UDC 615.2
DOI: 10.15587/2519-4852.2025.336968

EFFECTS OF NONI LEAF EXTRACT (*MORINDA CITRIFOLIA* L.) ON THE HISTOPATHOLOGICAL APPEARANCE OF MOUSE AORTA

Ruqiah Ganda Putri Panjaitan, Andi Besse Tenriawaru, Nurul Hayati, Hurriah Dewi Sartika Panjaitan, Dona Fitriawan

Hypercholesterolemia is a metabolic disorder that can lead to the formation of atherosclerotic plaques. One method to manage atherosclerosis is by lowering cholesterol levels. Cholesterol reduction can be achieved through the use of medications or medicinal plants. One of the plants that can be used to lower levels is the noni leaf (Morinda citrifolia L.).
The aim. *The aim of this study is to investigate the histopathological changes in the aorta of mice after treatment with noni leaf extract.*
Materian and methods. *This study was conducted using 25 male mice aged 2–2.5 months with a body weight of 25–30 grams, divided into 5 treatment groups, each consisting of 5 mice. The first group was left untreated as the normal control (KN). The second group was given 0.5% CMC-Na at a dose of 0.28 ml/20 g body weight as the negative control (K(–)). The third group received simvastatin at a dose of 0.026 mg/20 g body weight as the positive control (K(+)). The fourth (P1) and fifth (P2) groups were administered noni leaf extract at doses of 5.6 mg/20 g body weight and 11.2 mg/20 g body weight, respectively.*
Result. *The results of the study indicate that the histopathological findings of the mouse aorta in each treatment group are consistent with the average damage scores obtained for each group. The histopathological findings of the aorta in the normal control, negative control, positive control, extract dose 1, and extract dose 2 groups showed average damage scores of 0.00, 0.20, 1.40, 0.53, and 0.27, respectively.*
Conclusion. *It can be concluded that the noni leaf extract at doses of 5.6 mg/20 g body weight and 11.2 mg/20 g body weight can improve, reduce, and diminish the histopathological damage to the mouse aorta, although not as effectively as simvastatin at 0.026 mg/20 g body weight*
Keywords: *atherosclerosis, histopathological findings of mouse aorta, hypercholesterolemia, noni leaf extract*

How to cite:
Panjaitan, R. G. P., Tenriawaru, A. B., Hayati, N., Panjaitan, H. D. S., Fitriawan, D. (2025). Effects of noni leaf extract (*Morinda citrifolia* L.) on the histopathological appearance of mouse aorta. ScienceRise: Pharmaceutical Science, 6 (58), 45–51. http://doi.org/10.15587/2519-4852.2025.336968

1. Introduction

Hypercholesterolemia is a disorder and lipid metabolism dysfunction characterized by elevated levels of low-density lipoprotein (LDL), triglycerides, and total cholesterol, alongside reduced levels of high-density lipoprotein (HDL) [1]. Hypercholesterolemia is a contributing factor to the development of atherosclerosis [2, 3]. Hypercholesterolemia can lead to the formation of atherosclerotic plaques through increased lipid oxidation accompanied by a reduction in antioxidant enzymes [4, 5]. Hypercholesterolemia can trigger the formation of free radicals [1, 6]. Free radicals cause LDL to oxidize into oxidized LDL (LDL-ox) [6, 7]. Oxidized *low-density lipoprotein* (LDL-ox) leads to an endothelial inflammatory response [3, 7]. Macrophages ingest oxidized LDL, leading to the formation of *fatty streaks* [6, 8]. *Fatty streaks* consist of foam cells and represent the initial stage of atherosclerosis [6, 8].

