An assessment of Kelor (*Moringa Oleifera*) Seed Extract Toxicity Effect at Graded Doses on Pregnant Mice Uterus, Kidney, Hepar, and Teratogenic Influence on the Fetus

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ABSTRACT
Introduction: Various parts of this plant have a variety of important minerals, are a great source of vitamins, B carotene, protein, and amino acids, and can raise hemoglobin levels. Additionally, they share the same potential for preventing anemia in pregnant women as folic acid and iron supplements. Contrary to popular belief, Moringa oleifera leaves were commonly used as an abortifacient and to avoid unneeded pregnancy in the first trimester. After administering 100 mg/kg of the alcoholic extract, 100% of the rats miscarried. Contrarily, the alcohol extract, when administered at doses of 50 and 25 mg/kg body weight, respectively, resulted in abortion rates of 44.86% and 26.26%. This study intends to evaluate the teratogenic potential of moringa seed extract, its phytochemistry, and its effects on the uterus, hepar, and kidneys of pregnant mice.
Methods: Twenty-four pregnant female Balb/c mice were used in the experiment. Four groups were created from a random selection of them. Group K is allowed to have food and drinks at no cost. The doses of 10, 20, and 30 mg/kg bb of moringa seed or stem extract were given to Group P1–P3 after 7–18 days of pregnancy. On day 19, a Cesar surgery was done to remove the uterus and count the number of fetuses that were alive and dead, as well as any disabilities and other morphological abnormalities. Phytochemicals are the subject of both quantitative and qualitative investigation. The kidneys and hepar are also removed in order to look for signs of organ degradation.
Results and discussions: No absorption or abortion occurred during this experiment. The endometrium and myometrium's histological appearance showed mild epithelial destruction, uterine gland damage, and inflammatory cell infiltration. The comparisons between K and P2, K and P3, and P1 and P3 were significantly compared. There was significant damage in the histopathological appearance. The comparisons between K and P2, K and P3 were significantly compared. Histopathology slide found necrosis and degeneration, especially hydropic degeneration and infiltration in lymphocytes and erythrocytes in the microscopic description of mice's kidneys. The comparisons between K and P1, K and P2, and K and P3 were significantly compared. Qualitative Phytochemical Tests on seeds and stems contained Alkaloids, Flavonoids, Phenolics, Tannins, and Steroids. The stems, roots, and flowers of M. oleifera may contain phytochemical elements that might be detrimental, particularly during pregnancy
Conclusion: In conclusion, the ethanol extract of Moringa seed does not exhibit any impact on the uterus. However, it does induce microdamage and inflammation in the kidney and liver.
Keywords: *Moringa Seeds, Teratogenic, Phytochemical Analysis*

1. INTRODUCTION

The Moringaceae family contained just one genus, Moringa. Drumstick trees, horseradish trees, bin oil trees, and the Igbo names Okweoyibo, Zogale, and Igbaele all have English public names. Many tropical and subtropical nations cultivate the highly prized moringa plant. It has a wide variety of medical uses and is very nutritious. This plant's many components are a good source of vitamins, B carotene, protein, and amino acids and have a profile of vital minerals. The therapeutic efficacy of moringa oleifera makes it crucial. In addition to acting as cardiac and circulatory stimulants, this plant's leaves, roots, seeds, bark, fruit, flowers, and young pods also have hepatoprotective, Renoprotective, antitumor, cholesterol-lowering, antioxidant, antidiabetic, antidiuretic, antihypertensive, antipyretic, antiepileptic, antibacterial, and antifungal properties. (Ezejindu DN Anibeze C.I.P, 2016). The seeds or flowers of Moringa offered a viable alternative for enhancing bread. Likewise abundant in protein is moringa seed (Oyeyinka & Oyeyinka, 2018) Moringa leaf extract can raise hemoglobin levels and is just as effective in preventing anemia in pregnant women as folic acid or iron supplementation. As a result, it may be a substitute for treating pregnant women's anemia. (Hadju, As, & Buchari, 2015)

