ORIGINAL ARTICLE

Oxytocic and Abortifacient Activities of Xylopia Aethiopica Ethanol Fruit Extract on Female Wistar Rats

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ABSTRACT

Background: Pregnancy describes the period of fetal development in the uterus until delivery. Pregnancy, labour and puerperium present challenges that encourage use of medications to relieve symptoms, terminate pregnancy and prevent primary postpartum haemorrhage. Some pregnant women still rely on herbal remedies for treatment of pregnancy related problems. *X. aethiopica* is a natural spice used in preparing soup for women after delivery to prevent primary postpartum haemorrhage. ***Objective:*** To investigate the oxytocic effects of ethanol fruit extract of *Xylopia aethiopica* (*X. aethiopica*). ***Methods:*** This experimental study was done on Sixty six adult wistar rats comprising of 12 males for mating and 44 females that weighed 150–180g were used in this study. Acute toxicity test, qualitative phytochemical analysis, abortifacient and oxytocic studies were all done. The Median LD50 was established to be 1703 mg/kg in rats. ***Results:*** The phytochemical analytes were found to be Flavonoids, phenols, cardiac glycosides and steroids. There was dose dependent decrease in body weight of the animals treated with *X. aethiopica*. The extract did not have oxytocic effect on postpartum uterus like oxytocin. It rather caused relaxation of the uterus. ***Conclusion:*** Ethanol fruit extract of *X. aethiopica* did not exert oxytocic effect on female wistar rats. It is, therefore, not recommended in the prevention of primary postpartum haemorrhage.

Keywords: Oxytocin, abortion, postpartum haemorrhage, pregnancy.

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INTRODUCTION

The female uterus, also known as the womb, is a hollow, muscular organ in the pelvis that plays a crucial role in mensuration, pregnancy, and childbirth[1]. It forms between the fifth and sixth weeks of pregnancy through the fusion of Mullerian or paramesonephric ducts, forming the fallopian tube and the uterus and upper section of the vagina. The absence of circulating testosterone and anti-Mullerian hormone causes uterine development in female embryos[2]. The uterus undergoes significant changes

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throughout pregnancy, including hypertrophy and hyperplasia, and is responsible for fetal protection and expulsion at term. Oxytocin, also known as α-hypophamine, is a non-peptide hormone containing nine amino acids and plays a pivotal role during human labor and birth[3]. It is produced in neurons that originate in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus and is transported to the posterior pituitary where it is stored. During labor, oxytocin is released in pulses from the pituitary into the circulation to induce uterine contractions[3]. It performs a wide variety of functions, with pituitary gland secretions responsible for its peripheral functions and centrally projecting oxytocin neurons responsible for its behavioral effects[4]. Oxytocin is commonly used in maternity care to induce labor and prevent postpartum haemorrhage. However, the increased use of synthetic oxytocin raises questions about its potential impacts on endogenous oxytocin levels and its effects on mothers and babies[5]. Postpartum hemorrhage (PPH) is a leading cause of global maternal morbidity and mortality, accounting for approximately 30% of all pregnancy-related deaths in Asia and Africa. Any delay in achieving hemostasis after birth can result in a major loss of maternal blood volume, leading to hypotension, hypoxia, acidosis, renal failure, and even disseminated intravascular coagulation (DIC)[6].

Non-pharmacological agents used as oxytocics include methanol and ether crude extracts of Vernonia amygdalina, Melaleuca lanceolata, and Rhynchohyalus natalensis, Sida acuta plant extract, Nymphaea alba, Piper guineense seed Uvariodendron anisatum, and xylopia aethiopica[7]. *Xylopia aethiopica* (XA) is said to possess more uterine contraction property than Ocimum gratissium, comparable to standard oxytocin. However, it is recommended not to be used in early pregnancy as it could cause miscarriage[8].

Xylopia Aethiopica, a tall, slim, aromatic evergreen tree, grows in the Savanna region of Africa, including Nigeria, Ghana, Ethiopia Cameroon, and Senegal. Its fruits are small, twisted bean-pods with dark brown color, cylindrical shape, and 5 to 8 kidney-shaped seeds[9]. *X. aethiopica*, also known as Negro pepper, is used medicinally for its anti-infective properties, anti-emetic properties, and headache treatment. The stem bark of *X. aethiopica* is used in combination with other medicinal plants as an alcoholic decoction for postpartum breast infections. In Nigeria, *X. aethiopica* fruits and seeds are used to prevent fever, cough, and postpartum bleeding, and facilitate post-natal recovery[10]. Previous studies have reported antioxidant, hypolipidemic, antifungal, and antibacterial effects of whole *X. aethiopica* fruits, as well as their preventive effects against dysentery and male/female fertility challenges. However, the information on the relative abundances of proximate, mineral, and phytochemical constituents in the different anatomical parts of *X. aethiopica* fruits remains limited[11].

