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Original Research Article

Teratogenic Effect of Guava (*Psidium guajava* L.) Leaf Extract on Mice

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ABSTRACT

Psidium guajava leaves have been used traditionally to treat many diseases, but herbal extracts have been associated with adverse effects, bleeding, abortifacient, and sometimes teratogenic effects. This study investigated the fetal abnormalities (bleeding, morphological changes, live births, deaths, etc.) associated with *P. guajava* leaf extracts in pregnant Balb/c mice. Dried powdered leaves of the *P. guajava* were macerated with ethanol to obtain crude extract. Twenty female mice aged 10 weeks in fertile condition weighing 25-30 g were recruited for this study. The animals were divided into 4 groups of 5 animals each (The control group (K) and three other groups were given *Psidium guajava* leaf extract at doses of 100 mg/kg body weight (D1), 200 mg/kg body weight (D2), and 400 mg/kg body weight (D3). After the treatment with the extract in experimental mice, fetal weight from the control group had an average weight of 1.4 g, while the average body weight of the treatment group decreased significantly where D1 was 0.84 g, D2 and D3 were 0.80 g and 0.78 g respectively. Fetal length is also in line with fetal weight. At dose (D2), namely a dose of 200 mg/kg body weight causes hemorrhage in the tail and hind limbs of mice fetuses, while morphological defects were found in 1 fetus in the form of skin becoming thin like transparent. The study concludes that *Psidium guajava* leaf extract may have teratogenic effects, cause weight loss, reduction in fetal body length, alteration in fetal morphology, and hemorrhagic abnormalities.

***Keywords*:** *Psidium guajava* L., Haemorrhagic, *Mus musculus*, Teratogenic effects.

Introduction

The use of traditional medicines in Indonesia has been passed down from generation to generation since the time of our ancestors. Currently, the use of traditional medicines is well-developed to reduce the reliance on orthodox drugs.[1] The use of plants in traditional medicine may be due to their antibacterial, antioxidant, antifungal, antiparasitic, anticonvulsant, and anticancer properties.[1,2] Traditional medicine is not always safe when consumed, especially by infants and pregnant women.[3] Pregnant women usually have difficulty in finding effective medications to take during pregnancy, and most then prefer traditional medicine.[4,5] Traditional medicines are generally very safe and effective, but the same cannot be said for pregnant women.[3-5] There is a need for caution in the use of traditional medicines in pregnant women because plants possess various compounds which may have teratogenic effects.[4] Teratogenic compounds can also affect fetal development by causing growth delays or malformations, leading to fetal disabilities[6]. Many plants are often used as traditional medicines and may have teratogenic effects.[4-6] Plants with potential teratogenic effects include surian (*Toona sinensis*) leaves, gotu kola (*Centella asiatica*) plants, the crown of gods(*Phaleria macrocarpa*), parasitic plants, soursop (*Annona muricata*) leaves, and Jarong (*Achyranthes aspera*) root extract.

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These plants, often used in traditional medicine, have been implicated in fetal abnormalities both externally and internally: stunted fetal growth, bleeding, disability, fetal deaths, decreased fetal length, and body weight.[6-8]

Apart from the plants above, other plants are commonly used by humans, including guava (*Psidium guajava*). *Psidium guajava* leaves have many pharmacological benefits, including anti-diarrheal, antibacterial, anti-diabetic, anti-inflammatory, platelet-boosting, and anti-hypertensive.[9] The phytochemicals in *P. guajava*leaves include flavonoids (quercetin), alkaloids, quinones, polyphenolics, tannins, triterpenoids, and essential oils. Flavonoid, tannin, and saponin compounds have various pharmacological activities, including restoring injured skin cells.[10]

Several studies have shown the benefits of *P. guajava* leaves in traditional medicine. However, there is a lack of reports on the teratogenic effects of *Psidium guajava* leaves in the literature. This current study aimed to evaluate the teratogenic effects of *P. guajava* leaves on fetal abnormalities in mice treated with *P. guajava* leaf extract during the developmental period (organogenesis) both in terms of fetal morphology, number of live and dead fetuses, fetal length, weight, or bleeding.