Atherosclerosis is characterized by the stiffening and fragility of arteries due to the thickening and hardening of blood vessel walls [9, 10]. This condition is marked by endothelial dysfunction [5, 11]. Endothelial dysfunction is caused by oxidative stress, which can increase macrophage formation [12, 13]. Endothelial dysfunction leads to the accumulation of LDL in the intima layer, enhancing vascular permeability and resulting in the migration of monocytes to the intima. These monocytes transform into macrophages, which then develop into foam cells, indicating the onset of atherosclerosis [10, 14]. The accumulation of lipids, macrophages, and platelets in the intima and media can cause thickening of the blood vessel walls, leading to the narrowing of the lumen diameter [12]. Additionally, the presence of foam cells, along with smooth muscle cell proliferation and migration, can also contribute to the thickening of the vessel walls and further narrowing of the lumen diameter [6, 15]. Moreover, the narrowing of the blood vessel lumen can be exacerbated by the rupture of atherosclerotic plaques, leading to thrombus formation [7].

One approach to managing atherosclerosis is by reducing cholesterol levels [6]. Cholesterol reduction can be achieved using statin drugs [5, 6]. Statin works by inhibiting the enzyme HMG-CoA reductase, thereby lowering cholesterol levels [4, 13]. Long-term use of such medications can be costly and may lead to potentially harmful side effects [6, 12]. Due to these side effects, there is a need for alternative methods to lower cholesterol levels, such as the use of medicinal plants [7, 12].

One plant that can lower cholesterol levels is noni (*Morinda citrifolia* L.) [16]. Noni originates from tropical Asia and has spread to several countries, including Indonesia [17]. Noni is widely available in Indonesia [18] and growing abundantly in yards and gardens [19]. Noni fruit has been shown to reduce total cholesterol levels in male Wistar rats at a dose of 200 mg/kg body weight [16]. Phytochemical tests have revealed that noni fruit contains alkaloids, tannins, flavonoids, steroids, saponins, and phenolics [20, 21]. Flavonoids, in particular, can lower cholesterol levels by stabilizing free radicals and inhibiting the activity of HMG-CoA reductase, thus reducing cholesterol biosynthesis [1, 7]. On the other hand, previous studies have reported that noni leaves contain saponins, tannins [22, 23], alkaloids, flavonoids [18, 23], triterpenoids [18, 22], steroids [18, 23], phenols [22], polyphenols, and quinones [18]. Furthermore, previous studies have also reported that noni leaves can lower blood glucose levels [23, 24]. Although there is currently no research on noni leaves' potential to lower blood cholesterol levels, the compounds present in the noni fruit are also found in the noni leaves. Therefore, it can be assumed that noni leaves may also have the potential to reduce blood cholesterol levels. If one organ of a plant has a particular potential, it is assumed that other organs may have similar potential [25]. Therefore, this study aims to investigate the histopathological changes in the aorta of mice after treatment with noni leaf extract

2. Planning (methodology) of the research

Hypercholesterolemia is a metabolic disorder that can cause atherosclerotic plaque. One way to treat atherosclerosis is by lowering cholesterol levels. Lowering cholesterol levels can be done with alternative treatments using plants such as noni. In a study, noni fruit can lower cholesterol levels in mice. Noni fruit contains alkaloids, tannins, flavonoids, steroids, saponins, and phenolics. However, on the other hand, noni leaves also contain compounds in the form of saponins, tannins, alkaloids, flavonoids, triterpenoids, steroids, phenols, polyphenols, and quinones. Therefore, noni leaves are also assumed to be able to lower cholesterol levels. The aim of this study was to investigate the histopathological changes in the aorta of mice after treatment with noni leaf extract. The research method plan used can be seen in (Fig. 1).

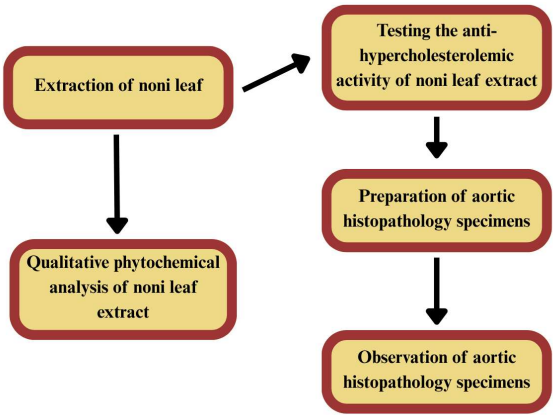

Fig. 1. Research method plan

3. Materials and methods

3. 1. Tools and materials

The tools used in this study include filter paper, mouse cages, a gastric tube, a 1 cc syringe, surgical instruments, and a microscope. The materials utilized are *Morinda citrifolia* L. leaves, male white mice, Standard AD II feed (PT Japra Comfed, Indonesia), pure cholesterol 95% (PT Sigma Aldrich, USA), 96% ethanol, distilled water, CMC-Na 0.5% (PT Sigma Aldrich, USA), and simvastatin (PT Novell Pharmaceutical Laboratories, Indonesia).