METHODS

This experiment was carried out at the Pharmacology Departments of both Ebonyi State University Abakaliki and University of Nigeria Teaching Hospital, Enugu, Nigeria. Dry fruit of XA was collected from the local forest together with its cobs. The plant was identified and authenticated by an expert working in the Department of Applied Biology, Ebonyi State University, Nigeria. A total of 66 Wistar rats weighing 150 to 180g were used for this study. The animals were procured from the animal house of the Faculty of Medicine/Pharmaceutical Sciences of Nnamdi Azikiwe University, Awka, Anambra State, Nigeria. The rats were separated into male and females during the period of acclimatization in the Pharmacology Laboratory, Ebonyi State University, Abakaliki that lasted for two weeks. Twelve were males and were used for mating, while another twelve female Wistars were used for the acute toxicity test. Thirty pregnant rats were divided into 5 groups of 6 rats each and were used to study the abortifacient effect of the extract. Twelve pregnant rats were used to study the oxytocic effect of the extract. Drugs/chemicals/reagents used included ethanol, cytotec, oxytocin, tween 80 and De Jalon solution. We also used clean glass tube, filter paper, stainless plates, water bath, organ bath, refrigerator, cages and kymograph.

Extraction technique: The dry fruits of *X. aethiopica* was washed and air dried at room temperature. It was ground into powdered form and weighed. Five hundred and forty grams (540g) of the powdered *X. aethiopica* fruit was macerated in 2 litres of ethanol. The extract was shaken and starred intermittently for 24 hours, after which it was sieved into a clean glass tube using the filter

paper. The filtrate was poured into stainless plates and dried on a water bath at a reduced temperature of 45°C to recover the extract. The final extract was 27% w/w Semi-solid brown powder. The dried extract was stored in airtight sterile containers in a refrigerator until the experimental period.

Before the administration to the experimental animals, 1000mg was dissolved in 2 ml of tween 80 since the extract was not soluble in water and dissolving it in ethanol would result in making the animals drowsy and possibly unfit for the study. After which 8 ml of distilled water was added to make it to 10 ml for easy calculation.

Phytochemical screening of the X. aethiopica: The preliminary phytochemistry of *X. aethiopica* ethanol fruit extract was carried out to determine different secondary metabolites and these include tests for tannins; some quantities of *X. aethiopica* extract about 0.5g by approximation was dissolved in 1ml of distilled water, stirred and filtered. Some drops of ferric Chloride reagent were introduced into the filtered solution. The presence of blue-black, green or blue green precipitate indicates the presence of tannins.[12] For alkaloids, 0.5g of the *X. aethiopica* extract was turned in 5ml of 1% diluted HCl_{aq} on heated water bath. Thereafter, 1ml of the resulting solution was added with some few drops of Mayer's reagent, Dragendorff's reagent, and picric acid solution. The presence of precipitates was seen an indication of the presence of alkaloids in the extract.[13] For saponins, approximately 0.5g of *X. aethiopica* extract was dissolved in water and thoroughly shaken in a test tube. The continuous appearance of frothing upon heating was seen as indication of the presence of saponin[13]. For steroids, about 0.5g of the *X. aethiopica* was collected and liquefied in water and filtered thereafter. 1ml of the resulting solution was introduced to 2ml of H_2SO_4 in a test tube. Steroid was taken to be present so long as reddish brown ring is seen within the interface[13]. For terpenoids, some portion of *X. aethiopica* extract was dissolved in water and 5ml of the portion received 2ml of chloroform and subjected to evaporation by means of water bath. Thereafter, the resulting portion was boiled in 3ml of concentrated H_2SO_4. The appearance of grey colouration was taken to indicate the availability of terpenoid. For flavonoids, lead sub acetate test was used. 100mg of the extract of *X. aethiopica* was liquefy in 5ml of water and filtered thereafter. Lead sub acetate of about two to three drops was introduced. Precipitation of yellow colouration suggests the availability of flavonoids. For anthraquinones, some quantities of *X. aethiopica* was collected into a conical flask containing 10ml of benzene and was allowed to thoroughly mix for 10minutes. It was filtered and 10ml of solution of 10% ammonia was introduced to it and shaken very strongly within 30 seconds. Any appearance of pink, violet and or red colour suggest the presence of anthraquinones[14].

