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Research Article

Investigating the Fertility Activity of Ethanol Stem Root Extract of *Ozoroa insignis* (Anacardiaceae) in Female Rats

Ahmed, A. I.[1], *Bashir, A. I. J.[1], Adamu, A.[2], Ahmad, M. S.[3], and Abdullahi, Z.[1]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria
[2]Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria
[3]Department of Clinical Pharmacy and Pharmacy Management, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria
***Corresponding Author's email*: asmau1981.bashir@gmail.com; Phone: +2348100348071**

ABSTRACT
This study evaluated the fertility-enhancing effects of ethanol stem root extract of *Ozoroa insignis* in female rats. The oral acute toxicity (LD50) was assessed following OECD 425 (2008) guidelines and determined to be greater than 5000 mg/kg in mice, suggesting that the extract is relatively non-toxic. Phytochemical screening based on the Trease and Evans (1996) method revealed the presence of flavonoids, alkaloids, saponins, carbohydrates, and cardiac glycosides. The fertility potential was evaluated using the ovulation induction method. In the experimental study, administering the extract at doses of 100, 200, and 400 mg/kg body weight in both pre-mating and continuous treatment groups resulted in a significant ($p < 0.05$) dose-dependent increase in fertility rates and a greater number of pups compared to the control group (distilled water). The highest number of pups was observed in the continuous treatment group receiving 400 mg/kg of the extract, which yielded results nearly comparable to that of the positive control group (Clomiphene citrate). These findings suggest that the ethanol stem root extract of *O. insignis* possesses some fertility-enhancing activity and is relatively safe at the tested doses.

Keywords: Clomiphene citrate; Fertility-enhancing activity; Ovulation induction; *Ozoroa insignis;* Reproductive aid; Toxicity

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INTRODUCTION

Fertility is the state of having the ability to reproduce while infertility refers to the inability to conceive naturally following 12 months (or more) of consistent unprotected intercourse (Larsen, 2005). About 40 million couples worldwide, sought treatment for infertility, with over 30 million of them from developing countries (Obeagu *et al.,* 2023). Millions of people struggle with infertility, which also impacts their physical and mental health due to financial distress, social stigma, increased risk of domestic abuse and marital instability. This has a detrimental effect on the self-esteem of individuals who experience it. Women continue to bear a greater social burden from these adverse side effects than men do (Thoma *et al.,* 2021). Despite advances in assisted reproductive technologies, access to fertility treatment remains limited in many low-resource settings due to high cost and inadequate healthcare infrastructure. Therefore, the use of natural remedies such as plants and other traditional methods for the treatment of infertility (Ugwah-Oguejiofor *et al.,* 2011; Mo *et al*., 2023) can be a great way to overcome some of these limitations (WHO, 2013).

O. insignis is botanically also known as *Hearia insignis.* It is widely used in some African countries, such as Sudan and some parts of Nigeria, to name a few, in the traditional medical system to treat ailments such as fever, dysentery, muscle pain, ulcers, hypertension, respiratory infections, schistosomiasis and as an aphrodisiac among others (Liu and Abreu, 2006).

The "Ovulation Induction Method" was used for this study using Clomiphene citrate. As a nonsteroidal triphenylethylene derivative, clomiphene citrate (CC) demonstrates both agonist and antagonistic effects on estrogen levels. It is the medication of choice for inducing ovulation and treating a variety of infertility disorders (Clark and Markaverich, 1982). Several phytochemicals, including flavonoids and alkaloids, have been reported to influence reproductive function and hormonal balance.

A thorough review of various literature finds that no research on the validity of using *O. insignis* stem root extract as a reproductive aid has been done. Therefore, this study is aimed to evaluate the fertility-enhancing activity of ethanol stem root extract of *O. insignis* in female rats using the ovulation induction model. It is hypothesized that the extract possesses bioactive compounds capable of improving reproductive outcomes.

MATERIALS AND METHODS

Experimental Animals

Adult *rattus norvegicus* Wistar strain male and female rats (69-120 g) were obtained from Animal House, Department of Pharmacology and Toxicology, Ahmadu Bello University (ABU) and used for the study. All male and female rats were kept separately in well-constructed clean dry cages that allowed freedom of movement for two weeks for acclimatization to the environmental conditions before commencement of the study. They were maintained in a well-ventilated animal house at Kaduna State University (KASU) at a controlled temperature (25 ± 1 °C) and a 12 h dark/light cycle. The animals were given access to enough food and water *ad libitum.* They were treated in accordance with the National Institute of Health (NIH) Guide for the care and use of Laboratory Animals (Production No. 85-23, revised, 1996) and approved Institutional Research and Ethical Committee (Protocol Number; DPTAC/IVT-IVV/01500021). All experimental procedures were reviewed and approved by the University Animal Ethics Committee, Faculty of Pharmaceutical Sciences Kaduna State University, Kaduna.

