeria. A voucher specimen (UPH/P/414) was prepared and deposited at the Herbarium for reference. The fruits were separated into pulp and seeds. The pulps were air-dried at ambient temperature (approximately 37°C) and subsequently pulverized using an electric grinder. The pulverizd material was macerated in a hydroethanolic solvent (ethanol–water, 70:30 v/v) with intermittent stirring to ensure adequate extraction. The mixture was then filtered and concentrated using a rotary evaporator maintained at 60°C. The resulting extract was stored at 4 °C until further use (Ahmed et al., 2016).

Experimental Animals

Thirty (30) adult female Wistar rats (Rattus norvegicus) weighing 150-200 grams were used for the study. The Wistar rats were obtained from the Department of Physiology Animal House, University of Port Harcourt and housed under standard laboratory conditions (temperature 25 ± 2 °C, and 12-hour light/dark cycle). The rats were allowed free access to feed and clean drinking water ad libitum. All rats were allowed to acclimatise for 14 days before the commencement of the experiment.

Induction of Experimental Diabetes

Experimental Diabetes mellitus was induced in all test groups, except the normal control, by a single intraperitoneal injection of freshly prepared alloxan monohydrate at a dose of 150 mg/kg body weight, dissolved in 0.9% normal saline. To prevent initial hypoglycaemic shock, rats were provided with 5% glucose solution for 24 hours post-alloxan administration. After 72 hours, fasting blood glucose levels were measured using a glucometer via tail vein puncture. Rats with fasting blood glucose levels ≥250 mg/dL were considered diabetic and included in the study.

Experimental Grouping and Treatment Protocol

A total of thirty (30) rats were randomly assigned into six experimental groups (n = 10 per group) as follows:

1. Group 1 (Normal control): Non-diabetic rats administered distilled water.
2. Group 2 (Diabetic control): Alloxan-induced diabetic rats were administered distilled water.
3. Group 3: Diabetic rats treated with Azanza garckeana extract at 250 mg/kg body weight.
4. Group 4: Diabetic rats treated with Azanza garckeana extract at 500 mg/kg body weight.
5. Group 5: Diabetic rats treated with Azanza garckeana extract at 1000 mg/kg body weight.
6. Group 6: Diabetic rats treated with a standard antidiabetic drug (glibenclamide at 10 mg/kg body weight).

All treatments were administered orally once daily using an oral gauage for a period of 28 consecutive days.

Sexual Behaviour test

A 30 minute observation of sexual behavior of rats in the respective groups was made on 14th day of the treatment using an infrared camera. In a non-paced mating set-up, all sexual behaviours of the female; Proceptive and receptive behaviours were observed and evaluated (Roy et al., 2017).

Proceptive behaviours;

Darting Latency: time taken in seconds for the female rat to initiate darting.

Darting Frequency; number of darting runs during the observation period of 30mins

Hopping latency; time taken to hop

Hopping Frequency; number of hops during the observation period

Females were considered to be proceptive when two of these behaviors are showed during the testing period.

Receptive behaviors

Lordosis latency; time taken to assume posture that allows mounting of male

Lordosis frequency; number of lordosis during observation period of 30minutes.

Fertility Potential Test

The rats were given oral medication for two weeks before to mating at a 1:2 ratio with male rats for the fertility research. During this time, sperm in the vagina or a vaginal plug was used to identify the first successful conception. The pregnant rats were kept singly, and day 1 of the pregnancy was defined as the day on which a vaginal plug was identified or spermatozoa was detected in the vaginal smear (Mello et al., 2005; Ruiz-Luna et al., 2005).

Sample collection.

On day 14 after mating, all the animals were sacrificed by cervical dislocation. Hysterectomy was performed and implantation sites were checked and embryos counted and weighed (Ugwah-Oguejiofor et al.,2020)

At the conclusion of the experiment, the litter size was also noted. The formulas used to determine the gestational rate and fertility index were:

gestational rate = (number of females gestating/total number of females) × 100, and

fertility index = (number of mated/number of pregnant) × 100.(Ugwah-Oguejiofor et al., 2020; Subair et al, 2022)

Statistical analysis

The reproductive hormone level data results were analysed using one-way analysis of variance (ANOVA) followed by Tukey's HSD post-hoc analysis. The results were expressed as mean ± standard error of the mean (SEM). A p-value <0.05 was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21.0. Results were presented as mean ± Standard error of mean (SEM).