3. 2. Preparation of test animals

The test animals used in this study were 25 male white mice aged 2 to 2.5 months, with a body weight of 25–30 grams. Prior to testing, the mice were acclimated for seven days with a standard AD II diet and water provided ad libitum. During the acclimation period, the mice's health was monitored, including regular body weight measurements. This study received ethical clearance with the number 048/FIKES/PL/V/2023, issued by the Health Research Ethics Committee of the Faculty of Health Sciences, Universitas Respati Yogyakarta.

3. 3. Extraction

The plant sample used in this study is noni leaves (*Morinda citrifolia* L.), which were collected from Sami Village, Bonti District, Sanggau Regency, West Boneo, Indonesia. Noni leaves have been identified at the Biology Laboratory, Faculty of Mathematics and Natural Sciences, Tanjungpura University, with the number 288/A/LB/FMIPA/UNTAN/2025. The collection of noni leaves was conducted in March 2023. A total of 2 kg of noni leaves were used. The leaves were sorted, cleaned with running water, cut into small pieces, and dried to obtain a dry weight of 310 grams. Subsequently, the dried leaves were macerated with 96% ethanol for 3 × 24 hours, with the ethanol being replaced every 24 hours. The filtrate obtained from the maceration process amounted to 27,870 ml, which was then concentrated using a rotary evaporator (Buchi Labortechnik AG, Swis) at a temperature of 40°C to yield a thick noni leaf extract weighing 54.35 grams.

3. 4. Qualitative phytochemical testing

Qualitative phytochemical analysis of noni leaf extract included tests for alkaloids, flavonoids, saponins, terpenoids, steroids, and phenolics, following Harborne's methods (1987). The results of the qualitative phytochemical analysis of *Morinda citrifolia* leaf extract were documented in the Certificate of Analysis numbered 020/LABKIM/X/2023 issued by the Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, Tanjungpura University.

3. 5. Testing the anti-hypercholesterolemic activity of noni leaf extract

This study was conducted using a Completely Randomized Design (CRD) with 5 treatment groups,

each consisting of 5 male mice. The first group received no treatment as the normal control (KN). The second group was administered 0.5% CMC-Na at a dose of 0.28 ml/20 g body weight as the negative control (K(–)) [26]. The third group received simvastatin at a dose of 0.026 mg/20 g body weight as the positive control (K(+)) [27]. The fourth (P1) and fifth (P2) groups were administered *Morinda citrifolia* leaf extract at doses of 5.6 mg/20 g and 11.2 mg/20 g body weight, respectively. The dose of *Morinda citrifolia* leaf extract administered to the fourth group was based on previous research that used *Morinda citrifolia* fruit extract as an anti-hypercholesterolemia agent, which reduced total cholesterol levels in rats with a dose of 200 mg/kg body weight of fruit extract converted to mice [16]. The dose administered to the fifth group was a multiple of the dose administered to the fourth group.

Testing the anti-hypercholesterolemic efficacy of noni leaf extract refers to previous research by [26]. On day 0, all mice were fasted for approximately 15 hours, followed by measuring their cholesterol levels to ensure they were in normal condition. Subsequently, from day 1 to day 55, groups 2 to 5 were induced with pure cholesterol at a dose of 11.2 ml/20 g body weight once daily [27]. On day 56, groups 1 to 5 underwent cholesterol level measurement to confirm the increase in cholesterol levels indicating hypercholesterolemia (> 82.4 mg/dl) [28]. From day 57 to day 70, each group received the test preparation once daily. On day 71, surgery was performed to collect the mice's aorta.

