



Effects of *Xylopia aethiopica* Pod Extract on Reproductive Hormones in Female Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Plants and their metabolites have been used in the treatment of various disease conditions from time immemorial. This study investigated the effect of hydro-ethanolic extract of pods of *Xylopia aethiopica* on reproductive hormone (follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone) in female Wistar rats. Thirty female wistar rats were randomly divided into 5 groups of six animals per group, per cage (n=6). Group A served as the normal control group and was administered distilled water while group B served as positive control and was administered 5 mg of standard drug (Clomid-Clomiphene Citrate). Groups C, D and E served as the treatment group and was administered 50 mg/kg, 100 mg/kg and 200 mg/kg extract of *X. aethiopica* respectively for seven days. Administration of drugs and extract was done via oral route. The rats were thereafter copulated with their male counterparts for 72 hours and the female rats were observed throughout their gestation and the numbers of litters produced were recorded. The hormonal assay was carried out using Enzyme Linked Immunosorbent Assay. Result showed a significant increase in FSH and Progesterone level ($p < 0.05$) in treated group when compared with the control group while no significant difference ($p > 0.05$) was observed for the luteinizing hormone in the treated groups. The work thus showed that the plant could exert a positive effect on female fertility by enhancing levels of female reproductive hormones.

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1. INTRODUCTION

Today, reproduction, fertility, population planning and level of reproductive hormones are considered critical issues especially in developing countries [1]. Hormonal imbalances are the leading cause of infertility in women. Disorders like polycystic ovarian syndrome (PCOS) and anovulation can be as a result of hormonal imbalance in women [2,3]. The application of medicinal plants to female reproductive health issues is gaining interest, as reproductive disorders are considered an important public health and social problem [4]. Plant derived chemicals that influence endocrine activities in both humans and animals have received a great deal of attention due to their possible beneficial effects. Plants and their derivatives play a key role in health and have long been known to possess biological activity [5, 6]. It is a known fact that thirty per cent of all modern drugs are derived from plants, and available evidence suggests that approximately 80% of Africans rely on traditional healthcare practitioners and medicinal plants for their daily healthcare needs [7].

Several studies have shown that chemical compounds including plant extracts could alter the concentration and function of female reproductive hormones [8,9]. The use of plants abundant in our environment to solve this problem remains crucial. One of such promising medicinal plant is *Xylopi*a *aethi*o*pica*.

*Xylopi*a *aethi*o*pica* (*X. aethi*o*pica*), commonly known as "African guinea pepper" or "Ethiopian pepper is an angiosperm of the *Annonaceae* Family, and grows predominantly in humid forest zones of West Africa [10]. In Nigeria, it is found all over the lowland rain forest and most fringe forest in the savannah zones [11]. Its common names include; African pepper, Guinea pepper, spice tree, Negro pepper, West African pepper and Senegal pepper [12]. In Nigeria it is called "Uda" (Igbo), "Chimba" (Hausa), "Eeru" (Yoruba), "Ata" (Efic), "Urhirien" (Urhrobo) [13]. *Xylopi*a *aethi*o*pica* matures as a slim, tall tree of approximately 60 cm in diameter and up to 30 m high with a straight stem having a slightly stripped or smooth bark. It bears odoriferous fruits, which are slender pods slightly curved with about 15 carpels and are arranged in capitula to form bouquets of 12-20 bacciferous-like capsules

[14]. *Xylopi*a is a compression from the Greek words "xylonpikron" which mean "bitter wood". The second part of the plant's binomial name, *aethi*o*pica*, refers to its origin, Ethiopia [15].

According to ethnomedicinal survey, the plant is used in managing a myriad of ailments and the fruits are widely consumed within many localities in Nigeria. These includes antiplasmodial [16], analgesic [10], anti-inflammatory [17], antidiabetic [18], antimicrobial effects [19, 20], membrane stability [21] among others. Aside the aforementioned benefits of the fruits of *X. aethi*o*pica*, the fruits are also used as spices and the aqueous decoctions are used especially after child birth, probably due to its haemostatic potential to arrest bleeding [22]. However, some plants can have different effect in the sex organ.

Some chemical compounds have been characterized and isolated from different parts of *X. aethi*o*pica* and have been alleged to be responsible for its diverse therapeutic and pharmacological properties. These includes saponins, sterols, carbohydrates, glycosides, mucilage, acidic compounds, tannins, balsams, cardiac glycosides, volatile aromatic oils, phenols [21, 23, 24], rutin and fixed oils [25, 26].