Materials and Methods

Plant Collection and Identification

Psidium guajava leaf samples were collected in June 2022 from Syiah Kuala, Kota Banda Aceh, Aceh, Indonesia (5°34′44″N 95°22′03″E, 107.60932232621624). The plant sample was identified by a taxonomist at the Institute of Technology Bandung of Indonesia, Bandung, where a voucher specimen with number 3687/II.CO2.2/PL/2022 was deposited. This research was carried out at the UPT Experimental Animal Laboratory, UIN Ar-Raniry, between June and August 2023.

Extraction

The dried and powdered sample (300 g) of *Psidium guajava* leaves was extracted by maceration in 700 mL of 70% ethanol and then re-extracted

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with 300 mL ethanol. The extract was filtered using Whatman No. 1 filter paper and concentrated to dryness using rotary evaporation at 65° C.[12]

Animals

Twenty mice aged 10 weeks in a fertile state, weighing 25–30 g, were used for this experiment.[11] The International Standards for the Care and Use of Laboratory Animals protocols were adopted in this study. The animals were kept in plastic cages, and they had access to rodent pellets and drinking *ad libitum*.

Ethical approval

The research was approved by the Research and Community Service Institute of Medan State University with the number IC220131/IC2RSE/LPPM/2024.

Animal treatment

Experimental animals were divided into four groups of five animals each. The control group (K) and three other groups were given *P. guajava* leaf extract at doses of 100 mg/kg body weight (D1), 200 mg/kg body weight (D2), and 400 mg/kg body weight (D3). Oral extract administration was carried out during the organogenesis period – a crisis period during pregnancy between the 6th and 15th day of gestation. This is the stage of organ formation and the process of cell differentiation[13].

Data collection

On the 18th day, the animals were anesthetized with chloroform in a closed container and were subsequently dissected, and the fetuses were observed. Data obtained in the form of fetal body weight, fetal body length, live and dead fetuses, hemorrhage, and morphological defects were then analyzed descriptively, and the results obtained from each treatment group were compared with the control group.[13]

Statistical analysis.

One-way analysis of variance (ANOVA) (to check statistically significant differences among all groups) followed by a Turkey post hoc test (for significant differences between two groups) was conducted to analyze the data regarding embryonic growth indices. Descriptive statistics followed by a chi-square test was performed to calculate the percentage of malformations and check the difference between groups. Data analysis was done by Statistical Package for Social Sciences (SPSS) version 24 and the results were expressed as mean ± standard deviation of mean and percentage of malformations. p-value <0.05 was considered statistically significant.

Results and Discussion

Psidium guajava leaf extract was given to pregnant mice from the 6th to the 15th day of gestation and dissected on the 18th. Data on fetal weight, fetal length, number of live and dead fetuses, morphological defects, and hemorrhages were obtained and analyzed.

Fetal body weight is one of the parameters measured in the teratogenic test. The fetuses' weights were measured immediately after their removal from the uterus and cleaned of amniotic fluid. The results of their body weights are reported in Table 1. From the fetal weight analysis, the average weight in the control group was 1.4 g. In contrast, the treatment group given *P. guajava* leaf extract at different doses (100, 200, and 400 mg/kg body weight) has significantly different fetal weights compared to the control group. Each increase in the dose given has an impact on fetal body weight. The group (D1) treated with 100 mg/kg body weight of the extract for 10 days had an average fetal weight of 0.84 ± 0.38 g, while group D2 (200 mg/kg body weight) had an average fetal weight of 0.80 ± 0.35 g.

In comparison, the group given the highest treatment dose of 400 mg/kg body weight had the lowest average fetal body weight of 0.78 g. Similarly, results of the fetal body length measured from the head's tip to the tail's base using a block of millimeter paper and a ruler are reported in Table 2. From the results, the average fetal body length in the control group was 24.32 mm. Meanwhile, the treatment groups showed fetal body length different from that of the control group.