Mice weighing up to 5 g were used for the LD_{50} at 2000 mg/kg and 5000 mg/kg.

Plant Collection and Identification

The stems and roots of *O. insignis* were obtained from the surroundings of Plateau State around the rocky forest areas on the 10th of April, 2023. They were identified at the Taxonomy unit of the Department of Botany, Kaduna State University (KASU) by Mallam U.S Gallah. Voucher specimen was deposited in the herbarium with voucher accession number KASU/BSH/0123.

Plant Preparation and Extraction

The stems and roots collected were washed with tap water, cut into pieces and air dried under shade to constant weight. The dried materials were pulverized manually using mortar and pestle into a dry powder and weighed. Ethanol stem root extract of *O. insignis* was prepared in Pharmacognosy Department, Faculty of Pharmaceutical Sciences, Kaduna State University (KASU). About 600 g of the plant powder was extracted with 1 L of 70% ethanol (mixture of 30% w/w water and 70% w/w ethanol) using cold maceration method. The plant powder was macerated with the solvent and allowed to stand for 72 h with occasional shaking after which the extract was filtered through a Whatman filter paper with the aid of filtration assembly and concentrated on a thermostatic water bath at 50 °C. The extract was labelled as OIE then stored in a glass jar and stored in a fridge from where it was used when required.

Percentage yield was calculated as follows:

$$\% \text{ Yield} = \frac{\text{Weight of extract (g)}}{\text{Weight of powdered plant material (g)}} \times 100$$

Phytochemical Screening of Crude Plant Extract

Phytochemical screening of the plant extract was carried out at the Department of Pharmacognosy and Drug Development, Faculty of Pharmaceutical Sciences, Kaduna State University, using the method described by Trease and Evans (1996). The extract was screened for the presence or absence of phytochemical constituents including flavonoids, alkaloids, saponins, steroids, carbohydrates, tannins, cardiac glycosides, triterpenes, and anthraquinones.

Acute Toxicity Test (OECD 425, 2008)

Using the OECD 425 (2008) approach, the acute oral LD_{50} investigation of *O. insignis* ethanol extract (OIE) was conducted at the Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, KASU. The study employed five mature female Swiss albino nulliparous mice weighing between 26 and 30 g. For the limit test, 2000 mg/kg was the dosage. Oral administration was used. One mouse was given 2000 mg/kg body weight of the extract orally after being

starved of food and water for 3 h. The mouse was observed for symptoms of toxicity such as facial twitching, hypersalivation, sniffing, grooming, sedation, rearing and mortality after 4 h and subsequently 24 h. The remaining four mice received the same oral dosage of 2000 mg/kg and observed for symptoms of toxicity and death after 4 h and then for 24 h. They were all under constant observation for over 14 days. Limit test 5000 mg/kg was conducted using five mice. All of the tested mice were kept under observation for a further 14 days (2 weeks) after which the test was terminated due to absence of mortality. Using the following formula, the LD_{50} was calculated mathematically:

$LD_{50} = \sqrt{(D_0 \times D_1)}$

D_0 = Highest non-lethal dose

D_1 = Lowest lethal dose

Evaluation of fertility activity of *O. insignis*

The potential effect of *O. insignis* as a fertility aid was evaluated using the "Ovulation Induction Experimental Model". The goal of the current study is to determine whether the aqueous extract of *O. insignis* increases fertility in female *Rattus norvegicus* Wistar strain of reproductive age by measuring the number of implanted embryos and birthed pups at different concentrations of the extract and contrasting it with clomiphene citrate.

Study Design

The animals were randomly assigned to experimental groups using a simple randomization method. Each animal was assigned a number, and a group allocation was performed using a random number table to ensure unbiased distribution.

60 female rats weighing between 69 and 120 g were randomly selected and divided into two major groups (pre-mating treatment group and Continuous treatment group). The pre-mating treatment group was used to assess the effect of pre-treatment of the animals with the extract before mating, while the continuous treatment group was used to assess the effect on continuous treatment of the animals with the extract.

