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Research Article

Effect of aqueous fruit extract of Xylopia aethiopica fruit on some fetal growth parameters and histology of uterus in Wistar rats

Keren O. Anagor, Sani H. Garba, Joseph V. Zirahei, Nathan I. Dibal*

ABSTRACT

Introduction: *Xylopia aethiopica* (*X. aethiopica*) fruit is widely used in Africa as a food additive. It is also employed to prevent nausea during pregnancy, aid uterine contractions during childbirth, treat menstrual flow anomalies, uterine fibroids, and malaria. With the increased consumption rate among pregnant women, especially in Nigeria, the present study aimed to evaluate the effects of the aqueous fruit extract of X. aethiopica on developing fetuses and pregnancy in rats**. Methods**: Twenty pregnant female rats (gestation day zero) were randomly assigned to four groups of five rats each. Group I served as the control and received distilled water, while Groups II–IV were given *Xylopia aethiopica* fruit extract at doses of 100 mg/kg, 200 mg/kg, and 300 mg/kg, respectively, for 18 days (days 1 to 18 of pregnancy). All rats were euthanized under ketamine injection on day 19. The abdomen was opened, and the number of live and dead fetuses and the crown-rump length were measured. The uterine horns were fixed in 10% formalin for light microscopy. **Results**: Administration of the aqueous fruit extract of X. aethiopica at 100 mg/kg, 200 mg/kg, and 300 mg/kg for 18 days significantly reduced ($P < 0.05$) the number of live fetuses, fetal viability, and crown-rump length, while increasing the number of dead fetuses compared to the control. Histological examination of the maternal uterine horn revealed distortion of the uterine epithelium in rats treated with 200 mg/kg X. aethiopica, and degenerating uterine epithelium and endometrial connective tissue in rats treated with 300 mg/kg X. aethiopica. **Conclusions**: Continuous consumption of *X. aethiopica* fruit during pregnancy could be toxic to the developing fetus and affect maternal health. Hence, caution should be exercised when consuming *X. aethiopica* fruit during pregnancy.

Key words: Fetus, *Xylopia aethiopica*, uterine horn toxic, epithelium

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INTRODUCTION

Xylopia aethiopica (Dunal) A. Rich., also known as African or Ethiopian pepper, is a medicinal plant distributed in the lowland rainforests of the Guinea Savannah zones of Africa. It is cultivated in Angola, Ethiopia, Nigeria, Senegal, and Sudan[1]. This plant is commonly used in the preparation of African dishes, particularly in Nigeria, and in traditional medicine for managing various ailments such as skin infections, candidiasis, dyspepsia, cough, biliousness, febrile pains, bronchitis, rheumatism, dysentery, and boils[2,3]. Xylopia aethiopica has various pharmacological properties, including analgesic, anti-inflammatory, anti-allergic, anti-allodynic, antispasmodic, anti-hyperalgesic, antidepressant, antioxidant, and hypoglycemic effects[2,4–7].

The plant has demonstrated significant progress in reproductive medicine, including hastening fetal delivery, supporting prenatal development, and serving as a pre- and post-coital contraceptive[8]. Herbal medicine is often preferred due to its availability and a long history of proven effectiveness[9]. The female reproductive system is sensitive to environmental and chemical factors such as lifestyle, radiation, drugs, and toxicants[10]. Exposure to these factors may lead to congenital abnormalities in fetuses and affect adult physiology[11], potentially impacting reproductive capability[12]. Toxicity during pregnancy can exert various effects on fetal development and maternal health[13]. The reproductive and child health program aims to reduce maternal deaths and improve child health outcomes[14]. The use of plants for medicinal and traditional purposes to address health issues has been common in African and other societies for centuries[15]. Many herbal remedies are traditionally used as contraceptives (to prevent ovulation or fertilization), abortifacients (to prevent implantation), and as emmenagogues (to regulate uterine flow) or oxytocics (to stimulate uterine contractions, particularly to promote labor)[16].

There is growing concern about health hazards associated with the consumption of food additives[17,18], which may have teratogenic effects during preg-

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nancy[19]. Therefore, with the increasing consumption rate of Xylopia aethiopica fruit, especially among pregnant women, studies are needed to determine the health hazards associated with its continuous exposure during pregnancy and its effects on the developing fetus.

MATERIALS AND METHODS

Chemicals

Ketamine hypochlorite injection was obtained from the University of Maiduguri Clinic, while hematoxylin and eosin stains were purchased from BDH Chemical Ltd (Poole, England).