Contrary to reports, Moringa oleifera leaves were used as a broadside to avoid unneeded pregnancy and were reported to be an abortifacient in the first trimester. (S. Balamurugan, S. Vijayakumar, S. Prabhu, 2018). Rats were 100% aborted after receiving 100 mg/kg of the alcoholic extract. In contrast, the

Armalina, D., Saraswati, I., and Susilaningsih, N.
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1st International Conference on Medical Science and Health (ICOMESH 2023), pages 290-298.

alcohol extract produced abortion rates of 44.86% and 26.26% at doses of 50 and 25 mg/kg body weight, respectively. When dry extracts of moringa leaves were analyzed using qualitative phytochemical techniques, flavonoids, alkaloids, steroids, triterpenoids, saponins, and phenols were discovered. (Pragna Parikh, Chirag Patel, 2015). Other investigations revealed that the root extract has teratogenic and abortifacient effects in rats, as well as the potential to operate as a contraceptive. Both a post-coital antifertility effect and proven fetal resorptions in pregnant rats have been confirmed to be caused by the root in rats. (Onyewuchi, Aprioku, & Siminialayi, 2018)

The pharmacological activities and toxicity profiles of the various Moringa oleifera lam components have not yet been fully characterized. Only a small number of the various illnesses it has been used to treat over the years and was studied for. One of the top names recently in plant and medicine research is Moringa oleifera. There are now a lot of studies on the nutritional benefits of moringa, both in academic and lay literature. However, the results of carefully monitored and well-documented clinical studies are still indisputable valuable. (Paul & Didia, 2012)

Although the liver was adversely affected by the leaf extract of this plant, the current investigation revealed that it may be able to lessen the liver damage caused by cadmium. (Author & Kumar, 2014)

Despite the plant's purported nontoxicity, this is untrue. A very minor increase (three to four times the advised dose) can cause genotoxic harm even when supplement dosages appear safe from all evaluated toxicities. While greater doses clearly damage organs (namely the liver and kidneys), it may promote the growth of cancer. Additionally, taking supplements when pregnant is not advised due to the possibility that even very little supplement dosages could result in abortions in pregnant rats. (Abijo A Z, Adeeyo O O, Komolafe O A, Saka O S, 2019)

Although the ingestion of various Moringa oleifera lam components, including the roots, has been widely accepted for various purposes, it has been discovered that methanolic extracts of the plant's roots alter the histo-architecture of the guinea pigs' liver and kidneys. Both the passage of time and the dose affect these effects. Guinea pigs in the reversal group still had histo-architectural abnormalities in their liver and kidney. (Paul & Didia, 2012)

Previous investigations discovered that the extract of Moringa oleifera leaves had high levels of flavonoids, alkaloids, saponins, tannins, proteins, carbohydrates, and reducing sugars as well as steroids, terpenoids, and tannins. (Ufelle, Onyekwelu, Achukwu, Ezeh, & Ghasi, 2018) Based on the mechanism of action of antifertility substances, such as cytotoxic (tannins and abrin) and hormonal (alkaloids, flavonoids, steroids, and triterpenoid saponins), the findings of the literature study indicate that the bioactivity content of secondary metabolite compounds from various plant families that have the potential to be antifertility can be divided into two categories. (Rizky Agung Tambengi , Maulana Isman Naki , Ayu Brenda Sumariangen, 2023) One of the substances thought to have deleterious effects on humans and affect the structure and operation of the cells that make up the glomerulus is alkaloids. (Anggi Widyaningsih, Agung Janiks Sitasiwi, 2018)

Food generated from M. oleifera can be a substantial folate supply due to the significantly greater absorption in animals. Folate, one of the most important water-soluble vitamins, is important for a number of cellular metabolisms, including the oxidation and reduction of one-carbon units. Folate deficiency causes severe chronic illnesses, developmental issues, including anomalies of the neural tube at birth. To prevent anomalies of the neural tube and other chronic dysfunctions, a high-folate diet is strongly advocated during pregnancy. (Maizuwo, Hassan, Momoh, & Muhammad, 2017) In a previous investigation, it was discovered that oral administration of Moringa oleifera dried leaf powder up to 2000 mg/kg had no effect on clinical symptoms or gross pathology, and that its oral toxicity (LD50) was higher than 2,000 mg/kg. (Moodley, 2017) This study discovered minor liver and kidney damage, which may still be related to moringa's or pregnancy's physiological impacts. The daily dose that is often used in the community and is significantly below the hazardous amount was employed in this investigation. However, pregnant women must consume this extract with caution to avoid exceeding the dangerous dose.

