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Oral Administration of Moringa Leaf Ethanol Extract (Moringa Oleifera) for 14 Days Protects The Liver of Male White Rats (Rattus Norvegicus) from Acute Damage Caused by High Doses of Paracetamol

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Abstract

Paracetamol is a widely utilized medication globally and is the primary cause of poisoning incidents in high-income countries. Paracetamol induces hepatotoxicity that is depending on the dosage when taken in excessive amounts. The Moringa oleifera (MO), belonging to the Moringaceae family, is one of the medicinal plants investigated for its potential in treating hepatotoxicity. The MO tree extracts have been documented to possess inhibitory effects, primarily against hepatitis drug-induced hepatotoxicity, owing to their bioactive components. An experimental laboratory enrolled using 36 samples of male white rats (*Rattus norvegicus*), which were divided into six groups: standard control group (K), positive control group (K1) given paracetamol 3000mg/kg BW on 15th days; antioxidant control group (K2) given vitamin c 500mg/kg BW for 14 days; treatment group 1 (P1), treatment group 2 (P2) and treatment group 3 (P3) each given moringa oleifera leaves extract 200mg/kg BW, 400mg/kg BW and 800mg/kg BW for 14 days. Each group, except the standard control group, was given paracetamol 3000mg/Kg BW on the 15th day. On the 16th day, the mice were euthanized, and then their livers were made into histological preparations and examined using a microscope at 40 times magnification. The level of liver cellular damage was categorized into scoring based on the level of damage. Score 1 if no damage, score 2 if parenchymatous degeneration was found, score 3 if hydropic degeneration was found, and score 4 if necrosis was found. The average scoring per group was calculated as K: 1.1; K1: 3.17; K2: 1.57; P1: 1.5; P2: 1.73; P3: 1.9. K1 appeared necrotic. Inflammation and hydropic degeneration were found in K2, P1, P2, and P3. Data were analyzed using the Kruskal-Wallis Test, obtained $p = 0.000$ ($p < 0.05$). Moringa leaf ethanol extract affected hepatic induction by paracetamol because significant differences were found between groups P1, P2, and P3 with K1 ($p < 0.05$). There were no significant differences between groups K2 and P1 ($p > 0.05$), showing that the effect of giving 500mg/kg BW vitamin C was equivalent to providing 200mg/kg BW Moringa leaves. It was concluded that giving ethanol extract of Moringa oleifera leaves protected the acute histopathological damage of the liver of male white rats of the Sprague Dawley strain induced by paracetamol.

Keywords: Moringa oleifera leaf, hepatotoxicity, paracetamol

1. Introduction

Paracetamol (acetaminophen) is commonly misused and taken in excessive amounts for the purpose of suicide due to its widespread accessibility.[1] Paracetamol poisoning is the primary cause of acute liver failure in developed nations and is extensively studied as a kind of drug-induced liver damage.[2]

The Moringa oleifera (MO) tree, belonging to the Moringaceae family, is an exemplary medicinal plant that has been utilized in traditional medicine for many generations. The MO has been traditionally employed for treating many ailments such as skin infections, wounds, fever, diarrhea, and sore throats. The MO tree is extensively utilized because of its abundant presence of phytochemicals that act synergistically to elicit its therapeutic effects.[3] Scientifically, MO has been proven to have anti-inflammatory, antihypertensive, antibacterial, antioxidant, anti-diabetic, and antiviral properties. Furthermore, MO has demonstrated the ability

to enhance renal and hepatic functioning.[4] The several components of the MO tree, including as flowers, seeds, roots, and leaves, contain a diverse array of bioactive substances, including flavonoids and phenolic acids. Nevertheless, the leaves possess a substantial concentration of bioactive chemicals, which grants them a diverse array of medical attributes, including anti-inflammatory, anticancer, and antioxidant capabilities. The primary cause of the antioxidant effect of MO leaves is mostly ascribed to the presence of flavonoids, phenolic acids, and carotenoids. The main component found in MO leaves is quercetin, which makes up 43.75% of the total composition. Additionally, additional flavonoids are present in comparable proportions, accounting for 18.75% each.[5]

The objective of this study was to investigate the potential protective effects of an ethanolic extract derived from Moringa Oleifera leaves on acute hepatic damage produced by paracetamol in male rats. This was achieved through the assessment of liver damage using histological examination.

