



Protective effect of *Moringa oleifera* leaves extract against gentamicin induced hepatic and nephrotoxicity in rats

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Abstract

Gentamicin-specific non-targeted induction of hepato- and nephrotoxicity is a clinical challenge in human and veterinary medicine. This study investigates the hepato- and nephroprotective effect of *Moringa oleifera* leaves extract on Gentamicin-induced hepatic and nephrotoxicity in rats. C- group showed negative control and had no treatment. C+ group received 80 mg/kg/day/i.p of gentamicin (GM) for 8 days and exhibited positive control. T1, T2, and T3 groups were treated with *Moringa oleifera* (MO) leave extract orally for 14 days at doses of 150, 300, and 600 mg/kg respectively after GM treatment. After 21 days of MO leave extract treatment, all the rats had liver and kidneys excisions. The assessment was done for the macroscopic changes in the liver and the microscopic changes and measurement of the MDA level of the liver and kidneys. The histopathological examination of the liver and kidneys shows that gentamicin increased the damage in the liver (degeneration, necrosis, and fibrosis score), kidneys (glomerular damage, degeneration, and necrosis of tubulous score), and MDA level. The application of MO extract at a dose of 600 mg/kg in gentamicin-induced rats can prevent the increase in the MDA levels as indicated by a decrease in the MDA levels in the liver and kidneys. The study results highlight the preventive role of MO leaves extract for Gentamicin induced toxicity that could be attributed to the antioxidant properties of phytochemicals.

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Introduction

Gentamicin (GM), an antibiotic derivative of aminoglycoside, is widely used for the treatment of infectious diseases in humans and animals (1). GM is usually prescribed for moderate or severe infections caused by gram-negative bacteria (2) and can only be administered intramuscularly due to its low absorption in the digestive tract. Nevertheless, GM can accumulate in tubular epithelial cells and is toxic to the kidneys. This, in turn, causes enlarged kidneys and impaired kidney function. It is also reported that GM can be toxic in various organs such as the liver, lungs, and skin (3). Toxic reactions in the kidneys are unavoidable,

as GM excretion almost completely occurs in the kidneys through glomerular filtration and accumulates in proximal tubule cells (4,5). GM can trigger the formation of free radicals and cause oxidative stress. The resulting free radicals cause a decrease in glomerular filtration rate, inflammation by activating proteases, and tubular necrosis (6). The free radicals that form, causing oxidative stress in cells trigger widespread cell death and produce other free radicals. This worsens the previous condition due to an adverse chain reaction. To stop the dangers of oxidative stress, antioxidants are needed (7). The liver is the gateway to all materials that enter the body through the digestive tract and are highly susceptible to metabolic disorders, microbes,

and toxic substances (8). The GM induction at a dose of 80 mg/kg for 8 days in white rats (*Rattus norvegicus*) may cause a toxic reaction in the liver characterized by swelling hepatocytes, sinusoid dilation, and the presence of bleeding in some areas (9). The use of GM can increase the activity of free radicals and decrease in the inhibition of antioxidant mechanisms in the liver. This condition leads to increased production of reactive oxygen species (ROS) and cellular oxidative stress (10). Several studies related to various substances that are suspected to have antioxidant activity to prevent hepato- and nephrotoxicity due to GM induction have been conducted. This suggested research which is related to effective and non-toxic antioxidants is essential (4). On the other hand, the use of herbs as a medicine around the world is attributed to the assumption that natural ingredients are much safer (11). In addition, natural ingredients as a source of antioxidants also prevent the cellular damage caused by active stress. The administration of several types of plant extracts can reduce the toxic effects of various compounds or materials on the liver and kidneys (12). *Moringa oleifera* (MO) grows both in tropical and subtropical countries with many health benefits. The plant parts, leaves, seeds, roots, stems, and flowers are widely used for traditional medication. The leaves are more widely used as food and growth triggers because they contain considerable amounts of vitamins, minerals, amino acids, fatty acids, and beta-carotene (13). Flavonoids, carotenoids, phenolic, and ascorbic acid are compounds that have antioxidant activity possessed by MO (14). MO extracts derived from young or old leaves have strong antioxidant activity. They can prevent cellular damage that occurs due to oxidative stress (15). Therefore, the aim of this study is to prove the ability of MO leaf extract to prevent GM-induced hepato- and nephrotoxicity in rats as an animal model.