2. METHOD

2.1 Research design

Laboratory experimental research was conducted in the Department of Histology-Faculty of Medicine Diponegoro University, Animal Laboratory Faculty of Medicine Diponegoro University within six months.

2.2 Statistical analysis

All obtained data in this study were processed with the SPSS computer program. The Mann-Whitney U test was performed to see the effect of Moringa exposure on mice's uterus, kidney, and hepar.

2.3 Subjects and treatment of the study

Twenty female Balb/C strain mice, aged 8–10 weeks, weighing 25–35 g, were utilized as test subjects. They were all healthy and anatomically normal. For 12 hours, from 18:00:00 to 06:00:00, one male mouse was kept in each cage containing three female mice. Using the vaginal smear, a vaginal plug, and sperm count, it was possible to identify the day of conception.(Fonseca, Correia-da-silva, & Teixeira, 2016) The pregnant mice were divided into seven groups. Each group received six mice at random and went through a 7-day acclimation period. The control group was given food and drink at their discretion, whereas the P1-P6 treatment groups got doses of 10, 20, and 30 mg/kg bb of moringa seeds and stem. It has been studied how aggressive mice are, what they do during the day, and how they interact with one another in a cage up until the 18th day of pregnancy from the experiment's beginning. (Klaassen, 2008)

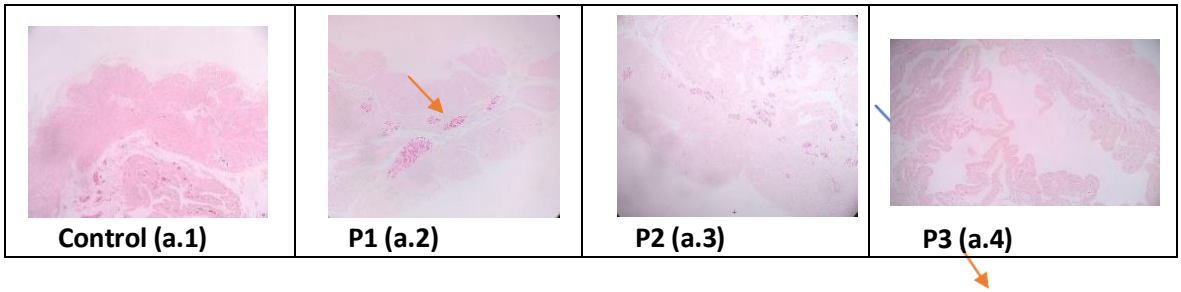
2.4 Histopathological examination

The termination of pregnant mice under anesthesia and a cesarean section were done on the 19th day to study the teratogenic effects on the embryos, and then a cervical dislocation was done to look at microscopic preparations on the kidney and hepar. The frequency of absorbed and living fetuses in each mouse and external malformation differences between the control (abnormality in the fetuses) were observed for teratogenic effects. (Klaassen, 2008) Mice's kidneys and hepars were prepared microscopically and stained with hematoxylin and eosin (HE). To determine each preparation's histopathological index, five fields of view were read and examined under a microscope. The Knodell score was applied to the hepar score to identify lobule degeneration, inflammatory cell infiltration, and fibrosis at the portal area, while the histopathology score was applied to the kidneys preparation reading to identify necrosis, degeneration, and infiltration in lymphocyte and erythrocyte of mouse kidneys. (Da, Surana, Kleiner, Heller, & Koh, 2020)(Meireles, Gomes, Lopes, Hinzmann, & Machado, 2020). This study was authorized by the Faculty of Medicine, Diponegoro Universities' Research Ethics Committee.

