African Journal of
Clinical Medicine and Pharmacy Research

ISSN: 1595-7993

Index: Harvard, Boston, Sydney University, Dimensions, Lens, ResearchGet Scilit, Semantic, Google Scholar, Base etc

https://doi.org/10.58578/AJCMPR.v2i3.7476

Preliminary Assessment of the Potential Embryotoxic Effects of *Alstonia boonei* De Wild (Apocynaceae) Stem Bark Extract during Organogenesis in Pregnant Sprague-Dawley Rats

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Article Info:

Submitted:	Revised:	Accepted:	Published:
Aug 15, 2025	Sep 8, 2025	Sep 20, 2025	Sep 25, 2025

Abstract

Alstonia boonei stem bark is widely employed in traditional medicine during pregnancy for obstetric purposes, including labour induction, prevention of postpartum haemorrhage, and expulsion of retained placenta. However, the safety of its use during gestation remains scientifically unverified. This study aimed to evaluate the embryotoxic and teratogenic potential of methanolic stem bark extract of *A. boonei* in pregnant Sprague-Dawley rats. Oral doses of 100, 200, or 400 mg/kg of the extract were administered to pregnant rats (n = 5 per group) from gestational day (GD) 8 to 15, while the control group received no treatment. On GD 16, the animals were euthanized for the assessment of teratogenic indicators, including fetal, placental, and uterine parameters. No statistically significant differences ($p > 0.05$) were observed in fetal weight, crown–rump length, anogenital distance, or placental and uterine metrics across all groups. However, a significant increase ($p < 0.05$) in fetal head circumference was recorded at the 400 mg/kg dose (3.49 ± 0.05 mm) compared to the control group (3.32 ± 0.03 mm), indicating possible disruption in central nervous system development. No fetal deaths, malformations, or resorptions were observed. These findings suggest that *A.*

boonei extract is non-teratogenic and embryotoxically safe at doses up to 200 mg/kg, but higher doses may pose risks of dose-dependent developmental alterations. Further investigations are necessary to clarify the mechanisms involved and establish a definitive safety threshold for its use during pregnancy.

Keywords: *Alstonia boonei*; Teratogenicity; Embryotoxicity; Pregnancy; Traditional Medicine; Sprague-Dawley Rats

INTRODUCTION

The use of herbal remedies is increasing worldwide, a trend also seen among expectant mothers. The typical use of herbal medicine during pregnancy across sub-Saharan Africa ranges from 32% to 45% (1). Studies show that approximately 21.7% of pregnant women in Ibadan, Oyo State, and 30% in Jos, Plateau State, Nigeria, utilise herbal medicine (2,3). Furthermore, about 51.3% of women with prior pregnancy experience report using herbal medicine during pregnancy (4). Many cultures have used herbal medicines during pregnancy to support maternal and fetal health, reduce nausea and vomiting, treat infections, ease gastrointestinal issues, prepare for labour, induce labour, or alleviate labour pains, often under the belief that they are safer than conventional medicine. However, these practices are unsafe and strongly discouraged, especially without the guidance of a professional (5). Several harmful compounds in ingested plants can cross the placental barrier, potentially causing teratogenic, toxic, or abortifacient effects (6). For example, plants such as *Ageratum conyzoides* (Asteraceae), *Alstonia macrophylla* (Apocynaceae), *Azadirachta indica* (Meliaceae), and *Curcuma longa* (Zingiberaceae) have been reported to have adverse effects on the developing fetus (7). *Alstonia boonei* De Wild, a member of the Apocynaceae family, is a deciduous tree that can grow up to 35 metres tall. Its leaves are oblanceolate, whorled at the nodes, with a rounded to acuminate apex and prominent lateral veins nearly perpendicular to the midrib. The white flowers are borne on lax terminal cymes. Its fruits consist of brown floss at both ends and are connected by slender follicles up to 16 cm long. Although the species are found worldwide, some are native to Africa. In Yoruba, the plant is known as Ahun; in Igbo, it is called Egbu or Egbu-ora; and in Efik, it is referred to as Ndodo. Common names include fever bark, Devil tree, Australian quinine, patternwood, cheesewood, stoolwood, and Australian fever bush (8–

10). The herb is used ethnomedically to treat hypertension, rheumatic discomfort, muscular pain, and ulcers. Additionally, resistant malaria is treated with a leaf decoction. *A. boonei* stem bark preparations are used to manage postpartum haemorrhage, induce labour, and remove retained placenta (11). Pregnant women also consume a decoction of the stem bark to relieve fever and vomiting. This research examines the embryotoxic potential of *A. boonei* methanol stem bark extract on pregnant Sprague-Dawley rats.