3. 6. Preparation of aortic histopathology specimens

Histopathological preparation of aortic specimens involves initially euthanizing experimental animals via cervical dislocation, followed by dissecting the aorta from each animal. The aortic segments are then washed with physiological NaCl and processed using standard histological techniques. Subsequently, staining is performed using hematoxylin-eosin (HE), and after processing, the slides are examined under a microscope. The histopathological assessment of the aorta is described using a scoring system based on the extent of aortic damage, with scores ranging from 0 (no pathological changes) to 2 (vacuolization and thickening of vascular tissue) [26].

3. 7. Data analysis

The data analysis of the observed histopathological images of mice aortic sections was conducted using ANOVA, followed by Tukey's post hoc test ($p < 0.05$) using SPSS. If the data were not normally distributed, the analysis was performed using the Kruskal-Wallis test ($p < 0.05$) in SPSS.

4. Result

4. 1. Qualitative phytochemical testing

Qualitative phytochemical testing of noni leaf extract indicated the presence of alkaloids, flavonoids, saponins, terpenoids, and steroids. The results of the qualitative phytochemical testing of noni leaf extract are presented in (Table 1).

Table 1

Phytochemical testing results of noni leaf extract

Test parameter	Test results
Alkaloid (Mayer)	+
Alkaloid (Wagner)	–
Alkaloid (Dragendroff)	–
Flavonoid	++
Saponin	+++
Terpenoid	++
Steroid	++
Phenolic	–

Note: (–) – does not contain; (+) – low concentration; (++) – moderate concentration; (+++) – high concentration.

4. 2. Histopathological observations of mouse aorta

Histopathological observations of mouse aorta in five treatment groups (Fig. 2) revealed that the KN group, which received no treatment, displayed a normal aortic structure with neatly organized intima (TI), media (TM), and adventitia (TA) layers (Fig. 2, *a*). In contrast, the K(–) group, treated with 0.5% CMC-Na at a dose of 0.28 ml/20 grams of body weight, showed hypercholesterolemia with disorganized intima, media, and adventitia layers, endothelial cell damage (*e*) in the intima, smooth muscle proliferation (*p*) in the media, cell infiltration in collagen fibers (*k*) in the adventitia, and macrophages (*m*) in all three layers, with foam cells (*b*) in the intima and media and thrombus (*t*) in the intima (Fig. 2, *b*). Histopathological observations of mouse aorta in the K(+) group, treated with simvastatin at a dose of 0.026 mg/20 grams of body weight, showed that the intima, media, and adventitia layers were neatly organized, with small and few foam cells (*b*) in the media and adventitia (Fig. 2, *c*). Similarly, in the P1 group, which was given noni leaf extract at a dose of 5.6 mg/20 grams of body weight, the intima, media, and adventitia were neatly arranged, with small and few foam cells (*b*) in the intima and media (Fig. 2, *d*). The P2 group, treated with noni leaf extract at a dose of 11.2 mg/20 grams of body weight, also displayed neatly organized intima, media, and adventitia layers, with small and few foam cells (*b*) in the intima and media (Fig. 2, *e*).

The histopathological damage scores of mouse aorta observations showed that the average score was lowest in the KN group, which did not differ significantly from the K(+) and P2 groups but was significantly different from the P1 and K(–) groups. The average histopathological damage score in the K(–) group was significantly different from the KN, K(+), P2, and P1 groups. However, the average damage scores in the K(+), P2, and P1 groups did not differ significantly. The histopathological damage scores for the mouse aorta are detailed in (Table 2).