3 RESULTS AND DISCUSSION

3.1 Fetus Observation in Kelor Seed extraction

Based on observation, the control and treatment groups exhibited an average of 8 to 9 mouse offspring during termination. No absorption or abortion occurred during this experiment. Based on a previous study, rats that were administered doses of 175 mg/kg of aqueous and 90% ethanol leaf extract derived from Moringa oleifera experienced complete abortion. (10). A further investigation revealed that the ethanol extract derived from the Moringa leaf had abortifacient properties by decreasing the number of offspring generated by rats administered with the extract. (9) The administration of moringa oleifera leaf and seed extracts orally at doses of 100, 200, and 400 mg/kg body weight/day resulted in a decrease in the number of offspring born. Pregnant women are advised to refrain from using the herb. (Obediah & Paago, 2019)



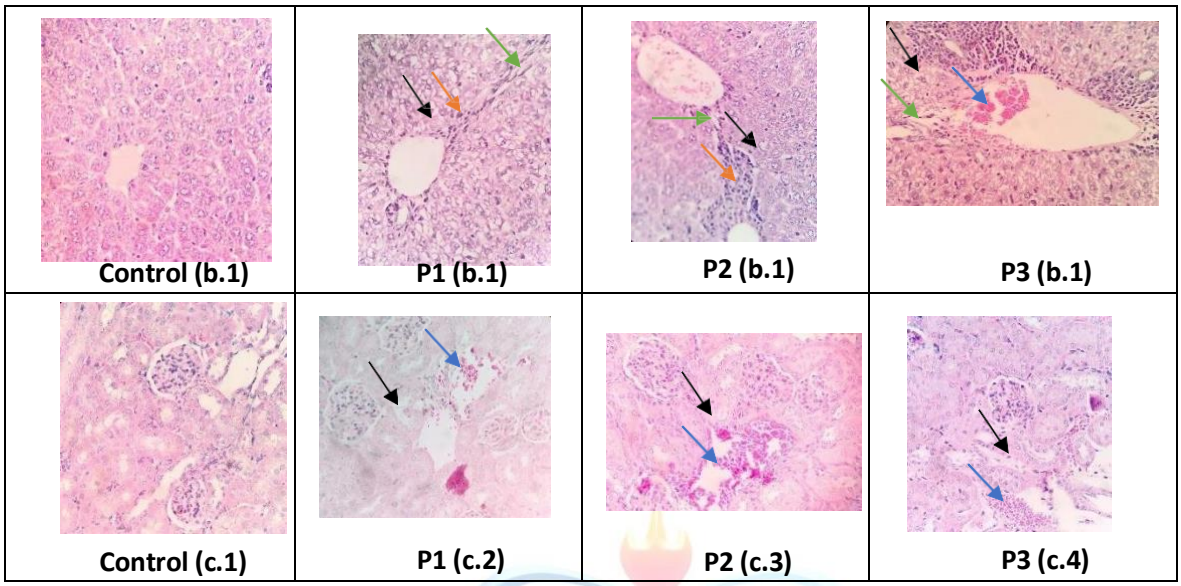


Figure 1. Microscopic organ appearances with Moringa extract Seed (a-c). Microscopic uterus with moringa extract seed (a.1-a.4), microscopic hepar with moringa extract seed (b.1-b.4), microscopic kidney with moringa extract seed (c.1-c.4), In the control (a.1-c.1) no damage found. Black arrow: degeneration, green arrow: necrosis, blue arrow: erythrocyte infiltration, yellow arrow: lymphocyte infiltration

3.2 Microscopic of Uterus Kelor Seed Extraction

The observational findings on the state of the mice during treatment revealed no signs of aggression in treated mice. The endometrium and myometrium's histological appearance showed mild epithelial destruction, uterine gland damage, and inflammatory cell infiltration.

	Group			
	K	P1	P2	P3
Mean	0,60	0,00	2,60	3,80
Median	1,00	0,00	3,00	3,00
Std. Deviation	0,55	0,00	1,52	1,10
Minimum	0,00	0,00	0,60	3,00
Maximum	1,00	0,00	4,00	5,00

Table 1. Descriptive of Microscopic of Uterus Kelor Seed Extraction

A significant difference was found between all groups (p = 0.004) in the Kruskal Wallis and continued with the Mann-Whitney tests' analysis.