2. Methodology

This study employed an experimental design, with male white Sprague Dawley rats as the subjects. The research has received ethical approval from the Research Ethics Commission of the Faculty of Medicine, University of Lampung, with the reference number 65/UN26.18/PP.05.02.00/2019. The research was carried out in the Faculty of Medicine, University of Lampung in December 2019. A total of 36 mice were used as research subjects.

The extract is produced in the Biochemistry Laboratory of FK UNILA by the process of drying Moringa leaves, subsequently reducing them into small fragments, and finally pulverizing them into powder using a grinder. The powder was subjected to Soxhlet extraction by mixing it with 2.6 liters of 96% ethanol solvent for a duration of 24 hours. The extract underwent filtration using filter paper and was subsequently concentrated using a rotary evaporator at a temperature of 50^0C until the ethanol was completely evaporated.[6-8]

The rat samples were categorized into 6 groups: 6 rats in the negative control group (K), 6 rats in the positive control group (K1), 6 rats in the vitamin C antioxidant comparison group (K2), and 6 rats in each of the treatment groups 1 (P1), 2 (P2), and 3 (P3). Over a period of 15 days, a total of 36 mice were acclimated and provided with unrestricted access to food. Throughout the adaption period, there were no instances of mouse mortality or weight reduction. Include Group K (-) as a negative control, which will not be subjected to the induction of paracetamol, Moringa leaf extract, and vitamin C. Group K1(+) served as a positive control and received a dose of 3g/kg BW of paracetamol on day 15. The purpose was to observe liver alterations in mice that were not generated by paracetamol or leaf extract. Moringa. The K2 group, serving as the control group, received a dosage of 500mg/kg BW of vitamin C for a duration of 14 days. On the 15th day, they were administered paracetamol at a dosage of 3g/kg BW to observe the effects on the mice's livers. Treatment 1, designated as Group P1, involved administering a dosage of 3g/kg BW of paracetamol on day 15, followed by a daily dose of 200 mg/kg BW of Moringa leaf extract for a duration of 14 days. Treatment 2, also known as Group P2, received a dosage of 3g/kg BW of paracetamol on day 15, followed by a daily dosage of 400 mg/kg BW of Moringa leaf extract for 14 days. Treatment 3, also known as Group P3, received a dosage of 3 grams per kilogram of body weight of paracetamol on day 15. Additionally, they were administered Moringa leaf extract at a dosage of 800 milligrams per kilogram of body weight per day for a duration of 14 days.[9]

On the 16th day, all groups of mice underwent a 10-hour fasting period. They were then anesthetized intraperitoneally with ketamine (75mg/kg BW) and xylazine (5mg/kg BW). Finally, the mice were terminated using the cervical dislocation procedure. The liver from each specimen in every group was extracted via laparotomy and preserved using a 10% formalin solution. The liver organs were dispatched to the Anatomical Pathology laboratory at the Faculty of Medicine, University of Lampung, for the purpose of creating liver preparations for each individual rat organ sample. Once the preparation is fully prepared, it was examined using a light microscope. Liver damage was evaluated by examining each sample under a microscope at a magnification of 40x. The assessment involved observing normal cells, parenchymal degeneration, hydropic degeneration, and necrotic cells in five different fields of view.[10]

The results of the observations were then scored based on the severity of liver cell damage. Score 1 if only Normal cells were found, score if Parenchymatous Degeneration was found, score 3 if Hydropic Degeneration was seen, and score 4 if necrotic cells were found.[9-10]

The Kruskal-Wallis test was carried out to see whether there were significant differences between the sample groups. Then, a Post Hoc Mann-Whitney analysis was carried out to see the relationship in each sample group.[7,8]

3. Result

The results of histopathological observations of white rat livers were different in each group (see Figure 1). The histopathological picture of the liver of the negative control group showed that the hepatocytes appeared normal. There seemed to be a few inflammatory cells; there was no visible swelling of the hepatocyte cells. The liver sinusoids also appear normal, are not enlarged, and have a radial pattern centered on the central vein. In the histopathological image of the liver of the positive control group (K1), there were changes in the hepatocytes which experienced extensive cloudy and hydrophic swelling degeneration and visible necrosis in some of the hepatocytes. In the histopathological picture of the liver of the vitamin C (K2) antioxidant comparison group, cells were seen experiencing parenchymatous degeneration. In the histopathological picture of the liver in treatment group 1, parenchymatous degeneration was seen in several parts of the liver hepatocytes. In the image of treatment group 2, extensive inflammation is still visible and is accompanied by parenchymatous degeneration in some hepatocytes. The histopathological picture of the liver in treatment group 3 showed extensive inflammation accompanied by parenchymatous degeneration in some hepatocyte cells, which was more severe than in treatment group 2 (P2).