Materials and methods

Ethical approval

All the research methods and practices and the use of experimental animals have been approved by the Animal Care and Use Committee (ACUC), Faculty of Veterinary Medicine, University of Airlangga, Surabaya, Indonesia with the certificate 1.KE.010.01.2020.

Plant extraction and extract phytochemical screening

Fresh MO leaves were collected, washed, cut into smaller pieces, dried by aerating, and grounded into a powder. Approximately, 2 kgs of MO leaf powder were put in a plastic container to which 5 liters of 98% ethanol were added. The immersion was carried out for 3 days and the resultant substance was then filtered using a size 1 Whatman paper. The ethanol extraction was evaporated using a rotatory evaporator and then dried using a water bath at 40°C. The obtained brown residue was placed in a container with a tight lid and stored in a refrigerator at 4°C to be

immediately used (16). MO leaves extract was screened (17) and contained flavonoids, tannins, saponins, and steroids.

Drugs and chemicals

Gentamicin (GM) (Globalvetdis, Genta-100[®], 40 mg/ml); Ketamine HCl (Kepro B.V., Ketamine[®], 100 mg/ml) and Xylazine HCl (De adelaar B.V., Xyla[®], 20 mg/ml). Na Cl 0.9 %, distilled water, trichloroacetic 100%, HCl 1 N, and Na Thio 1%.

Experimental animals and treatment

This study used 2-month 25 male rats weighing 150-200 grams. All rats were kept in individual cages, at normal temperatures, good lighting, and a well-conditioned environment. They were allowed to acclimatize for one week before the study. During the study, food and water were provided *ad libitum*. Rats were randomly divided into five groups with 5 replicates for each group. The C- control group was given CMC Na solution orally. C+, T1, T2 and T3 groups all received an intramuscular injection of GM, and respectively received treatment with CMC Na solution, 150 mg/kg bw, 300 mg/kg bw and 600 mg/kg bw MO leaf extract orally. CMC Na and MO leave extract solution was given orally for 14 days after receiving GM injection intraperitoneally at an 80 mg/kg bw dose for eight consecutive days. Blood samples were taken with an intracardiac puncture, and liver and kidney excisions were gathered at day 22 of the final stage of the research.

Macroscopic and histopathological examinations

Rats were treated at the end of the study with a combination of Ketamine and Xylazine (100 mg/kg bw and 5 mg/kg bw). Liver and kidneys were excised. Livers were macroscopically observed in terms of color, size, consistency change, and also the liver weight. After that, liver and kidneys were preserved in 10% buffer formalin for 24 hrs. The histopathological features of liver and kidneys were evaluated based on histopathological changes in HE is staining using a microscope and Olympus XC10 camera. The liver histopathological scoring method followed a modification of Knodell (18) with an assessment focusing on degeneration and necrosis. Kidney histopathological examinations scoring method adopted a modification of (19) focusing on glomerulus conditions, tubular degeneration, and tubular necrosis.

MDA Measurement

A thiobarbiturate reactivity-based fluorometric method was used to measure MDA levels. The excised liver and kidneys were washed with saline in an ice bath, cut into smaller pieces, and crushed using a mortar in a cold state using ice. 1 ml of NaCl was added in the next step. The homogenate was centrifuged at 8000 rpm for 20 minutes to obtain the supernatant. The supernatant (100 µL) was diluted by adding 450 µL of distilled water followed by 100 µL of

100% trichloroacetic, 250 μ L of 1 N HCl, and 100 μ L 1% Na Thio consecutively. The homogenization of the mixture was carried out by vortexing and centrifugation at 5000 rpm for 15 minutes. The supernatant was transferred to a new microcentrifuge tube and incubated in a water bath at 100°C for 10 minutes. A Spectrophotometer (Shimadzu UV-1800) with a 532.8 nm wavelength was used to measure the degree of absorbance. Based on the absorbance data, the MDA levels in the liver and kidneys were calculated using the standard curve (20).