Table 1: The mean weights of fetuses after treatment with *Psidium gujava* leaf extract

Treatment	Test					Total	Average (gr)
	1	2	3	4	5		
Control	1.36	1.13	1.51	1.54	1.49	7.03	1.40 ± 0.17a
D I	0.21	1.08	1.25	0.44	1.23	4.21	0.84 ± 0.38b
D II	1.09	0.62	0.66	1.2	0.46	4.03	0.80 ± 0.35b
D III	1.14	0.57	0.56	1.21	0.44	3.92	0.78 ± 0,36b

Control: No treatment
Doses I: 100 mg *P. guajava* Leaf Extracts /kg body weight
Doses II: 200 mg *P. guajava* Leaf Extracts /kg body weight
Doses III: 400 mg *P. guajava* Leaf Extracts /kg body weight
Results are expressed as mean± standard deviation of mean. b: significant difference compared to the control, p-value is <0.05.

Table 2: The mean body length of fetuses after treatment with *Psidium gujava* leaf extract

Treatment	Test					Total	Average (mm)
	1	2	3	4	5		
Control	23.5	23.9	26.2	23.8	24.2	121.6	24.32 ± 1.08a
D I	11.75	21	22.1	15.6	21.7	92.15	18.43 ± 4.57b
D II	22.3	17.6	15.6	21.9	14.5	91.9	18.38 ± 3.58b
D III	22.5	17.2	15.8	21	15.2	91.7	18.34 ± 3.24b

Control: No treatment
Doses I: 100 mg *P. guajava* Leaf Extracts /kg body weight
Doses II: 200 mg *P. guajava* Leaf Extracts /kg body weight
Doses III: 400 mg *P. guajava* Leaf Extracts /kg body weight
Results are expressed as mean± standard deviation of mean. b: significant difference compared to the control, p value is <0.05.

Dose D1 (100 mg/kg body weight) had a body length of 18.43 mm, D2 (200 mg/kg body weight) had a body length of 18.38 mm, and D3 (400 mg/kg body weight) had a body length of 18.34 mm.

Observation of live and dead fetuses was carried out when the fetuses were still in the uterus and after removal from the uterus and cleaned. Results showed that all fetuses in the control and D1 I (100 mg/kg body weight) groups were alive after 18 days of the experiment (Table 3). Meanwhile, animals in the D2 group (200 mg/kg body weight) showed a decrease in the number of live fetuses by an average of 92%, and the average number of dead fetuses was 8%. Dose 3 (400 mg/kg body weight) has the same effect on the number of live fetuses, accounting for 89%, and the average number of dead fetuses was 11%.

The observation of morphological defects and bleeding was carried out after the fetus had been weighed and measured. The head, eyes, ears, curvature of the fore and hind limbs, and tail of the fetuses were observed for morphological defects. Table 4, Figures 1 and 2 show fetal hemorrhage and morphological defects in the experimental mice fetuses. Based on the data from the tables and figures 1 to 6 for morphological and hemorrhagic defects, it was found that in the control group and D1 (100 mg/kg body weight), there were no morphological hemorrhages in the mouse fetuses. Meanwhile, there were no morphological defects at D2 (200 mg/kg body weight) but a hemorrhage on the hind limbs and tail of the experimental animals.

Table 3: Number of live and dead fetuses after treatment with *P. guajava* leaf extract

Treatment	Percentage (%)	
	live fetuses	dead fetuses
Control	100	0
D I	100	0
D II	92	8
D III	89	11

Control: No treatment
Doses I: 100 mg *P. guajava* Leaf Extracts/kg body weight
Doses II: 200 mg *P. guajava* Leaf Extracts/kg body weight
Doses III: 400 mg *P. guajava* Leaf Extracts/kg body weight

Table 4: Morphological and Hemorrhagic Disabilities in Mice Fetuses

Treatment	Test									
	Morphological Defects					Hemorrhage				
	1	2	3	4	5	1	2	3	4	5
Control	-	-	-	-	-	-	-	-	-	-
D I	-	-	-	-	-	-	-	-	-	-
D II	-	-	-	-	-	-	✓	-	-	-
D III	-	-	-	-	✓	-	-	-	-	-

