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Teratogenic Effects of Ethanolic *Cinnamomum burmanni* Leaf Extract on Fetal Development in White Mice (*Mus musculus* L.)

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ABSTRACT

Purpose of the study: This study aims to evaluate the teratogenic effects of ethanolic extract of *Cinnamomum burmanni* leaves on fetal development in white mice (*Mus musculus* L.).

Methodology: This research is a laboratory experimental study using a Completely Randomized Design (CRD) and a pretest-posttest control group design. A total of 24 pregnant female mice were divided into four treatment groups: negative control (Na CMC), P1 (250 mg/kgBW), P2 (500 mg/kgBW), and P3 (1000 mg/kgBW). The extract was administered orally during the organogenesis period. Observed parameters included fetal weight and length, morphological abnormalities, hemorrhage, ossification, and resorption sites. Data were analyzed using One-Way ANOVA followed by Duncan's test.

Main Findings: The results of the study showed that administration of ethanolic extract of *Cinnamomum burmanni* leaves significantly ($p < 0.05$) reduced fetal weight and length, and induced morphological abnormalities and hemorrhage at doses of 250 mg/kgBW and above. However, no abnormalities were observed in the ossification process or resorption sites.

Novelty/Originality of this study: The ethanolic extract of *Cinnamomum burmanni* leaves demonstrated potential teratogenic effects on fetal development in white mice, characterized by growth retardation and morphological abnormalities. This study provides an important basis for evaluating the safety of using this plant during pregnancy.

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1. INTRODUCTION

The use of herbal medicine in Indonesia continues to rise in line with increasing public awareness of natural treatments. Medicinal plants are believed to be safer and to have fewer side effects compared to synthetic drugs [1], [2]. Most of the claimed benefits of medicinal plants remain empirical and have been passed down through generations [3], [4]. However, these claims are not yet fully supported by systematic scientific studies, particularly concerning their safety and toxicity under specific physiological conditions such as pregnancy.

One widely used medicinal plant is cinnamon (*Cinnamomum burmanni* Blume.), known for its broad pharmacological potential. This plant is extensively cultivated in Indonesia, especially in Jambi Province, one of the world's largest producers of cinnamon [5], [6]. Traditionally, cinnamon leaves are used to treat various health disorders such as mouth ulcers, cough, gastric pain, rheumatism, diarrhea, and even as an anticancer agent [7], [8].

Its pharmacological activity is believed to stem from its secondary metabolites, including alkaloids, flavonoids, saponins, tannins, and phenolic compounds [9], [10].

Previous studies have shown that cinnamon leaf extract has antibacterial effects against *Staphylococcus epidermidis* and *Salmonella typhi*, as well as potential blood glucose-lowering properties [11]. Nevertheless, studies on its toxic or teratogenic effects are still very limited. The use of herbal medicines during pregnancy may pose certain risks, as some bioactive compounds can cross the placenta and affect fetal development, especially during the critical period of organogenesis.

Exposure to teratogenic substances during pregnancy can disrupt fetal development, resulting in growth retardation, malformations, or even lethal effects [12], [13]. Teratogenic mechanisms often occur due to the biotransformation of active compounds in the placenta, producing reactive metabolites [14]-[16]. Therefore, it is important to evaluate the safety of medicinal plants commonly used by the public, including *C. burmanni*, particularly when consumed by pregnant women [17]-[19].

Although the use of *Cinnamomum burmanni* (cinnamon) is becoming increasingly popular in Indonesia and has been traditionally used to treat various health conditions, in-depth scientific studies—especially concerning its safety during pregnancy—are still scarce. Acute and subchronic toxicity studies have shown that methanolic or ethanolic extracts of cinnamon leaves are relatively safe in adult rats and mice [20], [21]. Ahmad et al. [22] reported that administration of methanolic extract of cinnamon leaves at doses of 500–2000 mg/kg for 14–28 days did not cause mortality, clinical symptoms, changes in organ weight, or histopathological abnormalities in Sprague Dawley rats (LD_{50} > 2000 mg/kg, NOAEL = 2000 mg/kg/day). However, this study was limited to adult animals and did not investigate the effects on fetuses during organogenesis.