Plant Materials and Extraction

Dried fruits of *X. aethiopica* were bought from Monday Market, Maiduguri, Nigeria. Aqueous extraction was carried out as described by Adienbo et al.[5]. The fruits were pulverized, and 330 g of the powder was soaked in three litres of distilled water. The mixture was refluxed for two hours in a continuous extraction (Soxhlet) apparatus, and the solution was filtered with a thimble to remove debris. The filtrate was concentrated to a powder using a rotary evaporator.

Animals

Forty Wistar rats (20 male and 20 female), weighing between 150–200 g, were used for this study. They were purchased from the National Veterinary Research Institute Vom, Nigeria. The rats were housed in plastic cages at the animal house of the Department of Biochemistry, University of Maiduguri, Nigeria, to acclimatize to the laboratory conditions for two weeks. They were fed with grower mash (Vital Feed, Nigeria) and water ad libitum. The rats were weighed weekly throughout the study.

Experimental Design

The fetal study was carried out according to the method described by Aouni et al.[20], with minor modifications. Briefly, adult nulliparous female rats detected in the proestrus stage of the oestrous cycle were cohabited with male albino rats that had not been subjected to any experimental procedures, in a ratio of 1:1 per cage overnight. The presence of spermatozoa in a vaginal smear (identified with the aid of a light microscope) indicated successful mating and, as such, pregnancy was established. That day was considered gestation day zero. Mated females were randomly assigned into four experimental groups of five rats each. Group I served as the control and received distilled water daily, while Groups II–IV were treated with the aqueous fruit extract of X. aethiopica at doses of 100 mg/kg, 200 mg/kg, and 300 mg/kg, respectively. The administration was performed daily, starting from day 1 to 18 of pregnancy. Twenty-four hours after the last administration (day 19 of pregnancy), the rats were euthanized under ketamine injection. The abdomen was opened, and the number of live and dead fetuses, ovarian weight, as well as crown–rump length were measured. The percentage of live fetuses was estimated as the number of live fetuses divided by the total number of fetuses, multiplied by 100. The uterine horns were fixed in 10% formalin for light microscopy.

Histological study

The organs were dehydrated in graded alcohol, embedded in paraffin, and sectioned at 5µm with a rotary microtome (Leica RM2125 Rotary Microtome). The sections were stained with Hematoxylin and Eosin (H&E) and micrographs were taken using a microscope camera (AmScope, UK) at different magnifications.

Statistical analysis

Oestrous cycle and organ index data were analyzed with GraphPad Prism 7 (GraphPad, USA). One-way ANOVA and Dunnett posthoc test were conducted and the results were presented as Mean ± standard error of the mean (SEM). $P < 0.05$ was considered statistically significant.

RESULTS

Maternal Body Weight

According to **Table 1**, there was a non-significant ($P < 0.05$) increase in maternal body weights of rats that were orally administered the aqueous fruit extract of *X. aethiopica* at all doses compared to the control group. Pregnancy weight gains were not altered at any dose level of the extract.

Fetal Growth Parameters

The result from the fetal study (**Table 2**) in the present study revealed that all groups of rats that were orally administered the aqueous fruit extract of *X. aethiopica* at 100 mg/kg (1.54±0.05), 200 mg/kg (1.15±0.03) and 300 mg/kg (0.76±0.00) demonstrated a significant ($P < 0.05$) reduction in crown-rump length compared to the control (2.90±0.05). There was no significant decrease in the mean number of live fetuses of