Details :
✓: Available
- : Unavailable

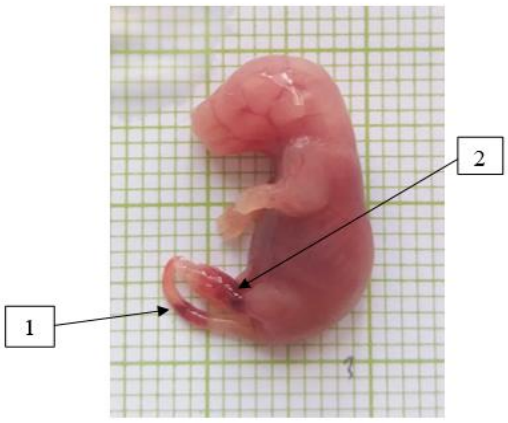

Figure 1: Hemorrhage in the fetus of the mice treated with a dose of 200 mg/kg body weight *Psidium gujava* leaf extract
Details:
1. Hemorrhage on the tail
2. Hemorrhage on the hind limbs

D3 (400 mg/kg body weight) showed morphological defects in 1 mice fetus in the form of thinning of the skin layer that looks transparent skin with no hemorrhage. The study showed that teratogenic testing of *Psidium guajava* leaf extract with different doses influenced body weight, body length, number of live and dead fetuses, and morphological and hemorrhagic defects. The *Psidium guajava* leaf extract treatment was done during the organogenesis period, from the 6th day to the 15th day of pregnancy, because it is the most vulnerable period for the fetus. On the 6th day of gestation, the new blastocyst implants in the uterine wall, and the teratogenic effect on fetal development could occur after the blastocyst has been implanted.

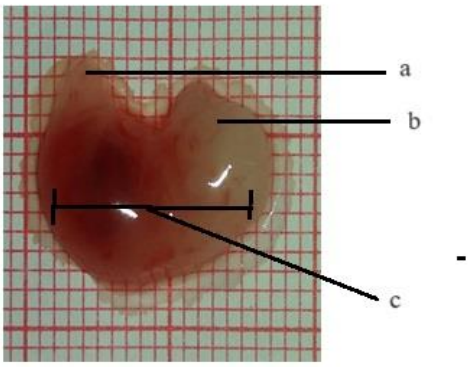

Figure 2: Morphological defects in transparent skin in fetuses from mice group treated with 400 mg/kg body weight *Psidium gujava* leaf extract
Details:
a. head
b. tail
c. the whole skin becomes transparent, hemorrhage occurs and no locomotor organs are formed

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Treating the mice with *P. guajava* leaf extract impacted the mice's fetal body weight. The body weight of the fetus in the control group and the treatment group differs. Control mice's fetal body weight showed an average value of 1.4 g. In a similar study, it was reported that the normal body weight of mice fetuses was 1.3 to 1.5g on the 18th day of gestation.[14] The treatment group, i.e., D1 (100 mg/kg body weight), had a fetal weight with an average value of 0.84 g. Dose 2 (200 mg/kg body weight) has a body weight with an average value of 0.80 g. Dose 3 (400 mg/kg body weight) has a body weight with an average value of 0.78 g. The three doses caused weight loss in the animals. Drastic weight loss of the fetus compared to the weight of the control fetus is a sign that teratologic effects have occurred leading to fetal malformations.
Drastic weight loss of the fetus compared to the weight of the control fetus is a sign that teratologic effects have occurred leading to fetal malformations.

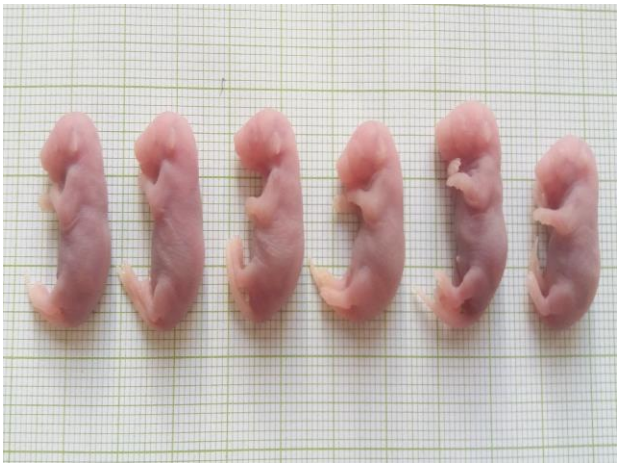

Figure 3: Mice (*Mus musculus*) fetus control group.
Details: All fetuses in the control group grew normally