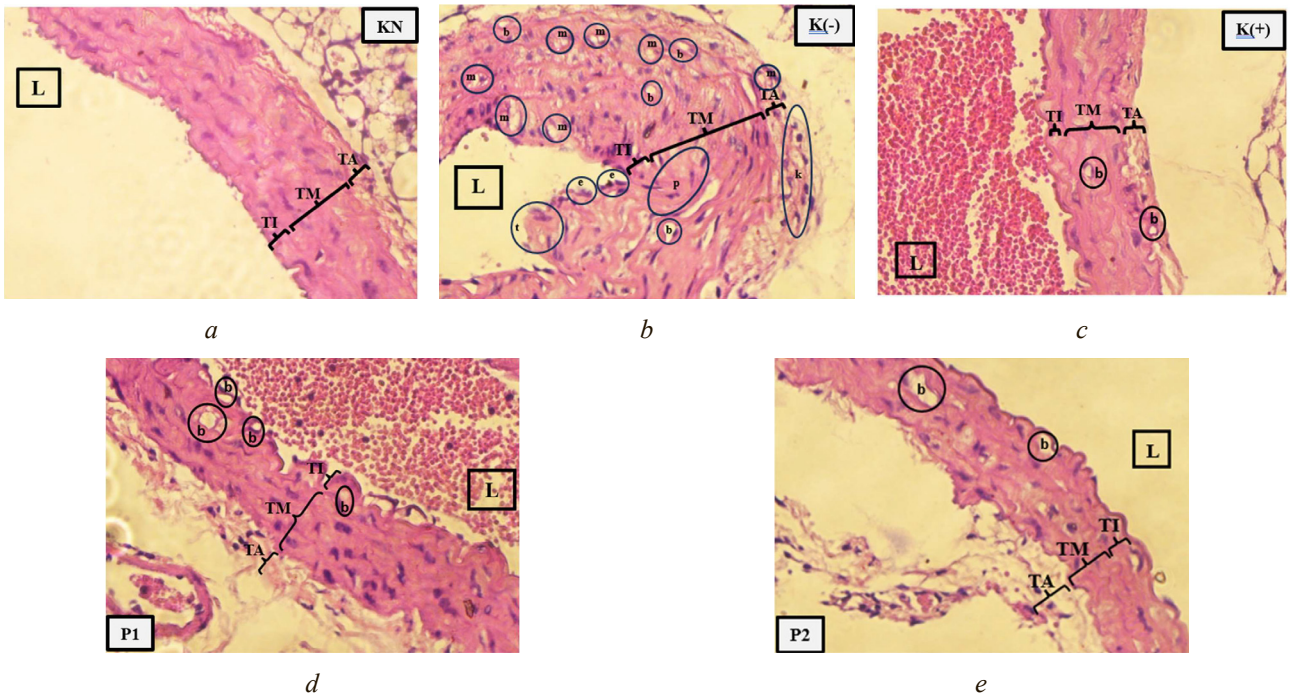

Fig. 2. Histopathological images of mouse aorta for each treatment group are as follows: *a* – the normal control group (KN), which received no treatment; *b* – the negative control group (K(–)), which was given 0.5% CMC-Na at a dose of 0.28 ml/20 g body weight; *c* – the positive control group (K(+)), which was treated with simvastatin at a dose of 0.026 mg/20 g body weight; *d* – the treatment group with extract dose 1 (P1), which was given noni leaf extract at a dose of 5.6 mg/20 g body weight; *e* – the treatment group with extract dose 2 (P2), which was given noni leaf extract at a dose of 11.2 mg/20 g body weight. The histopathological images show that the aortic vessels consist of TI – tunica intima; TM – tunica media; TA – tunica adventitia. Additionally, the images reveal: *e* – endothelial cell damage; *p* – smooth muscle proliferation; *k* – cell infiltration in collagen fibers; the presence of *m* – macrophages; *b* – foam cells; *t* – thrombus

Table 2

Average histopathological damage scores of mouse aorta

Treatment groups	Histopathological score of the aorta
Normal Control Group (KN)	$0.00^{a} \pm 0.00$
Negative Control Group (K(–))	$1.40^{c} \pm 0.51$
Positive Control Group (K(+))	$0.20^{ab} \pm 0.41$
Treatment Group with Extract Dose 1 (P1)	$0.53^{b} \pm 0.52$
Treatment Group with Extract Dose 2 (P2)	$0.27^{ab} \pm 0.46$

Note: the data presented show the mean ± standard deviation; superscripts with the same notation indicate that the average histopathological damage scores of mouse aorta are not significantly different ($p > 0.05$).