Statistical analysis

All the test results are expressed as the mean \pm standard deviation. Treatment effects to histopathological changes are evaluated using Kruskal-Wallis and followed by the Mann-Whitney test. MDA data is analyzed using a one-way analysis of variance followed by the Duncan post hoc test. The cut-off $P < 0.05$ is used to indicate the significant.

Results

Macroscopic of the liver

The result shows that in the C- group, the liver did not change in color, size, and consistency. In the C+ group, the liver did not have any color change. However, the liver had enlargement and the edges of the liver became blunt, while the consistency remained normal. The T1 group showed that the liver had a color change and became paler, enlarged, and dull at the edge. The consistency of the liver remained normal. The liver in the T2 group showed that the liver color and consistency remained normal, while the size changed with swelling. In the T3 group, the result showed that the liver did not change in color, the liver had enlargement but not as large as in the C+, T1, and T2 groups (Figure 1).

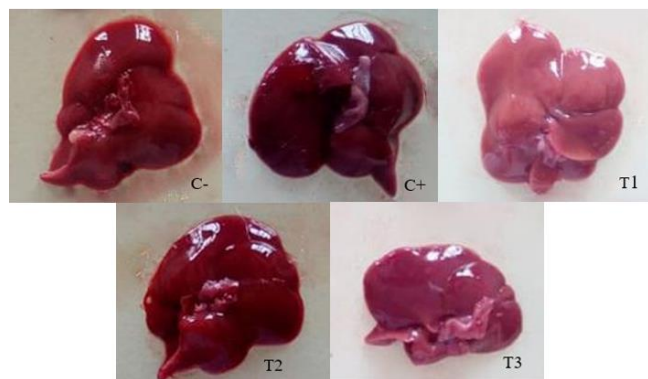


Figure 1: Macroscopic of the liver in C-, C+, T1, T2, and T3 group.

Liver histopathology

The statistical test of the histopathological scoring on degeneration and necrosis of the liver shows a significant difference among the treatment groups. The C- group is

significantly different from the C+ group ($P < 0.05$), and not significantly different from T1, T2, and T3 ($P > 0.05$). The C+ group is not significantly different from T1 ($P > 0.05$) but significantly different from T2 and T3 ($P < 0.05$). The T1 group is not significantly different from T2 and T3 ($P > 0.05$) (Table 1).

Group C- shows that most of the hepatocytes remain normal and sinusoids are not narrowed indicating that hepatocytes are not degenerating. In this group, only a small proportion of hepatocytes is necrotic. The necrosis is marked with karyopyknosis, which is characterized by denseness of the nucleus. In the C+ group, the sinusoid is narrowed and barely visible. The hepatocytes mostly undergo hydropic degeneration and necrosis. The hydropic degeneration is characterized with cells swelling and the cytoplasm of the cell looks cloudy. In the T1 group, most of the hepatocytes have hydropic degeneration and necrosis with karyopyknosis. The cells swell until the sinusoidal fissures are not visible at all. The cytoplasm of the cell looks cloudy. The hepatocytes that undergo necrosis are characterized with karyolysis, a very pale and barely visible cell nucleus. In the T2 group, most of the hepatocytes look normal, the cell nucleus is clearly visible, and the sinusoidal gap is clearly visible indicating that the cells are not degenerating. Only a small proportion of hepatocytes undergoes hydropic degeneration and necrosis. Necrosis in this group demonstrates karyopyknosis. In the T3 group, most of the hepatocytes and the sinusoids appear normal (Figure 2).

Table 1: Mean Rank of histopathological scoring on degeneration and necrosis of the liver

Group	Mean rank degeneration and necrosis
C-	6.90 ^a
C+	20.60 ^c
T1	14.60 ^{abc}
T2	13.10 ^{ab}
T3	9.80 ^a

*) Superscripts in the same column showed significantly different results ($P < 0.05$).