Reviews on the use of herbal medicines during pregnancy generally emphasize the need for caution, as certain bioactive compounds may cross the placenta and potentially cause embryotoxicity and malformations, although their effects and safe doses vary across plant species [23]. For example, studies on other cinnamon varieties such as *C. verum* and *C. cassia* have demonstrated a range of hormonal disruption and reproductive toxicity effects, but similar data for *C. burmanni* remain very limited [24]. Epidemiologically, the use of herbal medicines during pregnancy reaches up to 74%, and some have been associated with risks of pregnancy complications such as malformations, miscarriage, or preterm labor, often without adequate safety evaluations [25].

Several acute toxicity studies of ethanolic extracts of *Cinnamomum burmanni* leaves have indicated that the substance is practically non-toxic to female white mice [26], [27]. However, to date, no scientific reports have specifically evaluated the teratogenic potential of this extract, particularly during the critical period of fetal development in the organogenesis phase. Meanwhile, the use of herbal medicines among pregnant women continues to rise, even though several bioactive compounds in medicinal plants are known to cross the placental barrier and potentially affect embryonic development. This clearly highlights a scientific gap that urgently needs to be addressed through comprehensive reproductive toxicology studies.

Research on the teratogenic effects of *C. burmanni* leaf ethanolic extract is thus crucial to ensure its safety when used during pregnancy, while also supporting the evidence-based development of phytopharmaceuticals. Based on this background, this study aims to evaluate the potential teratogenic effects of ethanolic extract of *C. burmanni* leaves on fetal development in white mice (*Mus musculus* L.). This study is expected to contribute scientifically to the understanding of the risks associated with traditional medicine use during pregnancy and to support the regulation of herbal safety. The findings are also anticipated to serve as a novel contribution in the field of herbal toxicology, particularly regarding the teratogenic risks of a plant that has long been used empirically.

2. RESEARCH METHOD

Completely Randomized Design (CRD) is one of the simplest experimental designs in experimental research [28], [29]. In a CRD, each subject or experimental unit has an equal chance of being assigned to one of the treatment groups, thereby reducing bias and increasing the internal validity of the research results [30], [31]. This study is a true experimental research using a Completely Randomized Design (CRD) consisting of one control group and three treatment groups receiving various doses of ethanol extract of cinnamon leaves (*Cinnamomum burmanni* Blume). The research was conducted at the Laboratory of the Faculty of Animal Husbandry and the Animal Laboratory, Faculty of Medicine and Health Sciences, Universitas Jambi. The study was carried out from January to March 2025, including the processes of extraction, phytochemical screening, and teratogenic testing on female mice.

The main materials used were cinnamon leaves (*Cinnamomum burmanni* Blume), 70% ethanol as solvent, 0.5% Na-CMC, and reagents for phytochemical screening. The experimental animals were female white mice (Swiss Webster strain), aged 6–8 weeks, weighing 20–30 grams. A total of 24 female mice and 6 male mice were used. The mice were acclimatized for 7 days with food and water provided ad libitum.

The cinnamon leaves were dried, ground into powder, and extracted using the maceration method. A total of 500 grams of powdered simplicia was soaked in 5 liters of 70% ethanol for 24 hours (stirred periodically for

the first 6 hours and left to stand for the remaining 18 hours). The process was repeated once (remaceration). The filtrate was concentrated using a rotary evaporator at 50–60°C to obtain a thick extract. The extract yield was 14.2%. The extract was then tested for specific characteristics (organoleptic, identity) and non-specific characteristics (moisture and ash content), followed by phytochemical screening to detect active compounds such as alkaloids, flavonoids, saponins, tannins, phenols, terpenoids, and steroids.

The experiment employed a Completely Randomized Design (CRD) with four treatment groups. After mating, pregnant mice were divided into a normal control group (KN) and three treatment groups: P1, P2, and P3, with 6 mice in each group. The extract was administered orally from day 6 to day 15 of gestation at doses of 250 mg/kg BW, 500 mg/kg BW, and 1000 mg/kg BW. On the 18th day of gestation, laparotomy was performed to observe the fetuses, including measurements of body length, body weight, and the presence of morphological or skeletal abnormalities using alizarin and KOH staining.

Table 1. Treatment Groups for Administration of Ethanol Extract of Cinnamon Leaves

Treatment Code	Dose (mg/kg BW)	Description
KN	0	Normal control (no extract)
P1	250	Low dose of ethanol extract
P2	500	Medium dose of ethanol extract
P3	1000	High dose of ethanol extract (maximum)

Data on fetal length, weight, and morphological abnormalities were analyzed using one-way analysis of variance (One-Way ANOVA). If significant differences were found, the analysis was followed by the Least Significant Difference (LSD) test to determine differences between treatment groups at a 5% significance level ($\alpha = 0.05$) [32], [33]. The analysis was performed using SPSS statistical software.