Test for potential fertility effect of *O. insignis*

To minimize bias, the assessment of reproductive outcomes, including implantation sites, was performed by an investigator blinded to the treatment groups.

Female *Rattus norvegicus* Wistar strain from each of the two main groups were randomly selected and divided into 3 experimental groups (n = 6). Then 2 control groups (n = 6) were formed. The groups included:

Group 1(Control group) were orally administered 5 mL/kg of the vehicle (distilled water, DW), Group 2 (standard reference) were orally administered 5 mg/kg of Clomiphene citrate (CC), Group 3 were orally administered 100 mg/kg *O. insignis* extract (OIE), Group 4 were orally administered 200 mg/kg OIE and Group 5 were orally administered 400 mg/kg OIE.

Both the pre-mating and the continuous treatment groups used the distilled water and clomiphene treated group as control. With the exception of the clomiphene treated group, which received a dose for five days only, all experimental groups received treatment orally every day for fifteen days before mating. The administration of OIE for the pre-mating treatment group was stopped on the 16^{th} day, however, the continuous treatment group received treatment continuously until delivery.

Mating procedure

On the 16^{th} day, all the rats were grouped two per male animal in a cage. Every morning, vaginal smears were examined daily for presence of spermatozoa to confirm successful mating. The day on which there was presence of spermatozoa was considered first day of pregnancy.

Evaluation of animals

All the female rats were examined every day for indications of sickness, prolonged duration of pregnancy and miscarriage.

Caesarean section for implantation sites

During the mid-gestation stage, which represents the 20^{th} day of pregnancy, half of the females in each group were sacrificed by cervical dislocation. The embryos were numbered and the implantation sites were examined.

Reproductive indices

The remaining pregnant females were allowed to give birth to their pups. The animal cages were checked for births starting on the 32^{nd} day of pregnancy. The numbers of live and dead neonates were counted immediately after birth. Pups were observed at birth and consistently for up to 7days for any signs of deformity.

The following reproductive indices were calculated: Mating index defined as number of sperm positive females/number of mated females × 100, Pregnancy index defined as number of pregnant females/number of sperm positive females × 100, Delivery index defined as number of females delivering/number of pregnant females × 100, Birth live index defined as number of live offspring/number of offsprings delivered × 100, Post-implantation loss index defined as number of implantation sites -

number of live fetuses/number of implantation sites × 100.

Data Analysis

Quantitative data were expressed as mean ± SEM. One-way analysis of variance (ANOVA) and the Tukey post hoc test were used for the statistical analysis. P-values less than 0.05 ($p < 0.05$) were regarded as statistically significant. Significant differences between means were evaluated at the 95% level of significance.

RESULTS

Yield of The Ethanol Stem Root Extract of *O. insignis*

The OIE contained little droplets of oils on standing and concentrated form had a gummy/sticky texture and appeared reddish brown with a characteristic scent which is pleasant.

Percentage yield was calculated mathematically as follows:

$$\% \text{ Yield} = \frac{\text{weight of dried extract obtained (43.7g)}}{\text{weight of the crushed stem root extracted (600g)}} \times 100$$

% Yield = 7.3%

The percentage yield was 7.3%.

Phytochemical Constituent Screening

Phytochemical screening of ethanol OIE showed the presence of Carbohydrates, Cardiac glycosides, Saponins, Flavonoids, and Alkaloids (Table 1).

Table 1: Phytochemical constituents of ethanol stem root extract of *O. insignis*

Test	Result
Alkaloids	+
Anthraquinones	-
Carbohydrates	+
Cardiac glycosides	+
Flavonoids	+
Saponins	+
Tannins	-
Triterpenes/ steroids	-

+ Positive (Present), - Negative (Absent)

Acute Toxicity Study

Using the OECD 425 (2008) method, the extract was well tolerated by the mice with only sniffing and gnawing as signs of toxicity. The LD50 was found to be >5000 mg/kg body weight (Table 2).

Outcome of Fertility Test

All mated female animals in pre-mating treatment group were tested positive to pregnancy and there was no observable post implantation loss which was similar to the control groups (DW and CC) (Table 3).

All mated female animals in continuous treatment group were tested positive to pregnancy and there was no observable post implantation loss which was similar to the control groups (DW and CC) (Table 4).