Phytochemicals such as alkaloids, phenolics compounds, flavonoids, tannins, glycosides (terpene, sterols and deoxy-sugar) have been characterized in the plant [27]. *X. aethi*o*pica* have also been reported to possess vitamins (A, B, C, D and E), protein and minerals like manganese and zinc [24, 25]. Also, acidic compounds like kaurine, kolavane and trachylobanediterpenes have been isolated from the stem, bark and fruit of *X. aethi*o*pica* [28]. The plant is said to also contain annonaceine-an alkaloid resembling morphine.

Although, *Xylopi*a *aethi*o*pica* has wide ethnomedicinal and social acceptance and uses, especially in Nigeria, there is however dearth of literature reports on its physiological effect on reproductive hormones such as estrogen, follicle stimulating hormones (FSH), leutinizing hormones (LH). The antifertility effect of ethanolic extract of *Xylopi*a *aethi*o*pica* on reproductive organ of male Wistar rats was demonstrated by Nwangwa, [29] and Adenibo et al. [30] reported the contraceptive efficacy of hydro-methanolic fruit extract of *X. aethi*o*pica* in male albino rats.

Also, the inhibitory effects of aqueous extract of *Xylopiya aethiopicia* on reproductive hormones in male guinea pigs was reported by Adenibo et al. [31]. This work was therefore designed to evaluate the effect of *X. aethiopicia* on reproductive hormone (Progesterone, FSH and LH) in female Wistar rats.

2. MATERIALS AND METHODS

2.1 Sample Preparation

The dried fruits of *Xylopiya aethiopicia* were purchased from Nimo central market, Nimo, Anambra state, Nigeria. They were authenticated in the Botany Department, Faculty of Sciences, Nnamdi Azikiwe University, Awka, Anambra State and a voucher specimen number NAUH-08^A was allocated to the plant specimen. The dried fruits were carefully de-seeded and the seeds were discarded. The pods were pounded into small pieces using wooden mortar and pestle and then grinded into a coarse powdered form using mechanical grinding machine.

2.2 Extraction of Plant Material

The plant extraction was done using 70% ethanol. 200 g of the coarse powdered pod was weighed out and extracted in 300ml of ethanol (W/V) via maceration for 48 hours in an air tight container and placed in a dark chamber. The mixture was filtered with Whatmann No 3 filter paper. Using a vacuum rotary evaporator, the ethanol filtrate was concentrated at low temperature of 45 °C under reduced pressure, which yielded 30 g of the jelly-like extract using the formula:
$$\frac{\text{mass of extract}(g)}{\text{mass of powdered sample}(g)} \times 100 = \text{Percentage yield}$$

2.3 Experimental Animal

The experiment was performed with thirty (30) adult female Wistar (albino) rats and fifteen (15) adult male Wistar rats. 30 female wistar rats weighing (180 - 250 g) were obtained from Anagoye farm, Awka, Anambra State. They were transported and housed in the Animal house Unit, Department of Applied Biochemistry, Faculty of Biosciences, Nnamdi Azikiwe University, Awka. The rats were kept under standard laboratory condition and fed normal rat feed pellet and water *ad libitum*. The animals were kept in standard cage and allowed to acclimatize for one week under normal laboratory condition before being dosed with the test

substance. All the experimental procedures and protocols used in this study were in accordance with the guidelines principles of Laboratory Animal Care of the National Society of Medical Research.

2.4 Experimental Design

Thirty female rats irrespective of their estrous cycle were divided into 5 groups (n=6) according to their body weight. Group A served as normal control and was administered placebo. Group B served as positive control and was administered 50 mg/kg body weight of Ova-mit (clomiphene citrate). Group C, D and E served as the treatment groups and were administered 50, 100 and 200 mg/kg body weight respectively of the plant extract via oral gavage daily for seven days.

After 1 week of drug and extract administration, each group was divided into 3 (n=2) and placed in different cages with a male counterpart for copulation for a period of 72 hours, after which the male rats are removed from the cage. The female rats were thereafter placed under observation throughout their gestation period. The record of the number of litters by each rat was taken and their weight measured.

2.5 Sacrifice and Blood Collection

Twenty four hours (24 hr) after the end of the study, the rats were anesthetized in a jar one after another with chloroform vapour soaked in cotton wool, and were quickly brought out of the jar and sacrificed. 5 ml of Whole blood samples were collected into plain vials via cardiac puncture and was allowed to clot. The clotted blood was thereafter centrifuged at 3000 rpm for 10 minutes to obtain the serum which was used for hormonal analysis.