MATERIALS AND METHODS

Collection and identification of plant material

The stem bark of *A. boonei* (1 kg) was collected in March 2025 from the University of Benin Campus, Benin City, Edo State, Nigeria. A Taxonomist, Prof. Henry Akinibosun, authenticated the plant at the Department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, Benin City, Edo State. A voucher specimen was deposited at the herbarium section of the Department with specimen number UBH-A343.

Drying of plant materials

The stem bark of *A. boonei* was dried in the shade for 12 days to remove moisture. The dried plant Organ was ground using a mortar and pestle and then passed through a mesh sieve to prepare it into a powdered form, which was stored in the laboratory before extraction.

Extraction

The powdered plant's part (500 g) was extracted with methanol (absolute). The concentrate was then dried for 72 hours. The concentrated extract was weighed, placed in a labelled bottle, and stored in the refrigerator at 4 °C until required.

Acquisition of Experimental Animals

Ten (10) male and twenty (20) female Sprague-dawley rats (200–250 g) were obtained from the Animal House, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria. The animals were housed in standard plastic cages lined with softwood shavings and maintained under ambient room temperature with a 12-hour light/dark cycle. They were provided with standard rodent chow and water *ad libitum*. All procedures involving animal use conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH 45). Ethical approval (AKHREC/17/06/25/341)

was obtained from the Ethics Committee of the Ministry of Health, Akwa Ibom State, Nigeria.

Experimental Design

Analysis was conducted according to the method of Atoe et al (2023) with slight modifications. Mating was carried out by housing female rats with males in a 2:1 ratio overnight. The presence of a vaginal plug or spermatozoa in the vaginal smear the following morning was considered indicative of successful mating and designated as gestational day (GD) 1. Confirmed pregnant rats (n = 5 per group) were randomly assigned to four groups. Three groups received oral doses of the methanol extract at 100, 200, and 400 mg/kg body weight daily from GD 8 to 15. The control group received no treatment.

Assessment of Teratogenic Parameters

On GD 16, the pregnant rats were anaesthetised using inhalational chloroform and sacrificed. Following laparotomy, the uterus was exposed and examined for implantation sites, fetal resorptions, and viable fetuses. The number and condition of embryos and placentae were recorded. Placental weights were determined using a digital precision balance. Placental volume was estimated by volume displacement. Fetal parameters, including crown-rump length, head circumference, anogenital distance, and fetal weight, were measured (12).

Statistical analysis

Values are expressed as mean ± SEM. Differences between groups were analysed using analysis of variance (ANOVA) followed by Dunnett's post hoc test at a 95% confidence interval using GraphPad Prism version 6.01.

RESULTS

Table 1. Effect of the extract on the fetus of experimental animals

Dose(mg.kg	Fetal head circumference (mm)	CRL (mm)	AGD (mm)	Weight (g)
100	3.29 ± 0.03	4.79 ± 0.06	0.39 ± 0.02	3.96 ± 0.06
200	3.41 ± 0.06	4.77 ± 0.11	0.39 ± 0.02	3.92 ± 0.08
400	3.49 ± 0.05	4.84 ± 0.11	0.39 ± 0.02	4.14 ± 0.09
Normal control	3.32 ± 0.03*	4.85 ± 0.05	0.39 ± 0.01	3.91 ± 0.06

Data are expressed as mean ± SEM, *=p < 0.05 CRL=Crown-rump length, AGD=Anogenital distance

Table 2: Effect of the extract on the formative stage of the fetus

Dose (mg/kg)	Number of live fetuses	Number of deaths of fetuses	Percentage mortality	Number of deformed fetuses
100	10	0	0	0
200	11	0	0	0
400	12	0	0	0
Normal control	9	0	0	0

Data are expressed as mean to the nearest whole number.