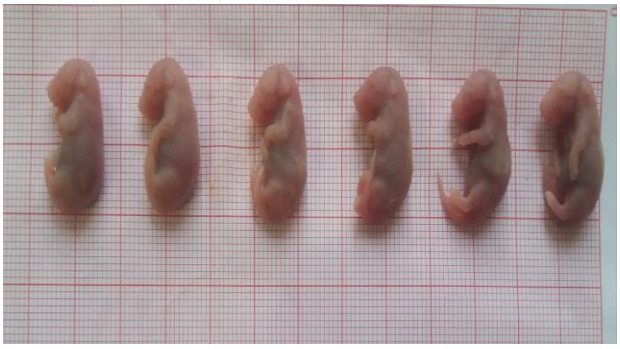

Figure 4: Mice (*Mus musculus*) fetuses of the D1 group (100 mg/kg body weight)
Details: All fetuses in this treatment grew normally but their size was smaller than the body size in the control treatment.

Alkaloids, tannins, flavonoids, and saponins in *P. guajava* leaves are thought to have teratogenic effects, this is in line with the results of teratogenic testing on *Imperata cylindrica* extracts which can also cause teratogenic effects because it is known that *I. cylindrica* extracts contain compounds such as saponins, tannins, and alkaloids.[15] Some derivatives of saponins, tannins, and alkaloids have medical benefits and can also act as teratologic agents.[15,16] These compounds are also found in *Foeniculum vulgare* leaves, which have been reported to cause teratogenic effects on fetuses at certain doses.[16]
The similarity in compound content between *P. guajava* leaves and *I. cylindrica*, namely alkaloids, and flavonoids, is also thought to be responsible for fetal weight loss, even the flavonoids and alkaloids contained in breadfruit roots were found to cause an increase in uterine muscle activity.[16] An increase in uterine muscle causes interference with the process of distributing nutrients that are important to the fetus. Flavonoids can pass through the placenta, connecting the mother to the fetus. If a substance can easily pass through the placenta, it can also easily affect the development of the fetus. The presence of flavonoids can also inhibit the distribution of nutrients, such as amino acids and folic acid, which affect the decrease in the weight and length of the fetus.[16,17] *Psidium guajava* leaf extract also influenced the body length of the mouse fetuses. There is a difference in body length between the control group and the treatment group. The control group has an average value of 24.32 mm, based on the results of previous studies stating that the average length of mice fetuses is 22-25 mm.[13] The length of the mouse fetus in the D1 group was 18.43 mm, D2 was 18.38 mm, and D3=18.34 mm.
Teratogenicity is an abnormal development that occurs in the fetus, can lead to fetal death, and interfere with the increase in the length of the fetus.[14]

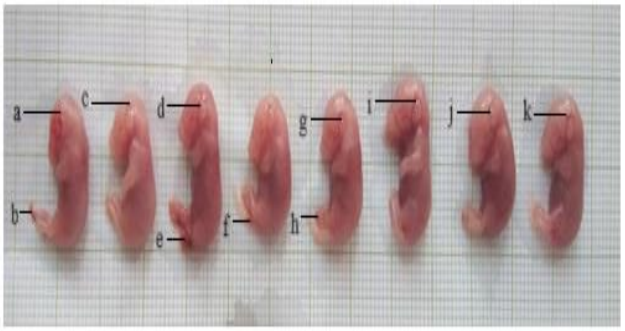

Figure 5: Mice (*Mus musculus*) fetuses dose group ii (200 mg/kg body weight)
Details: All fetuses in this treatment had hemorrhage on the head and tail (a, b, c, d, e, f, g, h, i, j, k). In addition, the body size of all fetuses was smaller than the size of fetuses in the control treatment.