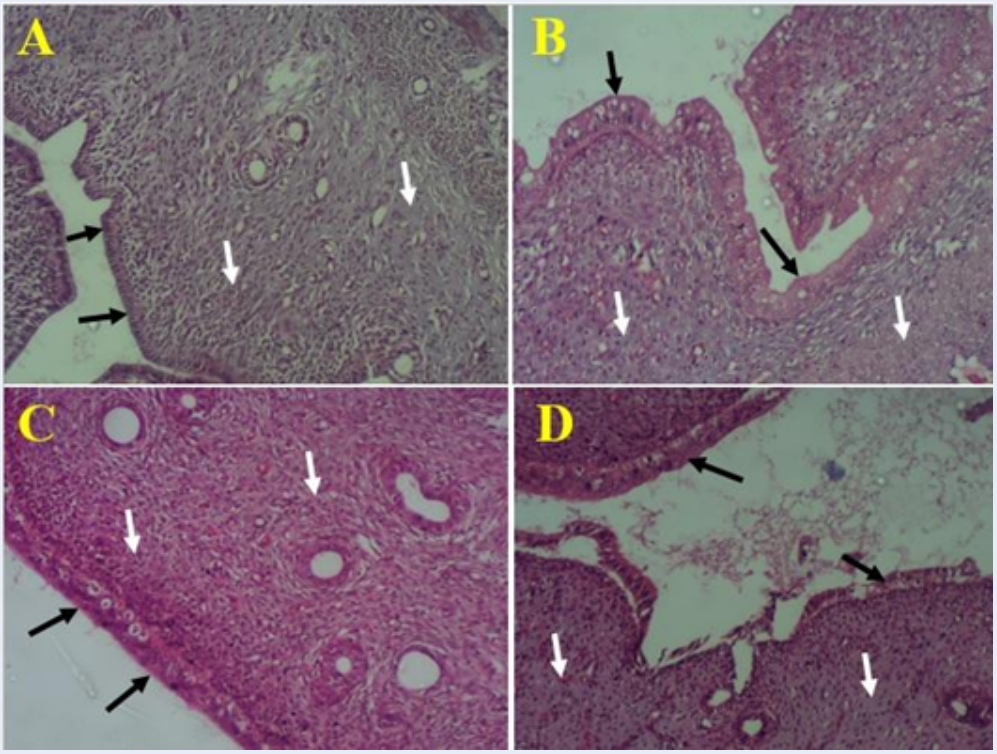

Figure 1: **Photomicrograph of uterine horn showing endometrial epithelial lining (black arrows) and connective tissues with glands (white arrows)**. A= control rats, B= rats treated with *Xylopia aethiopica* at 100 mg/kg, C= rats treated with *Xylopia aethiopica* at 200 mg/kg, while D= rats treated with *Xylopia aethiopica* at 300 mg/kg. H&E stain, x100 magnification.
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Table 1: Effect of Aqueous Fruit Extract of *X. aethiopica* on Maternal Body Weight in Albino Rats

Groups	Dose (mg/kg)	Initial Body Weight (g)	Final Body Weight (g)	Body Weight Differences (g)	Percentage Differences %
Control	0	154.48±9.44	217.76±14.73	63.28	40.96
XA	100	161.98±4.79	179.88±7.88	17.90	11.05
XA	200	150.30±4.11	189.44±17.63	39.14	26.04
XA	300	150.92±4.76	177.38±11.73	26.46	17.53

*All values are expressed as mean±SEM (n = 5). * indicates a significant difference with the control at P < 0.05. SEM = Standard error of the mean, XA= Xylopia aethiopica.*

rats that received *X. aethiopica* extract at all doses when compared to the control. On the other hand, a non-significant increase was observed in the mean number of dead fetuses in the treated groups relative to the control. A dose-dependent decrease was observed in rats treated with fetal viability, there was a reduction in a dose-dependent manner in tested groups, with *X. aethiopica* (25 % in 300 mg/kg) compared to the control (100%).

Histological Observations

The histological examination of the control rats' uterine horn showed normal simple columnar epithelium and extensive laminar propria that bears endometrial glands and myometrium (**Figure 1A**). Such histoarchitecture of the uterus did not show any visible change after administration of aqueous fruit extract of *X. aethiopica* at 100 mg/kg of the extract (**Figure 1B**). However, the uterine horn of rats that received 200 mg/kg revealed distortion of the uterine epithelium (**Figure 1C**) while those of rats

Table 2: Effect of Aqueous Fruit Extract of *X. aethiopica* on Fetal Growth Parameters

Groups	Dose (mg/kg)	Crown Rump Length (cm)	Live Fetuses	Dead Fetuses	Fetal Viability (%)
Control	0	2.90±0.05	6.80±0.37	0.00±0.00	100
XA	100	1.54±0.05*	4.20±1.53	0.40±0.40*	75
XA	200	1.15±0.03*	2.80±1.70*	0.60±0.40*	56*
XA	300	0.76±0.00*	1.00±1.94*	1.00±0.63*	25*

*All values are expressed as mean±SEM (n = 5). * indicates a significant difference with the control at P < 0.05. SEM = Standard error of the mean, XA= Xylopia aethiopica.*

treated with 300 mg/kg of *X. aethiopica* revealed degenerating uterine epithelia and connective tissue (**Figure 1D**).

DISCUSSION

The present study revealed that the administration of aqueous fruit extract of X. aethiopica to pregnant rats caused an increase in maternal mean body weight. This increase may suggest that growth was not impaired by the extract in all experimental groups. Additionally, changes in maternal body weight can be used to evaluate the integrity of maternal homeostasis[21]. This agrees with Onyegeme-Okerenta et al.[22], who reported that an aqueous extract of Millittia absences increased the body weight of pregnant rats. Although growth was not altered in all treatment groups, the extract still produced varying effects on some fetal growth parameters evaluated in this study.

Moreover, the present study showed a non-significant decrease in the weight of the maternal ovaries of rats that received the aqueous fruit extract of *X. aethiopica* compared to the control. The weight of the three endocrine tissues of the ovary—the stroma, follicles, and corpus luteum—constitutes the total ovarian weight[23]. Hence, the reduction in ovarian weight in this study may be attributed to the absence of gonadotropin or steroid hormones due to disrupted follicular activity[24].