Histopathological of the kidney

The results of statistical analysis of glomerular damage show that C+, T1, and T2 groups are not significantly different ($P > 0.05$) but they are significantly different from C- and T3 ($P < 0.05$). The lowest and the highest scores are found in C- and T3 (Table 2) (Figure 3).

The renal tubular cell degeneration in groups C- and T3 is not significantly different ($P > 0.05$), but they are significantly different from C+, T1, and T2 ($P < 0.05$). The cell degeneration is the lowest in C- and T3 groups and the highest is in the C+ group. The degree of renal tubular cell necrosis in groups C- shows a significant difference from C+, T1, T2, and T3 groups ($P < 0.05$). The lowest score is found in the C- group followed by T3, T2, T1, and C+ groups respectively (Table 2, Figure 4).

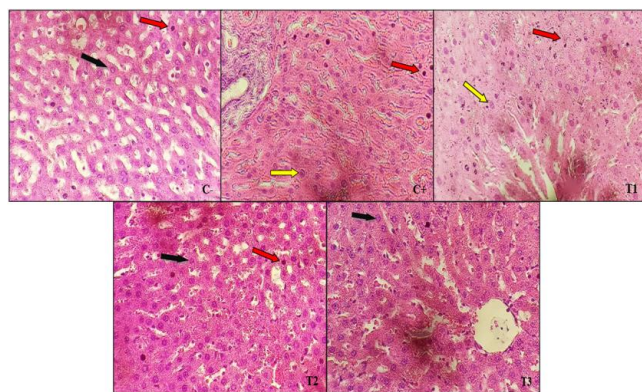


Figure 2: Histopathological features of the liver in each treatment (HE, 400X). Normal hepatocytes (black arrow), degenerated (yellow arrow), and necrotic (red arrow).

Table 2: Mean Rank of scoring of glomerular damage, renal tubular cell degeneration and renal tubular cell necrosis in each group

Treatment group	Glomerular damage	Renal tubular cell degeneration	Renal tubular cell necrosis
C-	5,10 ^a	6,70 ^a	3,80 ^a
C+	19,40 ^b	22,10 ^c	19,30 ^c
T1	17,90 ^b	15,20 ^b	19,30 ^c
T2	10,75 ^{ab}	14,30 ^b	12,90 ^b
T3	9,00 ^a	6,70 ^a	9,70 ^b

*) Superscripts in the same column showed significantly different results (P<0.05).

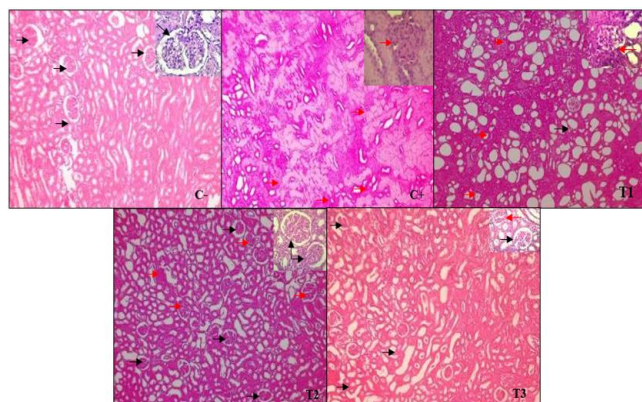


Figure 3: Histopathological features of glomerular damage in groups C-, C+, T1, T2, and T3 (HE, 400x). The kidney has normal glomerulus and Bowman's space (black arrows), swollen glomerulus, and/or narrowing of Bowman's space (red arrows).

Malondialdehyde (MDA)

Table 3 shows the data for the liver and kidney MDA levels in each group assessed after 21 days of treatment. The

differences in the mean liver MDA level for each group, ranging from 469 ± 31.32 to 1089 ± 73.34 , and in the kidney 523 ± 35.12 to $1,113 \pm 80.10$. The data analysis using ANOVA shows that there is a significant difference in the MDA level between groups (P<0.05). The lowest average MDA level in the liver and kidney is found in T3 and the highest is in the C+ treatment.