Table 3: Effect of the extract on the placenta of experimental animals

Dose (mg/kg)	Placenta weight (g)	Placenta volume (cm^3)
100	0.49 ± 0.01	0.49 ± 0.01
200	0.46 ± 0.01	0.50 ± 0.01
400	0.47 ± 0.01	0.46 ± 0.01
Normal control	0.48 ± 0.01	0.65 ± 0.17

Data are expressed as mean ± SEM,

Table 4: Effect of the extract on the uterus of the experimental animal

Dose (mg/kg)	Uterine weight (g)	Uterine volume (cm^3)
100	4.68 ± 0.10	4.80 ± 0.20
200	4.64 ± 0.17	4.72 ± 0.20
400	4.82 ± 0.15	4.80 ± 0.20
Normal control	5.00 ± 0.21	4.60 ± 0.25

Data are expressed as mean ± SEM

Table 5: Decision on the safety of the extract based on the teratogenicity result

Dose (mg/kg)	Teratogenicity	Remark
100	-	Safe
200	-	Safe
400	Caused a significant increase in the fetal head circumference	Un-safe

DISCUSSION

Teratogenicity is a pivotal aspect of developmental toxicology, encompassing the potential of chemical, physical, or biological agents to induce structural and/or functional abnormalities in the developing embryo or fetus (13). The manifestation and extent of teratogenic effects are modulated by multiple interacting variables, including the intrinsic properties of the teratogen (14) , its dosage and duration of exposure (15), the specific gestational stage at which exposure occurs, and the genetic predisposition (15) of the conceptus. While plants have historically served as prolific sources of therapeutic agents, certain species contain bioactive constituents with the capacity to disrupt normal embryonic and fetal development. These phytochemicals may exert teratogenic effects, leading to congenital deformities, intrauterine growth restriction, or functional deficits when ingested during pregnancy. This concern is particularly relevant in settings where traditional herbal medicines are widely used by pregnant women, often in the absence of rigorous scientific evaluation of their safety profiles (16,17).

Toxicological assessments have indicated that extracts of *Alstonia boonei* exhibit dose-dependent toxicity, with evidence supporting their safety at therapeutic doses. However, elevated or prolonged exposure has been linked to organ-specific toxicities, notably nephrotoxicity. (18). Findings by Alhassan et al. (2017) further revealed that the solvent extracts possess a high median lethal dose (LD_{50} > 5000 mg/kg), categorising them as practically non-toxic under acute oral toxicity conditions (19). Nevertheless, their safety during pregnancy remains a subject of concern, given the increased susceptibility of the developing fetus to toxicological insults during this critical period of rapid growth and tightly regulated developmental processes. Accordingly, the present study was designed to evaluate the potential teratogenic effects of methanolic stem bark extracts of *Alstonia boonei, with a* specific emphasis on external fetal morphology, placental and uterine indices, as well as maternal-fetal outcomes, to elucidate its safety profile during gestation.

Fetal Morphological Parameters

Fetal head circumference (HC) is a vital parameter in teratogenicity studies, serving as a sensitive and reliable indicator of central nervous system (CNS) development. Due to the rapid growth and differentiation of the fetal brain during gestation, disturbances in neurodevelopmental processes are often reflected in changes to cranial dimensions (20). As shown in Table 1, the control group had a mean HC of 3.32 ± 0.03 mm, while administration of the extract at a dose of 400 mg/kg caused a statistically significant increase ($p < 0.05$) in fetal HC to 3.49 ± 0.05 mm. This finding indicates that bioactive constituents in the extract may have teratogenic effects when exposure occurs during the organogenesis phase. Crown–rump length (CRL) is a commonly used morphometric measure for assessing embryonic and fetal growth in both clinical and experimental teratology. It serves as a crucial indicator for identifying developmental delays and growth restriction caused by teratogenic exposure (21). In this study, CRL measurements showed no statistically significant differences ($p > 0.05$) between the treatment and control groups, suggesting that the extract did not negatively impact overall fetal growth. Anogenital distance (AGD) is a widely recognised biomarker of fetal androgen exposure. It is commonly used to evaluate disruptions in reproductive tract development, including conditions such as cryptorchidism, hypospadias, and long-term fertility issues (22,23). In the present study, no significant change ($p > 0.05$) in AGD was observed across the experimental groups, indicating the absence of androgenic or anti-androgenic activity caused by the extract. Fetal weight is another vital indicator of intrauterine growth and overall developmental health, often used to identify the direct or indirect toxic effects of chemical exposures during pregnancy. Analysis of fetal weight showed no statistically significant differences ($p > 0.05$) between the treatment and control groups. This result suggests that the extract may not have overt toxic effects on fetal growth or viability under the conditions tested.