5. Discussion

Hypercholesterolemia is a condition characterized by increased levels of LDL, triglycerides, and total cholesterol, along with decreased HDL levels, which can lead to atherosclerosis [1, 12]. Atherosclerosis begins with hypercholesterolemia, which triggers the formation of free radicals that can increase LDL oxidation [8, 11]. Elevated oxidized LDL can result in endothelial dysfunction [5, 13]. This endothelial dysfunction leads to LDL accumulation in the intima, increasing vascular permeability and resulting in the migration of monocytes into the intima. Monocytes then transform into macrophages, which further convert into foam cells [10, 14]. The accumulation of lipids, macrophages, platelets in the intima and media, as well as foam cells, proliferation, and migration of smooth muscle cells, can cause thickening of the vessel wall, leading to lumen diameter narrowing [6, 15]. Lumen narrowing can also be caused by atherosclerotic plaques that rupture, forming a thrombus [7].

The study results indicate that the histopathological images of the mouse aorta in each treatment group are consistent with the average damage scores obtained for each group (Fig. 2, Table 2). The results show that the KN group exhibited normal histopathological images of the mouse aorta with the lowest average damage score. This is in line with [7, 9], who state that normal aorta condition consists of a neatly arranged intima with a single layer of flattened endothelial cells, media with smooth muscle cells bounded by neatly arranged elastic tissue, and adventitia composed of collagen fibers. In contrast, the histopathological images and average damage scores of the mouse aorta in the K(–), K(+), P1, and P2 groups, which were induced with pure cholesterol at a dose of 11.2 mg/20 grams of body weight, showed changes with average damage scores of 1.40, 0.20, 0.53, and 0.27, respectively. Histopathological damage is characterized by an intima, media, and adventitia that are not neatly organized [7, 9]. Additionally, histopathological damage is marked by the formation of macrophages, foam cells, and thrombus [7, 9]. The damage to the histopathological images of the aorta is caused by pure cholesterol induction, which can lead to hypercholesterolemia, triggering free radical formation and an inflammatory

response with the development of macrophages, foam cells, and thrombus, ultimately resulting in damage to blood vessels [7].

In the K(–) group, which was administered 0.5% CMC-Na at a dose of 0.28 ml/20 grams of body weight, the histopathological images of the mouse aorta showed the highest average damage score. This indicates that CMC-Na at this dose did not improve, reduce, or diminish the damage to the aorta's histopathological structure. This finding is consistent with [25], and [29], who reported that 0.5% CMC-Na is neutral and lacks compounds with antihypercholesterolemic properties, thus unable to ameliorate the histopathological damage. In contrast, the histopathological images of the aorta in the K(+), P1, and P2 groups showed relatively low average damage scores. This suggests that the K(+) group, treated with simvastatin at a dose of 0.026 mg/20 grams of body weight, the P1 group, treated with noni leaf extract at a dose of 5.6 mg/20 grams of body weight, and the P2 group, treated with noni leaf extract at a dose of 11.2 mg/20 grams of body weight, were able to improve, reduce, and diminish the histopathological damage to the mouse aorta.

Simvastatin was used in the K(+) group as a comparison because simvastatin is often used as the first line of treatment for hypercholesterolemia [30, 31]. In addition, simvastatin is relatively inexpensive and is provided by the Social Security Agency on Health (BPJS Kesehatan Indonesia) for patients with hypercholesterolemia in Indonesia [32, 33]. According to [8, 12], simvastatin can improve, reduce, and diminish histopathological damage in the mouse aorta. Simvastatin, a statin class medication, acts as an antihypercholesterolemic agent by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), which is essential in the production of mevalonate [6, 26]. Based on the histopathological images and average damage scores of the mouse aorta, it is assumed that noni leaf extract has antihypercholesterolemic properties that can improve, reduce, and diminish histopathological damage to the mouse aorta. Although not as effective as simvastatin, noni leaf extract at doses of 5.6 mg/20 grams of body weight and 11.2 mg/20 grams of body weight can also improve, reduce, and diminish histopathological damage. Furthermore, higher doses of noni leaf extract led to better histopathological outcomes in the mouse aorta.