Pregnancy confirmation: The animals were paired for mating in the ratio of 3 female rats to 1 male rat. After the period of acclamatization, the male and female rats were placed together in a large mating cage. Pregnancy was confirmed with the aid of vaginal plug in the females' vagina clearly seen with the help of a magnifying hand lens (×5 magnification) (as shown in Fig. 1) and weight gain. Thirty pregnant rats divided into 6 groups were used to study the abortifacient effects of the extract.

Figure 1: Vaginal plug in the females' vagina clearly seen with the help of a magnifying glass.

Acute toxicity study: This study followed Lorke's method and involved 12 adult female rats in two phases. In the first phase, three groups of rats were given different dosages of ethanol extract of *X. aethiopica* via orogastric administration. The rats were observed for signs of toxicity, such as hyperactivity, salivation, paw-licking, writhing, muscle paralysis, respiratory distress, and mortality within the first 4 hours and after 24 hours. In the second phase, three groups of animals were given different dosages of ethanol extract of *X. aethiopica*. The rats were observed for signs of toxicity and mortality at the first 4 hours, 24 hours, and 72 hours. Mortality was observed at the dosage of 2900 mg/kg and 5000 mg/kg. A fresh De Jalon solution was prepared and used for the organ bath experiment[15].

Histological examination: The uterine horns were examined for implantation and pregnancy resorption sites, and the number of fetuses. Endometrial samples were taken for histology, preserved with formalin, and sent to the Anatomy department of EBSU's histopathology laboratory. The tissue was fixed, embedded, sectioned, stained, and examined using a light microscope.

Assessment of oxytocic effect: The study involved a surgical procedure where rats were sacrificed, and a caesarean section was performed. The uterine horns were dissected and cut into equal halves, and the tissue was aerated with oxygen at 300C. The uterus was suspended in the De Jalon Solution and allowed to equilibrate for 30 minutes before the experiment. The drug introduction was allowed a contact time of 30 seconds before stimulation, and the tissue was washed three times to remove any remnant drug. The kymograph was used for tracing contractions. The experiment began with 0.1 to 1 international units of oxytocin, followed by varying concentrations of the extract in the organ bath. The effect of the fractions was also determined in the presence of 0.2 µg of calcium channel blocker verapamil. The procedure was repeated with both oxytocin and the extract, and the effects were recorded.

Data was meticulously documented and entered into the International Business Machine Statistical Package for Social Sciences (IBMSPSS) version 26, Chicago II, USA. Comparisons between groups were made using One-Way Analysis of Variance and Post Hoc Test, with a significance difference set at $P<0.05$. The qualitative components of the study were analyzed manually.

RESULTS

The acute toxicity of *X. aethiopica*'s ethanol fruit extract was assessed in rats after oral administration at dual doses (2900 mg/kg and 5000 mg/kg), with the median LD50 being 1703 mg/kg. We also analyzed the phytochemical constituents of *X. aethiopica* fruits' ethanol extract, revealing ten secondary metabolites including alkaloids, flavonoids, cardiac glycosides, phenol, phlobatannins, terpenoids, tannins, steroids, saponins, and anthraquinones, as well as other compounds.

Weight of the Pregnant Rats after 7 and 14 Days and comparison between groups: The mean±SD weights were 184.50±14.50, 171.80±16.84, 172.67±18.03, 168.17±17.02 and 157.67±11.88 for the female pregnant Wistar rats in groups 1, 2, 3, 4 and 5 respectively after 7 days. This study further indicated that 14 days, female pregnant wistar rats in groups 1, 2, 3, 4 and 5 presented mean±SD of 210.67±14.22, 171.00±18.93, 180.83±16.63, 166.50±19.38 and 149.17±25.69 correspondingly. No difference in weight was observed in the comparison of the weight of female pregnant wistar in group 1 to weight of female pregnant rats in groups 5 (P=0.676), 2 (P=0.694), 3 (P=0.400), and 4 (P=0.050) as well as the comparison of the weight of the female pregnant rats in group 5 to weight of female pregnant Wistar rats in groups 2 (P=1.000), 3 (P=0.995) and 4 (P=0.584) after 7 days. Significance difference in weight was observed in the comparison of the weight of female pregnant Wistar in group 1 to weight of female pregnant rats in groups 5 (P=0.019), 3 (P=0.005), and 4 (P=0.000) but no significance difference was observed in the comparison of the weight female pregnant in group 1 to weight of pregnant female Wistar rats in group 2 (P=0.089). No significance difference in weight was observed in the comparison of the weight of the female pregnant rats in group 5 to weight of female pregnant Wistar rats in groups 2 (P=0.916), 3 (P=0.995) and 4 (P=0.364) after 14 days as shown in table 2. Histological changes in different groups of Wistar rats are shown in Fig. 2-6. Response of uterus to oxytocin and ethanol extract of X. aethiopica: Ethanol extract of XA stimulated uterine contraction to peak once at 0.3cm which is like a twitch. On the other hand,