Fetal viability and development

Table 2 displays the results obtained during the formative stage of fetal development. This phase, also known as the organogenesis period, is a critical window in embryogenesis when the primary organ systems and anatomical structures begin to form. In rodents, this stage typically occurs between gestational days (GD) 6 and 15 (24). In contrast, in humans, it corresponds to approximately weeks 3 to 8 of gestation (25). The

experimental findings showed no fetal mortality, resorptions, or observable external malformations. These outcomes suggest that the administered extract, at the tested doses, exerted minimal or no teratogenic effects during the organogenesis phase of fetal development.

Placental Parameters

Table 3 shows the results regarding the extract's effect on placental parameters in the experimental animals. Placental indices are crucial biomarkers for evaluating the impact of potential teratogenic agents on pregnancy outcomes (26). As a vital organ during gestation, the placenta facilitates the necessary exchange of nutrients, gases, and metabolic waste between the mother and fetus. Any disruptions to its structural integrity or functional capacity can negatively influence fetal growth and development. In this study, administering the extract at doses from 100 to 400 mg/kg did not result in any statistically significant ($p < 0.05$) changes in placental weight or volume compared to the control group.

Uterine Parameters

Table 4 shows the effects of the extract on the uteri of the experimental animals. Assessing uterine parameters is crucial for evaluating the reproductive and developmental toxicity of a test compound. Since the uterus is the leading site for embryo implantation and fetal development, it is key in determining pregnancy outcomes. Changes in uterine weight may indicate underlying issues such as oedema, inflammation, or tissue remodelling, including hyperplasia or hypertrophy, which could be caused by the toxic or endocrine-disrupting properties of the administered substance (27). Moreover, the number of live and dead fetuses provides a direct measure of uterine capacity to support pregnancy; an increase in fetal death or resorption points to potential embryotoxic or fetotoxic effects, or impaired uterine function. In this study, no statistically significant differences ($p < 0.05$) were found in uterine weight or volume between the treatment groups and the control. These results suggest that the extract had minimal adverse effects on the maternal reproductive system.

Safety evaluation report

Table 5 presents the safety evaluation of the test extract based on observed teratogenic outcomes at various dose levels. At the lower doses of 100 mg/kg and 200

mg/kg, there was no evidence of teratogenic effects, indicating that the extract is well tolerated at these concentrations and does not adversely affect fetal development. These results suggest a favourable safety profile for the extract at sub-toxic doses, supporting its potential for safe use within this dosage range. However, administration of the extract at a higher dose of 400 mg/kg led to a statistically significant increase in fetal head circumference, which may indicate a disruption in standard central nervous system (CNS) development. Cranial anomalies, especially during critical periods of gestation, could reflect underlying neurodevelopmental changes or compensatory responses to in utero stress. Consequently, this finding implies a possible dose-dependent teratogenic effect of the extract at higher concentrations.

CONCLUSION

Based on these results, the extract is deemed safe at doses up to 200 mg/kg. However, the occurrence of significant developmental alterations at 400 mg/kg calls for caution and designates this dose as unsafe for use during pregnancy. Further studies are recommended to clarify the underlying mechanisms of the observed cranial changes and to establish a clear no-observed-adverse-effect level (NOAEL) for the extract.

Conflict of Interest

The authors wish to declare no conflict of interest.

Data Availability

Data generated during the course of this research is available upon reasonable request from the authors.

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