Tabel 1. Hepatic damages scoring

Groups	Averages hepatic damages score
K	1,1
K1	3,17
K2	1,57
P1	1,5
P2	1,73
P3	1,9

Table 2. The *Mann Whitney* test. * Significantly different

Groups	K	K1	K2	P1	P2	P3
K	-	0.003*	0.003*	0.003*	0.002*	0.003*
K1	0.003*	-	0.003*	0.003*	0.002*	0.003*
K2	0.003*	0.003*	-	0.553	0.068*	0.006*
P1	0.003*	0.003*	0.553	-	0.047*	0.007*
P2	0.002*	0.002*	0.068*	0.047*	-	0.043*
P3	0.003*	0.003*	0.006*	0.007*	0.043*	-

The scoring assessment showed that the mean hepatocyte damage score for the negative control group (K) was 1.1; the positive control group (K1) was given paracetamol 3g/kg BW on day 15 with a mean damage score

of 3.17; in the comparison group of antioxidant vitamin C (K2) which was given vitamin C 500mg/kg BW 1ml/day for 14 days and paracetamol 3g/kg BW on day 15, the mean score was 1.57; in treatment group 1 (P1) which was given Moringa leaf extract 200 mg/kg BW and paracetamol 3000g/kg BW on day 15, the mean score was 1.5; in treatment group 2 (P2) which was given Moringa leaf extract 400mg/kg BW and paracetamol 3g/kg BW on day 15, the mean score was 1.73; in treatment group 3 (P3) given 800mg/kg BW moringa leaf extract and 3g/kg BW paracetamol on day 15, the mean score was 1.9.

This study found that most of the data had significant differences (see table 2). Groups that had significant differences were between negative control (K) and positive control (K1) (p=0.003), negative control (K) and comparison control (K2) (p=0.003), negative control (K) and treatment 1 (P1) (p=0.003), negative control (K) with treatment 2 (P2) (p=0.002), negative control with treatment 3 (P3) (p=0.003), positive control (K1) with comparison control (K2) (p=0.003), positive control (K1) with treatment 1 (P1) (p=0.003), positive control (K1) with treatment 2 (P2) (p=0.002), positive control with treatment 3 (P3) (p =0.003), comparison control (K2) with treatment 3 (p=0.006), treatment 1 (P1) with treatment 2 (P2) (p=0.047), treatment 1 (P1) with treatment 3 (P3) (p=0.007), and treatment 2 (P2) with treatment 3 (P3) (p=0.043).