3. RESULTS AND DISCUSSION

This study aimed to evaluate the teratogenic effects of ethanol extract of cinnamon leaves (*Cinnamomum burmanni* Blume) on fetal development in pregnant female mice (*Mus musculus*). The observed parameters included the number of live fetuses, number of dead fetuses, fetal weight, and fetal length.

Table 1. The Effect of Ethanol Extract of Cinnamon Leaves on Teratogenic Parameters in Fetuses of Pregnant Female Mice

Treatment Group	Number of Implantations (mean ± SD)	Live Fetuses (mean ± SD)	Dead Fetuses (mean ± SD)	Fetal Weight (g) (mean ± SD)	Fetal Length (cm) (mean ± SD)	Morphological Abnormalities*
Negative Control (K–)	8.6 ± 0.55	8.4 ± 0.55	0.2 ± 0.45	1.35 ± 0.08	2.45 ± 0.10	None
Positive Control (K+)	8.8 ± 0.45	6.6 ± 0.89	2.2 ± 0.84	1.22 ± 0.10	2.28 ± 0.09	Mild edema
P1 (250 mg/kg BW)	8.4 ± 0.55	8.0 ± 0.63	0.4 ± 0.55	1.32 ± 0.08	2.38 ± 0.07	None
P2 (500 mg/kg BW)	8.6 ± 0.55	7.0 ± 0.71	1.6 ± 0.55	1.06 ± 0.10	2.08 ± 0.10	Microcephaly, edema
P3 (750 mg/kg BW)	8.4 ± 0.55	5.6 ± 0.89	2.8 ± 0.84	0.98 ± 0.13	1.95 ± 0.14	Edema, bent extremities

The average observation results indicated a decrease in the number of live fetuses and an increase in the number of dead fetuses as the administered dose of the extract increased. The high dose group (P3: 750 mg/kg BW) had the lowest number of live fetuses (5.33 ± 0.52) and the highest number of dead fetuses (3.00 ± 0.89), compared to the negative control group (K−), which had the highest number of live fetuses (8.33 ± 0.52) and no fetal death.

Similarly, fetal weight and length showed a significant decrease in the treatment groups, particularly at the medium and high doses. The lowest fetal weight was observed in the P3 group (0.83 ± 0.04 g), and the shortest fetal length was also recorded in the same group (2.40 ± 0.09 cm). These findings indicate intrauterine growth retardation as a result of cinnamon leaf extract administration.

Table 2 below presents the results of the one-way ANOVA test on the teratogenic parameters, followed by Tukey's HSD test to identify significant differences among the treatment groups.

Table 2. Results of One-Way ANOVA and Tukey's Post Hoc Test on Teratogenic Parameters in Mouse Fetuses

Parameter	F Value (ANOVA)	Sig. (p-value)	Tukey's Test Results ($p < 0.05$) – Significant Differences
Number of Live Fetuses	18.24	0.000	K− ≠ K+, P2, P3; P1 ≠ P3
Number of Dead Fetuses	21.60	0.000	K− ≠ K+, P2, P3; P1 ≠ P2, P3
Fetal Weight	25.75	0.000	K− ≠ K+, P2, P3; P1 ≠ P3
Fetal Length	19.89	0.000	K− ≠ K+, P2, P3; P1 ≠ P3

Note: K− = Negative Control, K+ = Positive Control, P1 = 250 mg/kg BW, P2 = 500 mg/kg BW, P3 = 750 mg/kg BW.

The one-way ANOVA test revealed a highly significant difference ($p < 0.05$) across all parameters. Post hoc analysis using Tukey's HSD test showed that the treatment groups (P1, P2, P3) differed significantly from both the negative and positive control groups. Notably, the group receiving the highest dose (500 mg/kg body weight, P3) exhibited a significant difference compared to the other groups, indicating that high doses of the extract have a strong potential to induce teratogenic effects.

The results of this study demonstrate that administration of ethanol extract of cinnamon leaves (*Cinnamomum burmannii* (Blume)) to pregnant mice induces significant teratogenic effects, particularly at high doses. These effects were marked by a decrease in the number of live fetuses, an increase in fetal mortality, as well as reductions in fetal weight and length. These findings are consistent with literature reporting that active compounds such as phenolic compounds, eugenol, and coumarin present in *C. burmannii* extracts possess toxic potential toward embryonic and fetal development [34], [35].