The antihypercholesterolemic properties of noni leaf extract can improve, reduce, and diminish histopathological damage to the mouse aorta due to its phytochemical content. Qualitative phytochemical tests show that noni leaf extract contains alkaloids, flavonoids, saponins, terpenoids, and steroids. Alkaloids can lower cholesterol levels by inhibiting pancreatic lipase activity, which leads to increased fat secretion through feces [26, 29]. Flavonoids work by inhibiting HMG-CoA reductase, resulting in decreased cholesterol production and increased LDL receptor density in the liver [7, 8]. Saponins lower cholesterol levels by binding bile salts, preventing their reabsorption, and facilitating their excretion in feces [7, 8]. Steroids reduce cholesterol levels by competing to inhibit cholesterol absorption in the intestines [29, 34].

Practical relevance. Noni leaf extract can be used as an alternative treatment for aortic damage caused by hypercholesterolemia.

Research limitations. This study was conducted using only two doses of noni leaf extract, namely 5.6 mg/20 grams of body weight and 11.2 mg/20 grams of body weight. In addition, the parameters presented in this paper are limited to histopathological descriptions of the aorta of mice.

Prospects for further research. Next, testing can be conducted to determine the effective dose range of noni leaf extract as an antihypercholesterolemic agent. In addition, acute toxicity and subchronic toxicity tests can be conducted on this preparation.

6. Conclusion

Noni leaf extract at doses of 5.6 mg/20 grams of body weight and 11.2 mg/20 grams of body weight can improve, reduce, and diminish histopathological damage to the mouse aorta, although it is not as effective as simvastatin at a dose of 0.026 mg/20 grams of body weight.

Conflict of Interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

Funding

This study was funded by the Faculty of Teacher Training and Education, Tanjungpura University through the Merdeka Belajar Kampus Merdeka (MBKM) program.

Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

Acknowledgements

The authors would like to thank the leadership of Faculty of Teacher Training and Education, Tanjungpura University and the organizers of the Merdeka Belajar Kampus Merdeka (MBKM) program for funding this research.

Authors' contributions

Ruqiah Ganda Putri Panjaitan: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition; **Andi Besse Tenriawaru:** Conceptualization, Methodology, Software, Validation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition; **Nurul Hayati:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Vi-

sualization, Supervision, Project administration, Funding acquisition; **Hurriah Dewi Sartika Panjaitan:** Conceptualization, Methodology, Software, Validation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition; **Dona Fitriawan:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition.

References

1. Giopratiwi, K., Thadeus, M. S., Yulianti, R. (2020). Efektivitas pemberian ekstrak biji ketumbar terhadap gambaran sel busa aterosklerosis aorta abdominalis tikus hiperkolesterolemia diabetes. Jurnal Muara Sains, Teknologi, Kedokteran Dan Ilmu Kesehatan, 4 (2), 369–380. https://doi.org/10.24912/jmstkik.v4i2.8250

2. Siddiqui, R., Ahamed, H. N., Yusuff, I. (2020). Bisflavonoids fraction from *Araucaria bidwilli* Hook., reverses hyperlipidemia induced atherosclerosis in high-fat diet induced hyperlipidemia. Future Journal of Pharmaceutical Sciences, 6 (1). https://doi.org/10.1186/s43094-020-00109-y

3. Shatoor, A. S., Humayed, S. A., Alkhateeb, M. A., Shatoor, K. A., Aldera, H., Alassari, M. et al. (2019). *Crataegus aronia* Protects and Reverses Vascular Inflammation in a High Fat Diet Rat Model by An Antioxidant Mechanism and Modulating Serum Levels Oxidized Low-Density Lipoprotein. Pharmaceutical Biology, 57 (1), 37–47. https://doi.org/10.1080/13880209.2018.1564930