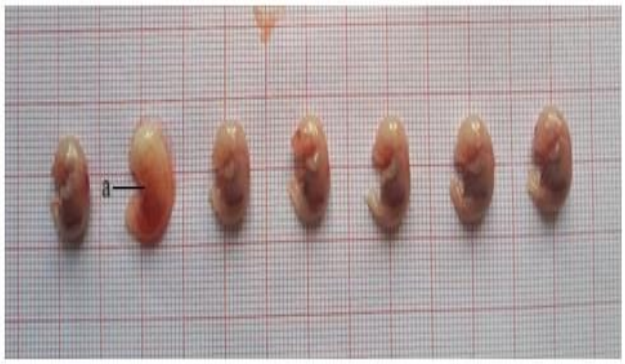

Figure 6: Fetus of mice (*Mus musculus*) of the D3 group (400 mg/kg body weight).
Details: All fetuses in this treatment experienced abnormalities such as transparent skin and bleeding, and there was even one fetus that experienced failure in the formation of head, tail, and limb organs (a).

Teratogenicity of certain compounds, such as amino acids, can affect the energy used for metabolism, thus affecting body length gain.[15,17] Cogon grass extract has the same compounds alkaloids and flavonoids, which can affect the fetus in mice. It is known that similar compounds found in *P. guajava* leaf extract are thought to cause fetal malformations in mice.[13,15] These compounds are thought to increase uterine muscle activity, disrupting the distribution of nutrients to the fetus through the placenta.[15]
This study also highlighted the effects of *P. guajava* leaf extract on the number of live and dead fetuses in the experimental mice. There were no dead fetuses in the control group and treatment group D1, which received 100 mg/kg body weight of the extract. However, there was a reduction in the number of live fetuses in group D2 and an increase in dead fetuses at an extract dose of 200 mg/kg BW. There was 92% in the

number of live fetuses in the D2 group and 8% deaths. The number of live and dead fetuses in the D3 group (400 mg/kg body weight) was 89% and 11%, respectively. Fetal death can be caused by cell death and by the individual's vulnerability to the environment. Fetuses that experience death may have experienced cell death at the proliferation stage, which may not be repaired thoroughly. The death of the fetus can also be caused by the individual fetal response to the extract treatment, which manifests in only a few fetuses dying. In a previous teratogenic study on bay leaf extract, it was reported that bay leaf extract had resulted in four dead mice fetuses in the treatment group.[18] The deaths of the fetuses were believed to be caused by genetic susceptibility factors (sensitivities) and individual susceptibility to the surrounding environment. Meanwhile, in the teratology study of red fruit extract, it was stated that the increase in the number of dead fetuses was due to the presence of alkaloids contained in red fruit, where these alkaloids are not only antiproliferative but also teratogenic and embryotoxic.[19] It is also assumed that the alkaloid content in *P. guajava* leaves can cause an increase in the number of dead fetuses.

The morphological and hemorrhage screening results showed one fetus with morphological defects in the form of transparent skin and one fetus with hemorrhage. Morphological defects occurred in the D3 (400 mg/kg body weight) group. Transparent skin occurs in mouse fetuses because, during the organogenesis period, they still have a single skin layer, while rapid skin development occurs on the 15th day of gestation. This is presumably because the content in *P. guajava* leaves (mainly flavonoids) can affect the differentiation of fetal skin cells.In teratogenic studies of cherimoya extract, abnormalities or defects were found in the form of skin that was getting thinner so that it looked like transparent skin, transparent skin occurs at concentrations of 0.05% and 0.125%.[20] Flavonoids contained in ant nest water extract are thought to affect the differentiation and division activity of skin cells so that they can cause skin cell death. Cell death in the skin can cause the skin not to form correctly or experience delays. *Psidium guajava* leaf extract has the same content as ant nests, which may have been responsible for the defects in the fetus (transparent skin) observed in only one mouse at a dose of 400 mg/kg body weight. This may be due to genetic susceptibility between individuals, where the body characteristics of the mice are not typical (transparent skin), and the fetus dies.Fetuses that experienced hemorrhage were in the second dose group (200 mg/kg body weight). Spontaneous hemorrhage can be caused by platelet dysfunction.[21]This is in line with the potential of *Psidium guajava* leaf extract as an antithrombotic or platelet inhibitory substance, which can cause platelet dysfunction, triggering hemorrhage. Hemorrhage may also be caused by damage to vascular endothelial cells, due to the absence of certain types of hematopoietic cells normally required to maintain vascular integrity, or these cells' dysfunction or failure to produce soluble factors that affect vascular integrity.[22]