Table 2: Effect of acute oral administration of ethanol stem root extract of *O. insignis* in mice

Route of administration	Dose (mg/kg)	Observation (mortality)
Oral	2000	No death
Oral	5000	No death

Table 3: Fertility test outcome in pre-mating treatment group

Outcome/Dose (mg/kg)	DW	OIE 100	OIE 200	OIE 400	CC 5
Mated females	6	6	6	6	6
Sperm positive females	6	6	6	6	6
Preg. **F**emales	6	6	6	6	6
Mating Index (%)	100	100	100	100	100
Preg. Index (%)	100	100	100	100	100
Post implant. loss index (%)	0	0	0	0	0

Preg.: Pregnancy, Implant.: Implantation, DW: Distilled water, OIE: *Ozoroa insignis* extract, CC: Clomiphene citrate

Table 4: Fertility test outcome in continuous treatment group

Outcome/Dose (mg/kg)	DW	OIE 100	OIE 200	OIE 400	CC 5
Mated females	6	6	6	6	6
Sperm positive females	6	6	6	6	6
Preg. Females	6	6	6	6	6
Mating index (%)	100	100	100	100	100
Preg. Index (%)	100	100	100	100	100
Post implant. loss index (%)	0	0	0	0	0

Preg.: Pregnancy, Implant.: Implantation, DW: Distilled water, OIE: *Ozoroa insignis* extract, CC: Clomiphene citrate

Reproductive Index for Fertility Outcome

The pre-mating treatment group showed a significant difference when compared to the control (DW). There was increase in number of pups as OIE dose was increased, with 400 mg/kg treatment group having the highest number of pups. However, the positive control group (CC) had the highest number of pups when compared to all the pre-mating treatment groups. Also, no external malformations were observed in all the pre-mating treatment groups which was similar to the control groups (CC, DW).

A significant increase in litter size was observed in pre-mating treatment group compared to control ($p < 0.05$), with the highest effect at 400 mg/kg.

The continuous treatment group showed a dose-dependent increase in litter size, with 400 mg/kg producing effects comparable to clomiphene citrate (Table 5).

Deformity

The pups were inspected at birth and daily for up to 7 days after birth. No external deformities were observed in all the pre-mating and continuous treatment groups (Table 6).

Table 5: Reproductive index for pre-mating treatment group

Reproductive index/ Dose (mg/kg)	DW	OIE 100	OIE 200	OIE 400	CC 5
No of (dams) pups	(3) 12	(3) 18	(3) 33	(3) 39	(3) 45
No of pups per litter	4 ± 2.02	6 ± 2.01	11 ± 2.65*	13 ± 2.04**	15 ± 2.01***
Delivery index (%)	100	100	100	100	100
Birth live index (%)	100	100	100	100	100
No of pups with external malformations	0	0	0	0	0

Values are presented as Mean ± SEM (n=3). *p < 0.05, **p < 0.05, ***p < 0.05 = Significant difference between treatment groups and control (DW) group using ANOVA and Tukey post hoc test; OIE: *Ozoroa insignis* Extract, CC: Clomiphene citrate, DW: Distilled Water

Table 6: Reproductive index for continuous treatment group

Reproductive index/ Dose (mg/kg)	DW	OIE 100	OIE 200	OIE 400	CC 5
No of (dams) pups	(3) 12	(3) 21	(3) 36	(3) 42	(3) 45
No of pups per litter	4 ± 2.02	7 ± 2.04	12 ± 1.03**	14 ± 2.03***	15 ± 2.01***
Delivery index (%)	100	100	100	100	100
Birth live index (%)	100	100	100	100	100
No of pups with external malformations	0	0	0	0	0

Values are presented as Mean ± SEM (*n = 3*). *p < 0.05, **p < 0.05, ***p < 0.05 = Significant difference between treatment groups and control (DW) group using ANOVA (Analysis of Variance) and Tukey post hoc test; OIE: *Ozoroa insignis* Extract, CC: Clomiphene citrate, DW: Distilled Water

DISCUSSION

The phytochemical profile of the stem root extract of *O. insignis* showed the presence of flavonoids, alkaloids, carbohydrates, saponins, and cardiac glycosides (Table 1). These constituents are recognized for their various pharmacological activities including potential effects on reproductive function (Sharma *et al.,* 2013; Yadav, 2023). In the present study, the observed increase in litter size and fertility indices may be associated with the presence of the bioactive compounds. Previous study indicates that flavonoids, including quercetin and apigenin, are recognized for their ability to reduce oxidative stress, restore hormonal balance, and enhance follicular development and oocyte quality, ultimately leading to improved fertility outcomes (Abbaszadeh *et al*., 2024). However, the exact mechanism of action of *O. insignis* was not investigated in this study.