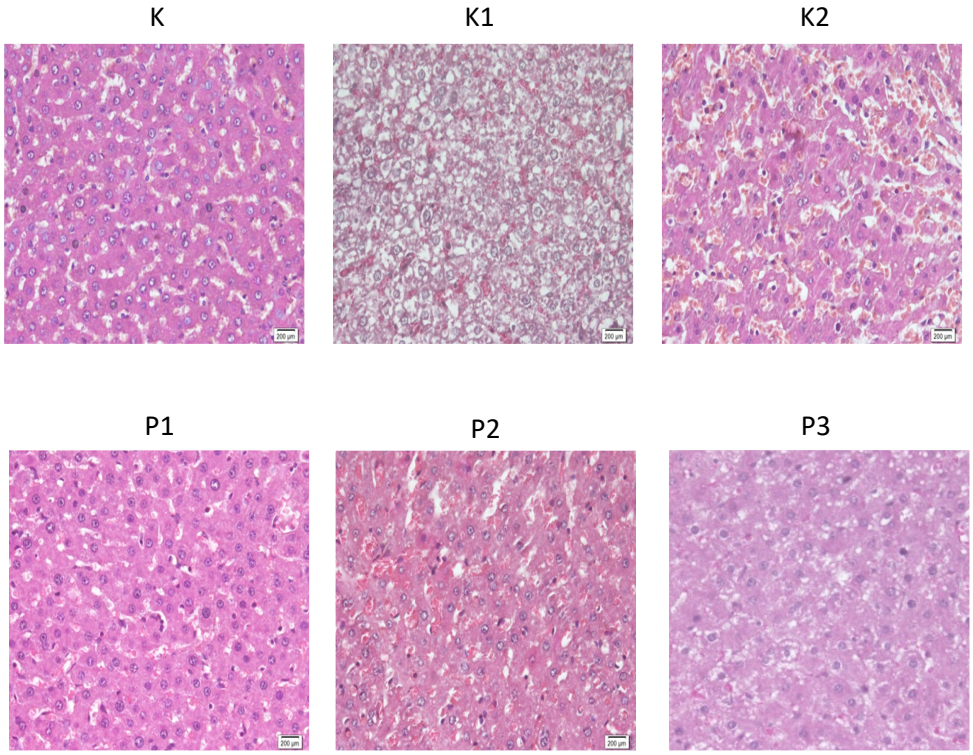

Figure 1. The liver section of neutral mice exhibited cells and their nuclei that were consistently similar in size and staining properties, displaying a normal look of hepatic sinusoids (Fig. K). The histological micrograph of rats treated with acetaminophen revealed the presence of inflammatory cells infiltrating the liver tissue, disruption of the typical arrangement of hepatic cords, and darkly stained nuclei, indicating pyknotic alterations and aggregation of nuclear material (Fig.1 K1). Treatment with either 200 (P1), 400 (P2) or 800 (P3) mg/kg BW of M. oleifera ethanolic extract or ascorbic acid (K2) led to a decrease in liver injury and a significant enhancement of histological parameters.

4. Discussion

Microscopic observation showed that the negative control group (K) not given Moringa leaf extract, vitamin C, or paracetamol had the lowest average hepatocyte damage score of 1.1. The food given to mice is not an irritant. Overall, the negative control group (K) still looked normal.[9]

The results of microscopic analysis of liver preparations from group K1, which were given paracetamol at a dose of 3g/Kg BW on day 15, showed that the liver damage was highest compared to other groups; it was found that hepatocyte cells experienced parenchymatous degeneration, hydropic degeneration, and necrosis. The average damage score is 3.17. The appearance of injury in K1 hepatocyte cells is due to the paracetamol metabolite, NAPQI, which has hepatotoxic properties and binds directly to hepatocyte cells. As a result, there is a subsequent depletion of GSH and antioxidant enzymes, leading to an increased production of reactive oxygen and nitrogen species. Variations in the appearance of injury are a manifestation of the phase leading to irreversible injury caused by the binding of NAPQI and hepatocyte cells, namely starting from parenchymatous degeneration; if no improvement occurs, hydropic degeneration will occur, then if antioxidants remain inadequate, oxidative stress will occur which leads to irreversible injury in the form of necrosis.[11]

The results of microscopic analysis of the antioxidant control group (K2) who were given vitamin C at a dose of 500mg/Kg BW for 14 days and continued with paracetamol 3g/Kg BW on day 15 showed a mean score that was lower or looked slightly better compared to the positive control group (K1) with an average damage score of 1.57. The injury picture obtained in the antioxidant comparison group (K2) was parenchymatous degeneration, and no hydropic degeneration or cell necrosis was found. Vitamin C or ascorbic acid is an antioxidant agent that can prevent the occurrence of a free radical chain reaction between paracetamol and hepatocytes or eliminate free radicals before they reach the target hepatocyte cells, with research results in mice showing significant results at a dose of 500mg/kg bb.[12]

The results of microscopic analysis of treatment group 1 (P1) which was given 200mg/Kg BW Moringa leaf extract for 14 days and continued with 3g/Kg BW paracetamol on day 15 showed a lower mean score compared to the positive control group (K1) with a mean score of 1, 5. The lower mean liver damage score is due to the content of saponins, tannins, alkaloids, and flavonoids, which act as antioxidants in Moringa oleifera leaf extract preparations that will bind with NAPQI metabolites, preventing injury, thus producing hepatoprotective effect against paracetamol.[13,14] The extract of Moringa oleifera suppressed the production of nitric oxide and maintained the levels of GSH. GSH is necessary for the detoxification of paracetamol metabolites and NAPQI, which are responsible for causing liver damage.[15]

The results of the analysis of treatment group 2 (P2), which was given 400mg/Kg BW Moringa leaf extract for 14 days and continued with 3g/Kg BW paracetamol on day 15, showed a lower mean score than the positive control group (K1) with a mean score of 1.73. The antioxidant content of Moringa leaf ethanol extract preparations such as saponins, tannins, alkaloids, and flavonoids will bind with NAPQI metabolites, which will prevent injury so that a scoring value that is close to normal is obtained due to the resulting hepatoprotective effect.[16]

The results of the analysis of treatment group 3 (P3), which was given 800mg/Kg BW Moringa leaf extract for 14 days and continued with 3g/Kg BW paracetamol on day 15, showed a lower mean score compared to the positive control group (K1) with a mean score of 1.9.