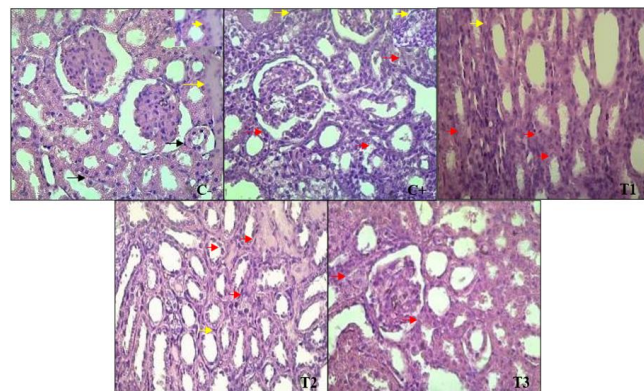


Figure 4: Histopathological features of the kidney of white rats (*Rattus norvegicus*) on groups C-, C+, T1, T2, and T3). A picture with a magnification of 400x with Hematoxylin Eosin (HE) staining, normal cell (black arrows), degenerated (yellow arrows), and necrosis (red arrows).

Table 3: Differences of Average Level of MDA in Liver and Kidney (nmol/g)

Group of Treatment	Liver MDA Level	Kidney MDA Liver
C-	545 ± 34.21^a	619 ± 41.22^a
C+	1089 ± 73.34^d	1 ± 80.10^d
T1	911 ± 39.33^c	954 ± 51.27^c
T2	663 ± 27.97^b	722 ± 46.23^b
T3	469 ± 31.32^a	523 ± 35.12^a

*) Superscripts in the same column showed significantly different results (P<0.05).

Discussion

Aminoglycoside antibiotics, one of which is Gentamicin, is the antibiotic treatment option for various infections caused by gram-negative bacteria. The reason for its use is because it has a broad spectrum and is potent and inexpensive. However, this drug has shown to cause nephrotoxicity in humans and experimental animals. Gentamicin directly causes acute tubular necrosis of the proximal tubule (21). Gentamicin is also toxic to various organs such as liver, lungs, and skin because it induces free radicals and oxidative stress (4,22,23).

Hepatotoxicity due to gentamicin induction in the form of degeneration and necrosis in hepatocytes has been

reported by several previous researchers (22-25). In this study, the gentamicin-administered (C+) groups show results that are linear with the related previous studies. There are many hepatocytes that experience degeneration and necrosis compared to the other treatment groups. However, the C+ group shows remarkable degenerative changes and necrosis in the hepatocytes; mononuclear cells infiltrate within portal areas and proliferation of Kupffer cells. Based on the degree of severity, the damage that occurs to hepatocytes can still be prevented and repaired (26).

Hepatic histopathology recovery treatment principally maintains hormonal balance, increases antioxidants in the body, and ensures the availability of nutrients needed for the body to support metabolic processes oriented towards energy products, and the formation of new tissues (27). The results of the liver histopathology of the white rats in T2 and T3 groups show that the hepatocytes provide the ability to regenerate or repair cells due to the high dose of MO leaf extract in this group which is high enough to enable the antioxidant levels that enter to rebalance the oxidative stress conditions which result from the exposure to gentamicin. The regeneration ability can occur by means of the hepatocyte division mechanism and continues until tissue mass repair is achieved (28). When gentamicin enters the body, it is reabsorbed in the proximal tubule and causes acute tubular necrosis (ATN) through a process that takes a quite long time. The damage is characterized by loss of brush border integrity, severe degeneration, necrosis of tubular epithelial cells, and mononuclear cell infiltration in the interlobular area (6,29,30). In this study, the C+ group shows severe glomerular damage, vacuolar or hydrophilic degeneration, and necrosis of proximal tubular epithelial cells.

Histopathological evaluation of liver and kidney shows that the administration of 600 mg/kg of MO leaf extract can reduce hepato- and nephrotoxicity induced by gentamicin. The co-administration of MO leaf extract with gentamicin has a hepatoprotective and nephroprotective effect as indicated by the low degeneration and necrosis levels in the hepatocytes and renal tubular cells. When gentamicin is used, Hepato- and nephrotoxicity trigger the process of oxidative stress due to excessive ROS production. ROS cause cellular injury, degeneration, and necrosis through mechanisms such as membrane lipid peroxidation (characterized by increased MDA levels), protein denaturation, and DNA damage. The antioxidant compounds have proved to reduce the risk of liver and kidney injury due to the use of gentamicin (25,31-33).