Conclusion

The teratogenic study of guava (*Psidium guajava*) leaf extract on mice fetuses concluded that it is teratogenic because it can cause decreased fetal body weight and length, morphological defects, hemorrhage, and fetal death. *Psidium guajava* extract at doses of 100, 200, and 400 mg/kg BW showed an apparent teratogenic effect in the treated group of mice. The highest treatment dose of *P. guajava* extract (400 mg/kg BW) provided the most severe teratogenic effect compared to all treatment dose groups. The teratogenicity test is only required in the pregnant state. Male rats, non-pregnant females and young rats will not experience these effects. Our findings suggest that it is necessary to conduct teratogenic tests with more varied doses and more varied fetal malformation parameters to determine the impact of morphological defects and hemorrhage on the mice fetus.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Süntar, Ipek. Importance of Ethnopharmacological studies in drug discovery: role of medicinal plants. *Phytochem* Rev. 2020; 19(5):1199-1209.
2. Diningrat DS, Harahap NS, Risfandi M, Sari AN. Antioxidant and antibacterial activities of *Coix lacryma-jobi* seed and root oil potential for meningitis treatment. Jordan J Biol Sci. 2021; 14(5): 881-887. https://doi.org/10.54319/jjbs/140501
3. Tengku Mohamad, Tengk Azlan Shah, Farida Islahudin, Malina Jasamai, and Jamia Azdina Jamal. Preference, perception and predictors of herbal medicine use among Malay women in Malaysia. Patient Pref Adher. (2019): 1829-1837. DOI: 10.2147/PPA.S227780
4. Illamola, Sílvia M, Ogochukwu U, Amaeze, Lubov V. Krepkova, Angela K. Birnbaum, Ashwin Karanam, Kathleen M. Job, Valentina V. Bortnikova, Catherine MT Sherwin, Elena Y. Enioutina. Use of herbal medicine by pregnant women: What physicians need to know. Front Pharmacol. 2020; 10: 1483. https://doi.org/10.3389/fphar.2019.01483
5. Balbontín YM, Stewart D, Shetty A, Fitton CA, McLay JS. Herbal medicinal product use during pregnancy and the postnatal period: a systematic review. Obstet Gynecol. 2019;133(5):920-932.
6. Sarecka-Hujar B, Szulc-Musioł B. Herbal medicines—are they effective and safe during pregnancy? Pharm. 2022 Jan 12;14(1):171.
7. Bernstein N, Akram M, Yaniv-Bachrach Z, Daniyal M. Is it safe to consume traditional medicinal plants during pregnancy? Phytother Res. 2021;35(4):1908-1924. https://doi.org/10.1002/ptr.6935
8. Chamorro-Cevallos G, Mojica-Villegas MA, García-Martínez Y, Pérez-Gutiérrez S, Madrigal-Santillán E, Vargas-Mendoza N, Morales-González JA, Cristóbal-Luna JM. A Complete Review of Mexican Plants with Teratogenic Effects. Plants. 2022;11(13):1675. https://doi.org/10.3390/plants11131675
9. Rehman MA, Khan I. Medicinal and pharmacological potential of Guava leaf powder, A Review. IJNMHS. 2022;1(2). https://doi.org/10.52461/ijnms.v1i2.834
10. Bharathi DR, Marati KK, Mahesh C, Ajay BV, Meera V, Kumar R, Ramesh B. A review on traditional uses and pharmacological action of *Psidium guajava* linn plant. J Pharmacognosy Phytother. 2022:127-131. https://doi.org/10.46796/ijpc.v3i4.369
11. Jing S, Liu C, Zheng J, Dong Z, Guo N. Toxicity of zearalenone and its nutritional intervention by natural products. Food & Funct. 2022;13(20):10374-10400. DOI: 10.1039/d2fo01545e
12. Pandhi S, Kumar A, Rai DC. Efficacy evaluation of extraction technologies for guava (*Psidium guajava* L.) leaves extract. Ann Phytomed. 2022;11(1):413-418. http://dx.doi.org/10.54085/ap.2022.11.1.47
13. Neogi SB, Roy DK, Sachdeva AK, Sharma R, Gupta R, Ganguli A. Evidence of prenatal toxicity of herbal-based indigenous formulations for sex selection in rat models. J Tradit. Complement Med. 2021; 11(1):9-15. https://doi.org/10.1016/j.jtcme.2019.09.005
14. Rusdi MS, Efendi MR, Hilma H. Teratogenic Effects of Durian Fruit (*Durio Zibethinus* Linn) on White Mice Fetus (*Mus musculus*