Table 1: Outcome of the Phytochemical Screening of the Ethanol Extract of *X. aethiopica* Fruit

Phytochemical Constituents	Designation
Alkaloids	+
Flavonoids	++
Cardiac glycosides	++
Phenols	++
Phlobatannins	+
Terpenoids	++
Tannins	+
Steroids	++
Saponins	+
Anthraquinones	+

Keys: + and ++ denoted less and more presence

the administration of oxytocin resulted to uterine contractions peaking at 1.4 cm decreasing to 0.8 cm and peaking to 1.3 cm which is the normal oxytocin curve as shown in Fig. 7.

Table 2: Mean Weight of Female Pregnant Wistar Rats after 7 and 14 days and Comparison of Weight of Female Wistar Rats in Group 1 to weights of Pregnant Rats in Groups 5, 2. 3 and 4 and Weight of Pregnant Rats in Group 5 to Weight of Pregnant Rats in Groups 2, 3 and 4

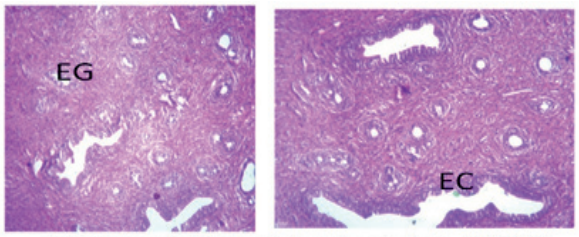
		Weight (g)	P-values [N]	P-values [P]
	Groups	Mean ± SD		
7th Days	1 (Negative Control)	184.50±14.50		
	5 (Positive Control)	171.80±16.84	0.676	
	2	172.67±18.03	0.694	1.000
	3	168.17±17.02	0.400	0.995
	4	157.67±11.88	0.050	0.584
14th Days	1 (Negative Control)	210.67±14.22		
	5 (Positive Control)	171.00±18.93	0.019	
	2	180.83±16.63	0.089	0.916
	3	166.50±19.38	0.005	0.995
	4	149.17±25.69	0.000	0.364

N and P are the P values when group 1 was compared to groups 5, 2, 3, and 4 as well as when group 5 was compared to group2, 3 and 4 correspondingly.

DISCUSSION

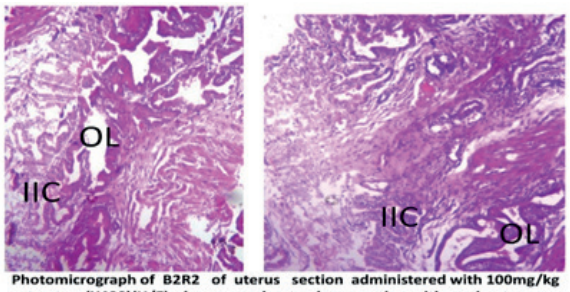
Phytochemicals, found in plants, are antinutrients with various nutritional, biological, and pharmacological properties. They play a crucial role in human health, influencing antioxidant activity, hormone mimicking, and disease suppression. Minerals in spices and food products are essential for human health and maintaining certain physicochemical processes. Some compounds, such as alkaloids, flavonoids, and terpenoids, can be toxic due to their ability to stimulate oxidative stress[16]. A study found that the ethanol extract of *X. aethiopica* fruits had a lower LD50 (1703 mg/kg in rats) than the aqueous LD50 (2154 mg/kg)[17]. This study also found that the weight of female Wistar rats decreased with increasing dosage of the ethanol fruit extract, consistent with previous studies. The ethanol fruit extract caused a dose-dependent reduction in body weight, with death occurring in extreme cases.

The ethanol fruit extract of *X. aethiopica* did not show significant oxytocic effect in the organ bath experiment, as it only showed a twitch that



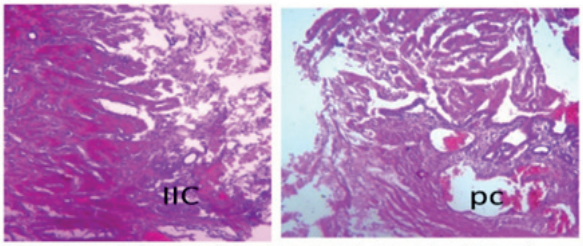
Photomicrograph GP A1 control section of uterus (x400)(H/E) shows normal uterine tissue with numerous active endometrial gland (EG). And active epithelia cell (EC_ .