In the acute toxicity study, the LD50 following oral administration was determined to be greater than 5000 mg/kg body weight. No mortality was observed at either dose used (Table 2), indicating that the ethanol stem root extract of *O. insignis* is relatively safe at tested doses. This finding ia consistent with previous reports suggesting *O. insignis* having low toxicity profiles depending on the plant part and extraction method. For instance, an oil preparation demonstrated no mortality at doses up to 2000 mg/kg in mice, indicating an LD_{50} greater than 2000 mg/kg (Ouoba *et al*., 2022). While some studies have reported cytotoxic activity of *O. insignis* extracts (Mbuthia *et al*., 2012; Rea *et al*., 2003; Dube *et al*., 2021). Collectively, these findings indicate that while *O. insignis* contains bioactive constituents with potential cytotoxic effects, the lack of toxicity and mortality observed in this study at doses up to 5000

mg/kg suggests that the ethanol stem root extract is relatively safe within the tested range. Nevertheless, further toxicological studies are required to establish its long-term safety.

The fertility-enhancing effects observed in this study, as indicated by increased litter size and improved reproductive indices, suggests that the extract may positively influence reproductive performance. The effect was dose-dependent, with the highest activity observed at 400 mg/kg, particularly in the continuous treatment group. Although, the extract showed effects comparable to clomiphene citrate, it is important to note that the mechanisms of action may differ, as clomiphene citate is known to act through hormonal modulation (Kousta *et al*., 1997; Arshad *et al.*, 2024).

Additionally, there was no noticeable loss after implantation during pregnancy across all treatment groups, indicating that the ethanol stem root extract of *O. insignis* did not adversely affect pregnancy outcomes. According to the Prenatal Developmental Toxicity Guidelines, structural abnormalities in fetuses are key factors for evaluating teratogenic risk (OECD, 2018). This finding is important since many plant extracts that claim to enhance fertility may have embryotoxic or abortifacient effects. This suggests that the extract may be relatively safe during gestation at the tested doses. However, since parameters such as hormonal levels and uterine receptivity were not directly assessed, the underlying mechanisms responsible for these effects remains unclear.

The fertility-enhancing effects observed with *O. insignis* in this study align with previous research on other ethnomedicinal plants, such as *Ficus platyphylla*, which showed increased implantation rates and decreased post-implantation losses in female rats (Tanko *et al*., 2011). While *F. platyphylla* was examined as an aqueous extract from its stem bark, our study focused on an ethanolic extract from the stem root. This distinction may explain differences in phytochemical profiles and mechanisms of action. Nonetheless, both studies reported improved fertility indices without any signs of maternal or fetal toxicity, highlighting the potential of these plants as promising options for natural fertility enhancement, pending further pharmacological and toxicological assessments.

These findings collectively suggests that the ethanol stem root extract of *O. insignis* possesses fertility enhancing activity in female rats, possibly due to its phytochemical constituent. However, further studies are required to elucidate the exact mechanisms of action and to confirm its safety and efficacy in long-term use.

CONCLUSION

The findings of the current study suggests that the ethanol stem root extract of *O. insignis* may have fertility-enhancing activity in female rats, as evidenced by improved reproductive indices and increased litter size. The extract was also found to be relatively safe at tested doses. These findings support the traditional use of the plant; however, further studies are required to elucidate its mechanisms of action and to establish its safety and efficacy in humans.

This study has some limitations that should be considered when interpreting the findings. Although the ethanol stem root extract of *O. insignis* demonstrated fertility enhancing activity in female rats, the estrous cycle of the female rats was not monitored prior to mating. In addition, reproductive hormones such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone were not evaluated. Ovarian histological examinations were also not performed. Consequently, the mechanisms underlying the observed fertility-enhancing effects could not be established, and the conclusions of this study remain primarily observational.

Therefore, further studies should incorporate estrous cycle monitoring, reproductive hormone assays, and ovarian histopathological evaluations to provide mechanistic evidence for the fertility-enhancing activity of *O. insignis*. Further studies are recommended to elucidate the specific mechanism underlying the fertility-enhancing activity of *O. insignis*. In addition, comprehensive toxicological evaluations, including long-term safety studies, are required to establish its safety profile. Finally, further experimental clinical studies are required to confirm its potential role in fertility management.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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