Furthermore, this study revealed that administration of aqueous fruit extract of *X. aethiopica* to pregnant rats caused significant growth retardation (decreased crown-rump length), decreased number of live fetuses and fetal viability, and an increased number of dead fetuses in the uterine horns. This could explain the histological observations in the maternal uteri of the groups that received 200 mg/kg and 300 mg/kg body weight of the extract, which revealed distention of the uterine epithelium, reduction in endometrial glands, and distortion of the uterine endometrial epithelial lining compared to the corresponding control. This may result from disruption of pregnancy by interference with mitotic division of the fetus, causing destruction of the endometrial lining of the uterus[25]. Likewise, the present findings are in line with reports by Onyebuagu et al.[26] and Onyebuagu and Agbai27 on the activities of *X. aethiopica*. They also agree with the study by Aouni et al.[20], which documented that hydro-ethanolic extract of Marrubium vulgare induces severe histological changes in the pregnant rat uterus. This corresponds with the findings by Zade and Dinesh[27] and Choudhary et al.[28] on the mechanisms of aqueous leaf extract of Indigofera trifoliate and hydroalcoholic leaf extract of Alstonia scholaris. Additionally, reduction of endometrial glands is related to infertility and represents a defect in implantation, thus the uterus cannot accommodate a developing fetus to term[29].

In addition, administration of aqueous fruit extract of *X. aethiopica* caused a reduction in crown-rump length, number of live fetuses, and fetal viability, as well as an increased number of dead fetuses in experimental groups. The study has shown that nearly all drugs administered during pregnancy will, to some extent, enter fetal circulation through passive diffusion[30,31]. Therefore, since *X. aethiopica* fruit extract was administered during the cleavage and blastula stages of rat embryonic development—before implantation—as well as at later stages of embryo and fetal development, it might interfere with the normal course of pregnancy. This could explain the negative adverse effects observed in the fetal growth parameters in the present study. This agrees with the findings of Garba et al.[8], that Cissampelos mucronata root extract negatively influences reproductive outcomes in pregnant rats. It is also in line with a study by Zade and Dinesh[27], who stated that Indigofera trifoliate leaf extract (aqueous, alcohol, ethyl acetate, and chloroform) harms developing fetuses. This was equally documented by Yakubu et al.[32] on the adverse effects of aqueous leaf extract of Senna alata on pregnant rat outcomes.

Furthermore, the study revealed that steroids, flavonoids, alkaloids, and phenolics found in a va-

riety of plants have antifertility activity, thereby altering normal fetal growth, development, and pregnancy[33,34]. Hence, in the present study, saponins, alkaloids, steroids, and flavonoid components of the aqueous fruit extract of *X. aethiopica* might have exerted their antifertility effects, leading to reduced crown-rump length, number of live fetuses, fetal viability, and increased number of dead fetuses in the experimental groups. Similarly, Nwafor and Kalio[35] documented that aqueous fruit extract of *X. aethiopica* has strong contractile potential on uterine smooth muscles. This strong contractile property may also contribute to the observed decrease in crown-rump length and number of live fetuses, along with an increased number of dead fetuses in the present study compared to the control. This may cause irritation and stretching of the uterine cervix, subsequently stimulating the posterior pituitary gland to increase its secretion of oxytocin[36]. Therefore, the presence of alkaloids, flavonoids, and saponins may, in part, contribute to the oxytocic effect of the aqueous fruit extract of *X. aethiopica*[37]. Since the fruits and seeds of X. aethiopica are sometimes added to meals of pregnant individuals to help ease childbirth, there could be health implications for both the mother and the developing fetus if the dosage is not minimized.

CONCLUSIONS

Findings from the present study revealed that repeated consumption of *X. aethiopica* fruit during pregnancy could be toxic to both the developing fetus as well as affecting maternal health. Hence, care should be taken while consuming *X. aethiopica* fruit in pregnancy.

ABBREVIATIONS

ANOVA: analysis of variance, **H&E**: hematoxylin and eosin, **SEM**: standard error of the mean, **XA**: *Xylopia aethiopica*.

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None.

AUTHOR'S CONTRIBUTIONS

All authors conceived and designed the research. KOA & NID provided study materials and conducted the research. All authors analyzed and interpreted the data. KOA & NID drafted the initial manuscript. SHG & JVZ revised the manuscript. All authors approved the final manuscript.

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Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Postgraduate Board of Studies, University of Maiduguri, and performed according to the animal research: reporting of in vivo experiments (ARRIVE) guidelines.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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