Figure 2. Tissue histology of group 1 Wistar rats



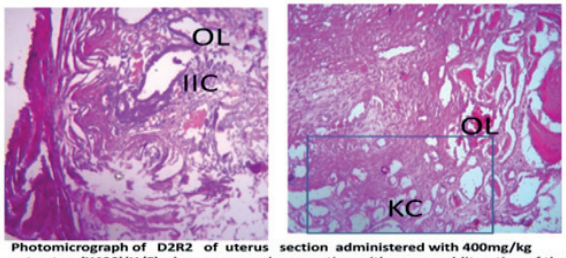
Photomicrograph of B2R2 of uterus section administered with 100mg/kg extract (X400)(H/E) shows moderate degeneration with moderate obliteration of the lumen (OL) with moderate infilteration of inflammatory cell (IIC) within the mucosa of the endocervix.

Figure 3. Tissue histology of group 2 Wistar rats



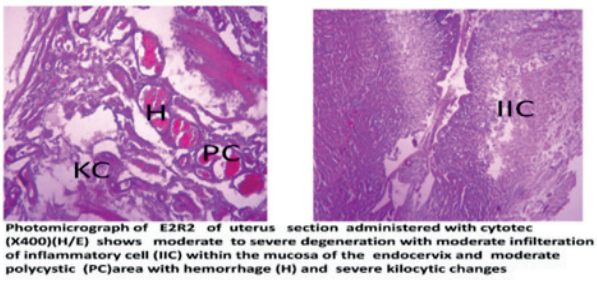
Photomicrograph of C2R2 of uterus section administered with 200mg/kg extract (X400)(H/E) shows moderate degeneration with moderate obliteration of the lumen (OL) with moderate infilteration of inflammatory cell (IIC) within the mucosa of the endocervix and moderate polycystic (PC)area with hemorrhage (H).

Figure 4. Tissue histology of group 3 Wistar rats



Photomicrograph of D2R2 of uterus section administered with 400mg/kg extract (X400)(H/E) shows sever degeneration with severe obliteration of the lumen (OL) with moderate infilteration of inflammatory cell (IIC) within the mucosa of the endocervix and severe kilocytic chages(KC) focal areas of hemorrhage (FAH)

Figure 5. Tissue histology of group 4 Wistar rats



Photomicrograph of E2R2 of uterus section administered with cytotec (X400)(H/E) shows moderate to severe degeneration with moderate infilteration of inflammatory cell (IIC) within the mucosa of the endocervix and moderate polycystic (PC)area with hemorrhage (H) and severe kilocytic changes

Figure 6. Tissue histology of group 5 Wistar rats

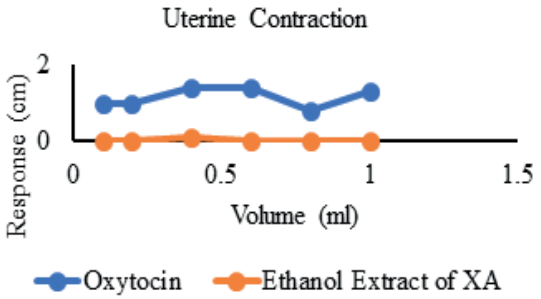


Figure 5: Comparison of uterine contraction in response to oxytocin and ethanol extract of XA

was not enough to sustain uterine activity. This could be linked to the various roles or possible interplay between the phytochemical constituents in causing postpartum uterine relaxation. Tannic acid, flavonoids, alkaloids, and phenols have been shown to possess uterine stimulating effects.

The N-haxane fruit extract of *X. aethiopica* showed some oxytocic effect at high doses on the guinea pig uterus more than *Ocimum gratissium*, but this was not statistically significant according to a previous finding[18]. Another study done by Wood et al reported that the ethanol fruit extract of *X. aethiopica* caused relaxation of the Wistar rat ileum, similar to the findings of a previous study[19]. Both the extract studied and oxytocin did not have effect on the virgin uterus, likely because oxytocin receptors develop in later dates of pregnancy.

CONCLUSION

In this current study, the investigation of the oxytocic effect of the *X. aethiopica* extract, it was found to cause postpartum uterine relaxation rather than contraction except the few occasional twitches caused by the extract.

Competing Interests: The authors declare no competing interests.

Financial Support: Nil

Ethical Clearance: The study was performed according to the protocols and guidelines approved by the Research Ethics Committee, Directorate of Research, Innovation and Commercialization of Ebonyi State, Nigeria (EBSU/DRIC/UREC/Vol 08/00).

Authors' Contribution: All authors were equally involved in conception and design of the study: data collection, analysis, validation and visualization, manuscript preparation, review, editing and submission.

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