2.6 Hormonal Studies

The serum was analyzed for Luteinizing hormone (LH), Follicle stimulating hormone (FSH), and progesterone by classical microplate enzyme immunoassay (ELISA) method, using Accu-Bind Elisa microwells kits (Monobind incorporated, lake forest, CA92630, USA).

2.7 Data Analysis

Hormonal profile results were expressed as mean \pm SD. Significance difference between mean groups was determined by one way

analysis (ANOVA). P value of < 0.05 was considered significant.

3. RESULTS

Table 1 showed the effect of *X. aethiopica* on the fertility potential of female wistar rats after 21 days of copulation. The results showed that the extract administered a dosage of 200 mg/kg body weight had the highest number of litters (11) babies while the normal control group produced no litters.

The result for the effect of *Xylopia aethiopica* extract on follicle stimulating hormone of female

Wistar rats is presented in Fig. 1. Results showed a significant increase ($P<0.05$) in group E animals administered with 200 mg/kg dose of *X. aethiopica* while there was no significant difference in the group C and D animals compared with the control groups.

Fig. 2 shows the effect of *Xylopia aethiopica* extract on luteinizing hormone of female Wistar rats. Results showed that there was no significant difference in groups D and E animals administered with 100 mg/kg and 200 mg/kg dose of *X. aethiopica* respectively while there was significant decrease in the group C animals compared with the control groups.

Table 1. Effect of *X. aethiopica* extract on fertility potential of female wistar rats

Group	Dose administered	No of adult male rats	No of adult female rats	No of litters after 21days observation
A	Distilled water	1	2	0
B	50mg/kg (clomiphene citrate)	1	2	10
C	50mg/kg (extract)	1	2	0
D	100mg/kg (extract)	1	2	5
E	200mg/kg (extract)	1	2	11

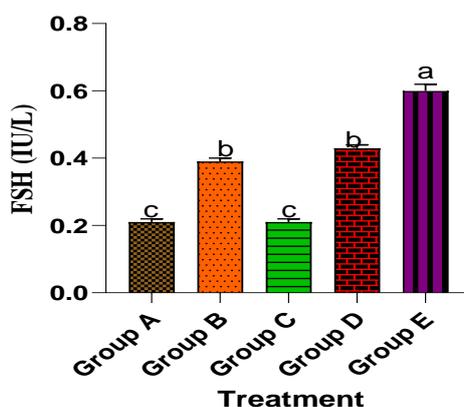


Fig. 1. Effect of *Xylopia aethiopica* extract on follicle stimulating hormone of female Wistar rats

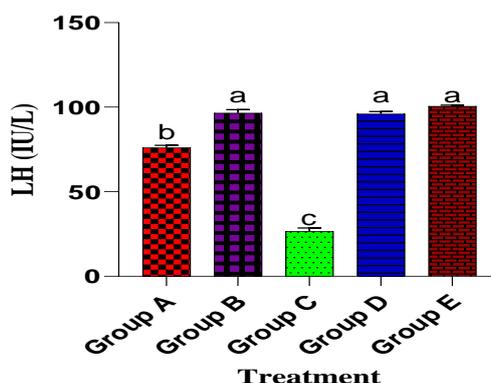


Fig. 2. Effect of *Xylopia aethiopica* extract on luteinizing hormone of female Wistar rats

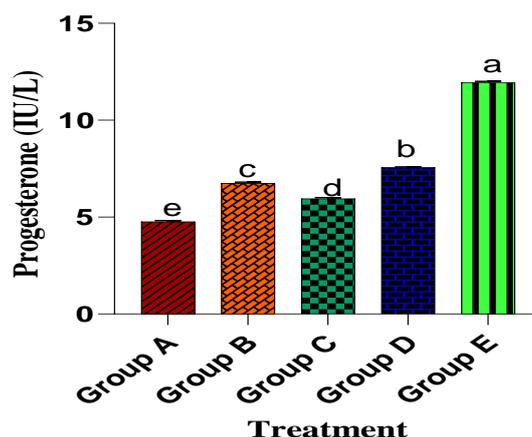


Fig. 3. Effect of *Xylopia aethiopica* extract on progesterone of female Wistar rats

The effect of *Xylopia aethiopica* extract on progesterone levels in female Wistar rats is presented in Fig. 3. A significant increase ($P < 0.05$) in groups D and E animals administered with 100 mg/kg and 200 mg/kg dose of *X. aethiopica* was observed while a significant decrease in the group C animals administered 50 mg/kg dose of *X. aethiopica* extract compared with the control groups was observed.