P values of Uterus damage with Kelor Seed Extract test results by Mann Whitney

	K	P1	P2	P3
K	-	0.701	**0.02***	**0.02***
P1		-	0.52	**0.007***
P2			-	0.443
P3				-

Table 2. Analysis of Microscopic of Uterus Kelor Seed Extraction

The comparisons between K and P2, K and P3, and P1 and P3 were significantly compared, whereas the comparisons between K and P1, P1 and P2, and P2 and P3 were not significantly compared.

3.3 Microscopic of Hepar Kelor Seed Extraction

According to Figure 1, there was a significant difference in hepar damage compared to the control group. There was significant damage in the histopathological appearance, necrosis of the portal area was found in mice's hepars, especially hydropic degeneration in lobules and inflammatory cell infiltration, as well as fibrosis starting at the portal area, which caused sinusoids to expand .

A significant difference was found between all groups (p = 0.008) in the Kruskal Wallis and Mann-Whitney tests' analysis results. P values of Hepar damage with Kelor Seed Extract test results by Mann Whitney

	Group			
	K	P1	P2	P3
Mean	0,60	6,20	6,40	7,40
Median	1,00	8,00	8,00	9,00
Std. Deviation	0,55	2,95	3,13	4,10
Minimum	0,00	3,00	3,00	3,00
Maximum	1,00	9,00	9,00	11,00

Table 3. Descriptive of Microscopic of Hepar Kelor Seed Extraction

	K	P1	P2	P3
K	-	0.015	**0.009***	**0.002***
P1		-	0.848	0.478
P2			-	0.604
P3				-

Table 4. Analysis of Microscopic of Hepar Kelor Seed Extraction

The comparisons between K and P2, K and P3 were significantly compared, whereas the comparisons between K and P1, P1 and P2, P1 and P3, and P2 and P3 were not significantly compared.

3.4 Microscopic Of Kidney Kelor Seed Extraction

Histopathology slide found necrosis and degeneration, especially hydropic degeneration and infiltration in lymphocytes and erythrocytes in the microscopic description of mice's kidneys. (Figure 1)

	Group			
	K	P1	P2	P3
Mean	1,00	2,40	2,80	3,00
Median	1,00	2,00	2,00	3,00
Std. Deviation	0,00	0,89	1,10	0,71
Minimum	1,00	2,00	2,00	2,00

Maximum	1,00	4,00	4,00	4,00

Table 3. Descriptive of Microscopic of Kidney Kelor Seed Extraction

A significant difference was found between all groups (p = 0.006) in the Kruskal Wallis and Mann-Whitney tests' analysis results.

P values of Kidney damage with Kelor Seed Extract test results by Mann Whitney

	K	P1	P2	P3
K	-	**0.02***	**0.005***	**0.001***
P1		-	0.614	0.356
P2			-	0.675
P3				-

Table 6. Analysis of Microscopic of Kidney Kelor Seed Extraction

The comparisons between K and P1, K and P2, and K and P3 were significantly compared, whereas the comparisons between P1 and P2, P2 and P3, and P1 and P3 were not significantly compared.

Senyawa metabolit sekunder	Reagen yang digunakan	Seed
Alkaloid	Dragendorff	+
Flavonoid	Mg, HCl dan amil alkohol	+
Saponin	HCl	-
Fenolik	$FeCl_3$ 1%	+
Tanin	$FeCl_3$ 5%	+
Kuinon	NaOH	-
Triterpenoid	Lieberman-Burchard	-
Steroid		+
Semi Kuantitatif Steroid		++

Table 7. Secondary Metabolite in Kelor Seed Extract

Qualitative Phytochemical Tests on seeds and stems contained Alkaloids, Flavonoids, Phenolics, Tannins, and Steroids. The examination was continued with a semi-quantitative examination on steroids. The results, namely steroid examination, obtained a more concentrated green color on the seeds.