Groups/Treatment(s)	Darting Latency	Darting frequency	Hopping Latency	Hopping frequency	Lordosis Latency	Lordosis frequency
Group 1: Negative control (untreated rats)	132.04 ± 6.22	1.80 ± 0.37	138.91 ± 6.36	2.00 ± 0.31	150.14 ± 6.03	1.40 ± 0.24
Group 2: Positive control (Alloxan only treated rats)	141.41 ± 5.94	1.00 ± 0.00 [a]	137. 52 ± 11.66	1.00 ± 0.00 [a]	176.28 ± 6.36 [a]	1.00 ± 0.00
Group 3: Alloxan + 250mg/kg AGF	105. 71 ± 3.81 [a, b]	1.20 ± 0.20	112. 02 ± 7.45 [a, b]	1.60 ± 0.24	134.83 ± 6.58 [b]	1.00 ± 0.00
Group 4: Alloxan + 500mg/kg AGF	89.81 ± 6.53 [a, b]	2.20 ± 0.20 [b, c]	82.93 ± 5.94 [a, b, c]	2.40 ± 0.24 [b, c]	109. 27 ± 5.26 [a, b, c]	1.00 ± 0.00
Group 5: Alloxan + 1000mg/kg AGF	63.69 ± 4.77 [a, b, c, d]	2.00 ± 0.31 [b, c]	52.14 ± 7.11 [a, b, c, d]	2.40 ± 0.24 [b, c]	84.37 ± 3.95 [a, b, c, d]	1.20 ± 0.20
Group 6: Alloxan + Glibenclamide	109.60 ± 12.34 [a, b, d, e]	1.40 ± 0.24 [d]	95.35 ± 11.63 [a, b, e]	2.00 ± 0.00 [b]	133.51 ± 14.68 [b, d, e]	1.00 ± 0.00

3. RESULTS

Table 1: Sexual behaviours in AGF treated female Wistar rats with alloxan-induced diabetes

Values represent mean ± SEM, n=5; [a] Significant at $p<0.05$ when compared to group 1; [b] Significant at $p<0.05$ when compared to group 2. [c] Significant at $p<0.05$ when compared to group 3; [d] Significant at $p<0.05$ when compared to group 4; [e] Significant at $p<0.05$ when compared to group 5. AGF = Azanza garckeana fruit .

Table 1 above shows the results for the Effect of AGF on sexual behaviour in female Wistar rats with alloxan-induced diabetes.

The results for Darting Latency indicated that the values for group 3 -6 (treated with Alloxan + 250mg/kg AGF, Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF and Alloxan + Glibenclamide respectively) were significantly ($p<0.05$) reduced when compared to group 1 and 2 (Negative and positive control) respectively. The degree of reduction is as follows; group 6 > group 3 > group 4 > group 5. The values of group 5 and 6 (treated Alloxan + 1000mg/kg AGF and Alloxan + Glibenclamide) were significantly ($p<0.05$) decreased and increased respectively when compared to group 4 (Alloxan + 500mg/kg AGF). The darting latency results for group 6 (Alloxan + Glibenclamide) was significantly increased when compared to group 5 (treated Alloxan + 1000mg/kg AGF).

For Darting frequency; the values of group 2 (alloxan only) were significantly ($p<0.05$) decreased when compared to group 1(negative control). The values of Groups 4 and 5 (Alloxan + 500mg/kg AGF and Alloxan + 1000mg/kg AGF) were significantly ($p<0.05$) increased when compared to groups 2 and 3 (treated with Alloxan only and Alloxan + 250mg/kg AGF) respectively. The darting frequencies of group 6 (Alloxan + Glibenclamide) was significantly ($p<0.05$) reduced when compared to group 4 (Alloxan + 500mg/kg AGF).

The values for hopping latency from group 3 -6 (treated with Alloxan + 250mg/kg AGF, Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF and Alloxan + Glibenclamide respectively) were significantly ($p<0.05$) reduced when compared to groups 1 and 2 (negative and positive control) respectively. The values of groups 4 and 5 (Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF

respectivey) were significantly ($p<0.05$) reduced when compared to group 3 (Alloxan + 250mg/kg AGF). The values of group 5 (Alloxan + 1000mg/kg HEAG-FP) was significantly ($p<0.05$) reduced when compared to group 4 (Alloxan + 500mg/kg AGF). While group 6 (Alloxan + Glibenclamide) values were significantly ($p<0.05$) reduced when compared to group 5 (Alloxan + 500mg/kg AGF).

The Hopping frequencies of group 2 (Alloxan only) was significantly ($p<0.05$) decreased when compared to group 1 (negative control). The values of groups 4, 5 and 6 (Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF and Alloxan + Glibenclamide respectively) were significantly ($p<0.05$) increased when compared to group 2 (Alloxan only). The values of group 4 and 5 (Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF) were significantly ($p<0.05$) increased when compared to group 3 (treated with Alloxan + 250mg/kg AGF).