4. DISCUSSION

The applications of medicinal plants have been found in many disease and health conditions including reproductive disorders. In developing countries like those in the sub-sahara Africa, reproductive disorders pose a major problem [32], and its considered as the second most prevalent health care problem in Africa [33].

Follicle stimulating hormone (FSH) is the central hormone of the female reproduction and it is responsible for gonadal development and maturation at puberty. It also controls growth and maturation of ovarian follicles by stimulating receptors located on the granulosa cells. Results from this research showed that FSH level was not significantly higher ($P > 0.05$) at lower concentrations of extracts (50mg/kg and 100 mg/kg), however at higher concentration of 200mg/kg, a significant increase in the hormone level was observed. This increase in the level of FSH at higher concentration of extract may foster folliculation and maturation of the follicle. It is possible that the extract might have exerted its effect on the anterior pituitary gland or the hypothalamus since the secretion of FSH is

controlled by the concerted interaction between the gonadotropin releasing hormones of the hypothalamus on the anterior pituitary gland. Previous studies also revealed the relationship between flavonoids, glycosides and sex hormones [34, 35, 36]. It is therefore possible that the increase in FSH at higher concentration could be as a result of increase in phytochemicals like flavonoids and glycosides at higher concentration of extract. This increase in FSH level would most likely promote follicle production and keep the function of the ovary and the uterus. This study however contrasted with the reports of Agbai et al. [37] and Onyebuagu et al. [38]. Both authors reported that the fruit extract of *X. aethiopica* did not cause any significant change in FSH level even at high concentration of 500mg/kg. Also, Nnodilim et al. [39] and Adenibo et al. [30], had a contrasting report where the plant lowered plasma concentration of FSH although both were observed in male Wistar rats and male Guinea pigs respectively. Although there is a dearth of literature reviews on the effect of *X. aethiopica* extracts on female reproductive hormones, some researchers have reported similar effects of different plant exerted on the female reproduction. For instance, Mahmoud, [40] reported an increase in serum level of FSH of female Wistar rats when treated with Ovatrine.

Luteinizing hormones stimulates the secretion of sex steroids from the gonads. Ovulation-rupture of mature follicle in the ovary, is induced by a marked increase in LH secretion during the pre-ovulatory periods in female reproductive cycle. It is also known that LH stimulates Ovulation growth of Corpus luteum and progesterone

release [41]. Therefore, LH acts to augment progesterone secretion by granulosa cells. After administration of extract, there was no significant difference of LH levels in rats treated with 100 mg/kg and 200 mg/kg of extract, however, there was a significant decrease in rats treated with 50 mg/kg of plant extract. This decrease could be attributed to the rise in serum progesterone as observed in this research. This is as a result of negative feedback of rising level of progesterone to the anterior pituitary gland. Nnodilim et al., [39] and Adenibo et al. [31], reported a significant decrease in plasma LH after treatment with *X. aethiopica* extract in male Wistar rats and Male Guinea pigs respectively. Agbai et al. [37] also reported a decrease in LH level of female Wistar rats following administration of animals with extracts from *X. aethiopica*.

Progesterone is produced by the ovaries, placenta and adrenal glands. It regulates the monthly menstrual cycle, prepare the body for conception and pregnancy [42] as well as stimulation of sexual desires [43]. It also encourages the growth of lactating glands in the breast during pregnancy. High level of progesterone before menstruation have been alleged to be partly responsible for the premenstrual syndrome (PMS), such as breast tenderness, bloatedness and mood swing. From the result presented at Fig. 3, the extracts at 100 mg/kg and 200 mg/kg were able to produce a significant increase ($p < 0.05$) in serum level of progesterone when compared to the control groups, however at lower extract dose of 50mg/kg, there was no significance difference when compared to the control groups. This observation is however in contrast with that by Agbai et al. [37], where they reported a significant reduction ($p < 0.05$) in serum progesterone levels in rats treated with extracts of *X. aethiopica* dried fruits. The increase in serum level of progesterone recorded in this present work may be due to steroids in the extract which could be easily converted to progesterone [44, 45]. This report however agrees with the report of Moshfegh et al. [46] and Heidarifar et al. [47] in which the *Phoenix dactylifera* and *Anethum graveolens* respectively cause a significant increase in serum progesterone concentration in treated rats.

5. CONCLUSION

This study indicated that the extract of dried pods of *X. aethiopica* was able to increase the levels of progesterone and follicle stimulating hormone in the experimental animals. Although, there was

an increase in LH, however it wasn't significant at $P < 0.05$. Thus, the result showed that the pods of *X. aethiopica* could exert positive effect on female fertility by enhancing levels of female reproductive hormones.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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