Some diseases can be prevented and treated using antioxidants. Organ damage, including liver and kidney, caused by gentamicin induction can be characterized by increased MDA levels due to the increase in the lipid peroxidation process (34). MDA levels in the liver and kidneys are significantly reduced due to the administration of MO leaf extract in this study, proving the ability of MO

leaf extract to counteract free radicals and prevent oxidative stress based on the administered dose. It is found that MO leaf extract 600 mg/kg significantly decreases MDA level in hepato- and nephrotoxicity in rats compared to other groups. Several related studies strengthen the results of this study. They state that gentamicin-induced mice causes a very significant increase in liver and kidney MDA levels (35,36).

The protective effects of MO leaf extract on the histopathological parameters of liver and kidney tissues in lesions of gentamicin-induced hepato- and nephrotoxicity rats have not previously been reported. The present study shows that the administration of 600 mg/kg bw of MO leaf extract has beneficial effects in decreasing liver and kidney MDA levels in hepato- and nephrotoxic rats. The histological analyses of the liver and kidneys indicate that the extract reduces the damage as compared to the gentamicin group. The administration MO leaf extract may prevent gentamicin-induced hepato- nephrotoxicity and the related oxidative stress by inhibiting free radical generation and restoring the antioxidant systems.

Conclusion

A 600 mg/ kg bw dose of Moringa leaf extract can improve the macroscopic, histopathological features and MDA levels of the liver and kidneys in rats induced with gentamicin.

Competing interest

We declare that we do not have a conflict of interest while conducting this research.

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لمستخلص أوراق *Moringa oleifera* على السمية الكبدية والكلىوية المحدثة بالجنتاميسين في الجرذان. لم يتم معاملة الجرذان في مجموعة السيطرة السالبة بأي علاج بينما عوملت مجموعة السيطرة الموجبة بالجنتاميسين بجرعة ٨٠ ملغم/كغم/يوم ، في الخلب ولمدة ٨ ايام. تم معاملة المجاميع الثلاثة الاخرى باستخدام مستخلص اوراق *Moringa oleifera* عن طريق الفم لمدة ١٤ يومًا وجرعة ١٥٠ ، ٣٠٠ و ٦٠٠ ملغم/كغم على التوالي بعد اعطاء الجنتاميسين. تم استئصال الكبد والكلى من الجرذان في المجاميع اعلاه بعد ٢١ يومًا من المعاملة بمستخلص اوراق *Moringa oleifera* وتم إجراء الفحص العياني للكبد بينما تم فحص التغيرات المجهرية وقياس مستوى المألوندايديهايد للكبد والكلى. يُظهر الفحص المرضي-النسجي للكبد والكلى ان الجنتاميسين زاد من الضرر في الكبد (التنكس ، التنخر ومرتبة التليف) والكلى (تلف الكبيبة ، التنكس ومرتبة التنخر للانابيب الكلوية) وكذلك زاد من مستوى المألوندايديهايد. وادى استخدام مستخلص اوراق *Moringa oleifera* بجرعة ٦٠٠ ملغم/كغم في الجرذان إلى منع الزيادة في مستويات المألوندايديهايد التي سببها الجنتاميسين في الكبد والكلى. تسلط نتائج الدراسة الحالية الضوء على الدور الوقائي لمستخلص اوراق *Moringa oleifera* ضد السمية المحدثة بالجنتاميسين والتي قد تُعزى إلى الخصائص المضادة للأكسدة للمواد الكيميائية-النباتية.

التأثير الوقائي لمستخلص أوراق *Moringa oleifera* ضد السمية الكبدية والكلىوية المستحدثة بالجنتاميسين في الجرذان

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الخلاصة

يعد احداث السمية الكبدية والكلىوية عند استخدام الجنتاميسين تحديًا سريريًا في الطب البشري والبيطري. بحثت هذه الدراسة التأثير الوقائي