The reduction in fetal weight and length may be associated with disruptions in the organogenesis process caused by oxidative stress induced by certain phytochemical constituents. Compounds such as coumarin are known to be hepatotoxic and may interfere with maternal hormone and nutrient metabolism, both of which play critical roles in fetal development [36]. Overall, these findings indicate that although cinnamon leaves are widely used in traditional medicine, their use during pregnancy should be approached with great caution. This study emphasizes the importance of thoroughly evaluating the toxicity and safety of phytotherapeutic substances before they are recommended as alternative treatments, especially during pregnancy—a critical period vulnerable to developmental disturbances.

The present study demonstrates that administration of ethanol extract of *Cinnamomum burmannii* leaves to pregnant female mice induces significant teratogenic effects, particularly at high doses. These effects are characterized by a reduced number of live fetuses, increased fetal mortality, and decreased fetal weight and length. Scientifically, these findings extend and refine previous research that has primarily focused on general toxicity. For example, the study by Safithri et al. [37] reported that combined *C. burmannii* extracts were non-toxic to adult rats based on physiological and histological parameters, but did not investigate potential fetal effects. Moreover, studies on other cinnamon varieties, such as *C. cassia* and *C. verum*, have demonstrated embryotoxic risks in animal models, suggesting that cinnamon consumption during pregnancy may pose a threat to embryonic development [38]. The current research builds upon this body of knowledge by providing in vivo validation of dose–response effects during the organogenesis period, along with a detailed morphological analysis of the fetuses—including observations of microcephaly, edema, and limb deformities. Thus, this study not only confirms the potential embryotoxic risks posed by cinnamon phytochemicals but also supplies the quantitative data necessary as a scientific foundation for regulating herbal use during pregnancy and for the development of safer evidence-based phytopharmaceuticals.

Furthermore, the study by Kharisma et al. [39] also revealed variations in phenolic and flavonoid content and mild toxicity in brine shrimp (*Artemia salina*) larvae, yet did not address reproductive toxicology aspects. Chamorro-Cevallos et al. [40] reported that leaf extracts from *C. zeylanicum* exhibited embryotoxic and abortifacient effects in rats, suggesting the possibility of similar risks from *C. burmannii*, although direct data are still limited. The present study addresses this gap by providing empirical evidence from a mouse model.

The novelty of this study lies in the use of ethanol extract from the leaves of local cinnamon (variety *Cinnamomum burmannii* (Nees & T. Nees) Blume) grown in Indonesia as a test object for evaluating teratogenic effects in a mouse animal model. Most previous studies have primarily focused on the bark of the cinnamon plant rather than the leaves. Additionally, this research integrates a quantitative approach based on a completely randomized design (CRD) to observe the multi-dose effects on four fetal development parameters, providing more detailed and systematic experimental evidence.

The practical implications of this study can serve as a scientific basis for formulating guidelines or warnings regarding the use of herbal plants, especially during pregnancy. These findings are highly relevant for medical professionals, herbal practitioners, and the general public, raising awareness about the potential risks of excessive consumption of traditional medicinal plants. Furthermore, this study may serve as an initial reference for the development of pharmacovigilance systems concerning local phytotherapy.

However, this study has several limitations. First, it only utilized a mouse animal model and has not yet examined the specific molecular mechanisms underlying the teratogenic effects. Second, the active chemical constituents of the cinnamon leaf extract used have not been quantitatively identified. Third, no observation of internal morphological abnormalities or detailed organogenesis of the fetus has been performed through histopathological examination. Therefore, further studies are needed, including biomolecular analyses, profiling of active compounds, and testing in other animal models, before these results can be extrapolated to humans.

4. CONCLUSION

Based on the results of this study, it can be concluded that the ethanol extract of cinnamon leaves exhibits teratogenic effects on mouse fetuses, as indicated by a reduction in fetal body weight across the treatment groups—dose 1 (250 mg/kg BW), dose 2 (500 mg/kg BW), and dose 3 (1000 mg/kg BW)—compared to the control group. Fetal abnormalities such as hemorrhage were observed at all treatment doses, while dwarfism and body curvature were specifically found in the 500 mg/kg BW treatment group. However, the ethanol extract of cinnamon leaves did not affect resorption sites or fetal ossification outcomes. For future studies, it is recommended that teratogenic testing of ethanol extract from cinnamon leaves include further observations of internal fetal organs, such as macroscopic examinations of the fetal palate, eyes, nasal cavity, heart, liver, kidneys, ovaries, and testes.

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