The lordosis latency values of group 2 (Alloxan only) were significantly ($p<0.05$) increased while groups 4 and 5 (Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF) were significantly ($p<0.05$) decreased when compared to group 1 (negative control). The values of group 3-6 (treated with Alloxan + 250mg/kg AGF, Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF and Alloxan + Glibenclamide respectively) were significantly reduced when compared to group 2 (Alloxan only). The degree of reduction is as follows; group 3 > group 6 > group 4 > group 5. The values of group 4 and 5 (Alloxan + 500mg/kg AGF, Alloxan + 1000mg/kg AGF) was significantly ($p<0.05$) reduced when compared to group 3 (Alloxan + 250mg/kg AGF). The values of group 6 (Alloxan + Glibenclamide) was significantly increased when compared to group 5 (Alloxan + 1000mg/kg AGF).

There was no significant difference when the values of lordosis frequencies were compared between the various groups. Although the values were reduced when compared to the negative control.

Table 2: Fertlity Indices in female Wistar rats exposed to Alloxan treated with AGF

Groups/Treatment(s)	Females Cohabited	Females mated	Pregnant females	Non-Pregant females	Fertility index (per cent)	Gestational index (per cent)
Group 1: Negative control	10	10	8	2	80	100
Group 2: Positive control	10	10	0	10	0	0
Group 3: 250mg/kg AGF	10	10	8	2	80	100
Group 4: 500mg/kgAGF	10	10	8	2	80	100
Group 5: 1000mg/kg AGF	10	10	6	4	60	100
Group 6: Glibenclamide	10	10	3	7	30	60

No. of rats in each group=10

Table shows 0 per cent fertility index in the alloxan induced group and 80 per cent in the low and medium dose treated groups , 60 per cent fertility index in the high dose and 30 per cent in the group treated with standard drug.*

4. DISCUSSION

Sexual behavior in alloxan induced female wistar rats treated with hydroethanol extract of Azanza garckeana fruit pulp (AGF)

The outcome of the study on sexual behaviour showed significantly longer duration ($p<0.05$) of darting latency, hopping latency and lordosis latency and reduced the frequencies in the alloxan induced phases when compared with the negative control. This is in line with recent studies done by Enzlin et al., 2009; which reported that women with type 1 diabetes have increased rat of sexual dysfunction

including loss of sexual interest or desire, arousal or lubrication difficulties, painful intercourse or loss of ability to reach orgasm. However, the extract ameliorated this condition as evidenced by markedly shorter period ($p<0.05$) in darting latency, hopping latency, lordosis latency with markedly higher frequencies ($p<0.05$). Results have shown that alkaloids and steroids /triterpenes and specifically, the active ingredients present in this plant have aphrodisiac activities and antidiabetic, due to their actions on specific receptors in hypothalamo-pituitary axis. Thus the presence of high levels of these phytochemicals could be the cause of the increased aphrodisiac activity (Ahmed and Aslam, 2018; Edo et al., 2023).

Aphrodisiac activity or sexual arousal is known to be due to neuroendocrine stimulation of increased genital blood flow, neurogenic discharge that brings about vagina lubrication, partial buffering of acidity, and rise in oxygen tension—all of which improve spermatozoal survival and function. The consequent uterine and vaginal contractions produce the orgasm feeling (Salonia et al., 2010). Another report have it that aphrodisiac plants can be used in the management of erectile dysfunction (ED) in men (Salonia et al., 2010). Considering these submissions alongside the foregoing finding of the present study, it is suggestible to state that the plant may be potent in stimulating the hypothalamo-hypophyseal axis in a yet to be understood manner. Thus, further molecular evaluation of different concentrates of plant may unravel more useful aspects of it on reproductive functions

Fertility potential in alloxan induced female rats treated with AGF

Results from fertility indices showed 0 per cent fertility index in Alloxan induced group. This is in line with Codner et al., (2012), who reported that patients with Type1 Diabetes Mellitus and insufficient metabolic control exhibited a high prevalence of amenorrhea, hypogonadism and infertility .

Fertility indices were elevated in the AGF treated groups with the low dose having 80 per cent fertility index. This is in line with Ukoh et al. (2022) and Ugwah-Oguejiofor et al., (2020).

This fertility boosting properties of AGF could be as a result of the presence of phytochemicals like triterpenes and the actions of the isolated active ingredients that have been proven to have high binding affinities for reproductive hormone receptors.

CONCLUSION

The study found that alloxan decreased sexual behaviour in the induced group, but the extract improved it by reducing latency and increasing frequencies. The plant's high levels of alkaloids and steroids/triterpenes may contribute to its aphrodisiac properties.

Fertility indices in the respective alloxan induced groups were elevated in the AGF treated groups with the low dose having 100 per cent fertility index. This is in line with Ukoh et al., (2022) and Ugwah-Oguejiofor et al., (2020).

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AUTHOR CONTRIBUTIONS

Laz-Okenwa J.O.A: Conceptualisation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing

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