The lower mean liver damage score is due to the similar compound content as in groups P1 and P2, namely saponins, tannins, alkaloids, and flavonoids, which act as antioxidants in Moringa oleifera leaf extract preparations, which bind to NAPQI metabolites, preventing injury., thus producing a hepatoprotective effect. Apart from that, some vitamins, such as vitamin C and vitamin E, which are also natural antioxidants, play a role in helping the elimination of NAPQI metabolites. Natural antioxidants inhibit the formation of reactive oxygen species (ROS) and eliminate free radicals.[15,16]

In this study, 200mg/Kg BW of Moringa leaves was an effective dose as a hepatoprotector. This is because as a treatment group, P1 with a dose of Moringa leaves of 200mg/Kg BW had the lowest liver damage score, namely 1.5, compared to a dose of Moringa leaves of 400mg/Kg BW with a score of 1.73 (there was a difference in scoring of 0.23), 800mg. /Kg BW with a score of 1.9 (a scoring difference of 0.4) and vitamin C dose of 500 mg/Kg BW with a score of 1.57 (a scoring difference of 0.07). Our findings were in line with the results of other research that concluded the biochemical data supported the histological findings, confirming the hepatoprotective action of the Moringa oleifera extract. Their findings consistently demonstrated that the transaminase level returns to normal as the hepatic parenchyma heals and hepatocytes regenerate. The administration of Moringa oleifera extract resulted in a notable reduction in serum levels of ALP in hepatotoxic rats, indicating an enhanced therapeutic efficacy of the extract. Their study demonstrated a notable enhancement following treatment with Moringa oleifera extract. Additionally, the prophylactic group substantially reduced TNF-α and TGF-β levels, which fell below the standard range. This can be attributed to the hepatoprotective properties of Moringa oleifera, which effectively mitigates liver inflammation by reducing the content of TNF-α in the liver.[17]

The extract of Moringa oleifera shown the ability to suppress lipid peroxidation produced by acetaminophen. The findings indicate that the extract of M. oleifera has the ability to either decrease the metabolism of paracetamol to NAPQI or enhance the replenishment of GSH. This extract provides an excess of cysteine as a substrate for the Krebs cycle, and it plays a significant role in scavenging free radicals and peroxynitrite.[18]

The difference in the scoring results of treatment 1 with treatment 2 Moringa leaves and treatment 3 Moringa leaves was statistically significant except for the vitamin C antioxidant comparison group, where the scoring comparison results were not statistically significant.

This research shows that a higher dose of Moringa leaves is directly proportional to a more significant liver damage scoring value. This occurs because of the antinutrient factors found in Moringa leaves, which inhibit the absorption and utilization of protein, carbohydrate, mineral, vitamin, and also antioxidant substances such as phenols, alkaloids, tannins, saponins, which are expected to help repair the liver. These antinutrients include tannin, phytate, oxalate, saponin, and hydrogen cyanide, which will increase if the amount of Moringa leaves consumed is more significant. So, the higher dosage of Moringa leaf ethanol extract will be proportional to the high levels of dissolved antinutrients, which cause the antioxidants to fail.[16] It can carry out its function as a hepatoprotector optimally. This had an impact on the scoring of treatment 1 (with a score of 1.5), treatment 2 (with a score of 1.73), and treatment 3 (with a score of 1.9), which got more prominent as the dose of Moringa leaf ethanol extract increased.

Based on this research, the ability of Moringa leaves to act as a hepatoprotection against paracetamol in male white rats of the Sprague Dawley strain is limited by the presence of antinutrients. The effective dose obtained is 200mg/Kg BW. 400mg/Kg BW and 800mg/Kg BW are still within the safe dose range for research object mice. The dose of Moringa leaves that caused mortality in mice was 5000mg/Kg BW. Meanwhile, in humans, administering 7000mg/Kg BW of Moringa leaf extract orally for 12 weeks (3 months) does not cause side effects in humans.[19]

5. Conclusion

Oral administration of Moringa Leaf Ethanol Extract (Moringa Oleifera) for 14 days protects the liver of male White Rats (Rattus Norvegicus) from acute damage caused by high doses of paracetamol. A dose of 200 mg/Kg BW can prevent acute liver damage caused by high doses of paracetamol administer. The leaves of the Moringa plant have great potential to be developed into an anti-oxidant supplement to prevent acute liver damage due to paracetamol overdose.

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