L). J Pharm Sci Health. 2021; 7(1):5-10. http://dx.doi.org/10.33772/pharmauho.v7i1.13489
16. Development after Oral Administration Ethanolic Extract of Cogon Grass Roots (*Imperata cylindrica* L). J Vet. 2021; 22(2). DOI: 10.19087/jveteriner.2021.22.2.246
17. Shayan M, Mehrannia K, Rastegar T, Khanehzad M, Ghantabpour T, Hassanzadeh G. Teratogenic effect of the aqueous extract of the *Foeniculum vulgare* (fennel) on fetal development in mice. J Contemp Med Sci. 2019; 5(5). dx.doi.org/10.22317/jcms.10201905
18. Costa PC, de Souza EL, Lacerda DC, Cruz Neto JP, Sales LC, Silva Luis CC, Pontes PB, Cavalcanti Neto MP, de Brito Alves JL. Evidence for quercetin as a dietary supplement for the treatment of cardio-metabolic diseases in pregnancy: A review in rodent models. Foods. 2022; 11(18):2772. https://doi.org/10.3390/foods11182772
19. Angelina M, Ovy A, Dewijanti ID, Mardhiyah A, Sjahfirdi L. Teratogenic Investigation of Bay Leaf (*Syzygium polyanthum* Wight.) Ethanol Extract on Morphology of Fetal Mice (*Mus musculus* L.) Strain DDY. Open Access Lib J. 2022; 9(4):1-3. doi: 10.4236/oalib.1108385.
15. Sudiman J, Priscilla M, Lubis A, Syamsunarno MR, Sumarsono SH, Widyastuti R. In-vivo Mice Pre-Implantation Embryo
20. Mafruchati M and Makuwira J. Analysis of Medicinal Plants on Embryo Development of Mice (*Mus musculus* L.) And White Rats (*Rattus novergicus*): A Syst. PCJN. 2022; 32-43. https://doi.org/10.58549/pcjn.v1i01.4
21. Iacopetta D, Fazio A, La Torre C, Barbarossa A, Ceramella J, Francomano F, Saturnino C, El-Kashef H, Alcaro S, Sinicropi MS. *Annona cherimola* Mill. Leaf Extracts Affect Melanoma Cells Growth and Progression. Foods. 2022; 11(16):2420. https://doi.org/10.3390/foods11162420
22. Wang N, Shen X, Zhang G, Gao B, Lerner A. Cerebrovascular disease in pregnancy and puerperium: perspectives from neuroradiologists. Quant Imaging Med Surg. 2021; 11(2):838. doi: 10.21037/qims-20-830
23. Thant TM, Aminah NS, Kristanti AN, Ramadhan R, Hasna IH, Aun HT, Takaya Y. Coumarins and Carbazole Alkaloid from *Clausena excavata* Roots and Investigation of their α-glucosidase Inhibitory Activity. Trop J Nat Prod Res. 2020; 4(8):334-337. https://doi.org/10.26538/tjnpr/v4i8.2