4 DISCUSSION

Moringa oleifera L., a perennial tree belonging to the Moringaceae family, is extensively planted in various tropical regions and may thrive in unfavorable environments. M. oleifera, commonly referred to as the miracle tree, has long been recognized for its use in traditional medicine. M. oleifera, in various forms, is utilized to address a range of illnesses including malnutrition, diabetes, blindness, anemia, hypertension, stress, depression, skin disorders, arthritis, joint disorders, and kidney stones. These therapeutic effects can be achieved through oral administration without any reported adverse reactions. (Meireles et al., 2020)

The stems, roots, and flowers of M. oleifera may contain phytochemical elements that might be detrimental, particularly during pregnancy. These constituents have the ability to induce uterine contractions, which can result in miscarriages in pregnant women. (Meireles et al., 2020). Another study found that the use of moringa leaves had positive or beneficial effects on majority of the measured factors, without any detrimental effects on male and female reproductive indicators. Nevertheless, the fertility of the plants was

negatively affected by other components. This implies that various sections of a plant may have varying effects on fertility, and it is important to consider this while consuming different parts of the plant. The variations arise due to disparities in the quantities or concentrations of phytochemicals in the different components. (Oa, Jo, Os, Nl, & Faluyi, 2017)

Within the examined animals, the administration of a moringa extract leads to a decrease in FSH and LH levels in a manner that is dependent on the dosage. Higher doses of the extract correspond to lower levels of these hormones, whereas smaller doses of the extract correspond to higher levels of these hormones. Animals administered a dosage of 400 mg/kg had significantly reduced levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) compared to those given dosages of 100 mg/kg, 200 mg/kg, or the control group. These findings indicate that the ethanolic extract derived from the leaves and seeds of moringa oleifera had the capacity to reduce the concentrations of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in living organisms.. (Obediah & Paago, 2019)

The uterine histology of the rat control exhibited characteristic architectural features. The endometrium consisted of a highly vascularized spongy layer including blood arteries and uterine glands, which were bordered by epithelial cells. Additionally, there were large epithelial cells with nuclei located at the basal and central regions. Multiple, chaotic, and intricate uterine glands are observable. The stroma exhibited laxity and maintained regular vascularity, but the uterine lumen displayed significant congestion. The histological section of the rat ovary showed a reduction in the size of the uterine gland and the luminal epithelium did not exhibit significant folding after being treated with 100 mg/kg of M. oleifera's ethanolic stem bark extract. The musculature experienced significant damage, and the stroma seemed dense and had little blood supply. (Zade & Dabhadkar, 2014). Prior studies have determined that Moringa oleifera is generally safe for human consumption. When administering a medication for an extended duration, caution must be exercised. Further investigation is recommended about the mutagenic, teratogenic, and carcinogenic effects of Moringa oleifera. (Awodele, Adekunle, Odoma, Teixeira, & Oluseye, 2012)

No histologically detectable negative effects were observed in the cerebrum, cerebellum, hippocampus, kidney, liver, and bone marrow components of the brain when exposed to moringa oleifera leaf extract. However, significant histological disruptions were observed in the testis and epididymis, indicating that it acts as an anti-fertility agent. The histomorphology of the kidney, spleen, and liver improved due to the effects of moringa extract treatment. (Owolabi & Ogunnaike, 2014)

It is recommended to add a dietary supplement of 200 mg/kg Moringa leaf extract to improve the growth performance, hematological parameters, liver, and kidney functions in Nile tilapia. When using Moringa extract at a concentration exceeding 200 mg/kg diet, caution must be exercised. (Emam et al., 2022)

5 CONCLUSION

In conclusion, the ethanol extract of Moringa seed does not exhibit any impact on the uterus. However, it does induce microdamage and inflammation in the kidney and liver. Consequently, the dosage of the research substance remained within limits/ not recommended for use by pregnant individuals. Nevertheless, further investigation is warranted to ascertain the effects on hormonal levels and determine if the observed inflammation in the kidneys and liver was caused by pregnancy or the administration of kelor extract

6 CONFLICT OF INTERESTS

There is no conflict of interest in this study.

7 ACKNOWLEDGMENT

The researcher would like to express gratitude to the sponsors, particularly the PHK-PKPD Diponegoro University Research Grant.

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