4. Ahmed, Q. A. (2023). Studying the possibility of using olive oil and its active components together with atorvastatin in the treatment of biochemical parameters and iron deposition in heart tissue with lung histopathology conditions induced by hypercholesterolemia in male rodent. GSC Biological and Pharmaceutical Sciences, 24 (2), 134–147. https://doi.org/10.30574/gscbps.2023.24.2.0310

5. Ibrahim Fouad, G. (2020). Synergistic anti-atherosclerotic role of combined treatment of omega-3 and co-enzyme Q10 in hypercholesterolemia-induced obese rats. Heliyon, 6 (4), e03659. https://doi.org/10.1016/j.heliyon.2020.e03659

6. Azima, F. (2021). Anti-Atherosclerosis Effect of Soy Milk in Rats Fed an Atherogenic Diet. Cardiovascular and Cardiometabolic Journal (CCJ), 2 (1), 16–22. https://doi.org/10.20473/ccj.v2i1.2021.16-22

7. Maghfiroh, R. M., Hariani, D., Khaleyla, F. (2021). Efektivitas Pemberian Ekstrak Daun Pepaya Jepang (*Cnidoscolus aconitifolius*) terhadap Kadar Kolesterol dan Struktur Histologi Aorta Mencit Hiperkolesterolemia. LenteraBio : Berkala Ilmiah Biologi, 11 (1), 89–100. https://doi.org/10.26740/lenterabio.v11n1.p89-100

8. Agustina, E., Saraswati, T. R., Tana, S. (2023). Respon Histologis Aorta dan Jantung *Rattus Norvegicus* Hiperlipidemia Setelah Pemberian Jus Buah Kersen (*Muntingia calabura* L.) dan Ekstrak Daun Lakum (*Cayratia trifolia* L.). Bioma : Berkala Ilmiah Biologi, 24 (2), 96–104. https://doi.org/10.14710/bioma.24.2.96-104

9. Saleh, S. A., Algharabawy, G. S., Hablas, M. G. A. (2019). Comparative Histological and Immunohistochemical Study on The Effect of Curcumin and Atorvastatin in Induced Atherosclerosis in Aorta and Cardiac Muscle of Male Rabbits. The Egyptian Journal of Hospital Medicine, 76 (2), 3500–3515. https://doi.org/10.21608/ejhm.2019.38653

10. Zarei, L., Farhad, N., Abbasi, A., Naji Haddadi, S. (2022). L-carnitine Improves Atherosclerotic Plaques in Hyperlipidemic Animal Model (Hyperlipidemic Rabbits). Egyptian Journal of Veterinary Sciences, 53 (3), 339–347. https://doi.org/10.21608/ejvs.2022.133398.1338

11. Ram, H., Jaipal, N., Charan, J., Kashyap, P., Kumar, S., Tripathi, R. et al. (2020). Phytoconstituents of an ethanolic pod extract of *Prosopis cineraria* triggers the inhibition of HMG-CoA reductase and the regression of atherosclerotic plaque in hypercholesterolemic rabbits. Lipids in Health and Disease, 19 (1). https://doi.org/10.1186/s12944-020-1188-z

12. Jannah, B. M., Isdadiyanto, S., Sitasiwi, A. J. (2020). Histopathological of White Rats Aorta Induced by High-Fat Feed After Administered by Neem Leaf Ethanolic Extract. Biosaintifika, 12 (3), 370–378.

13. Charan, J., Riyad, P., Ram, H., Purohit, A., Ambwani, S., Kashyap, P. et al. (2022). Ameliorations in dyslipidemia and atherosclerotic plaque by the inhibition of HMG-CoA reductase and antioxidant potential of phytoconstituents of an aqueous seed extract of *Acacia senegal* (L.) Willd in rabbits. PLOS ONE, 17 (3), e0264646. https://doi.org/10.1371/journal.pone.0264646

14. Nadhira, A. N., Nurwati, I., Budiani, D. R. (2023). Efek Ekstrak Etanolik Daun Kelor Terhadap Kadar HDL, Kadar LDL, serta Ketebalan Aorta Tikus Wistar Model Sindrom Metabolik. Plexus Medical Journal, 2 (1), 1–8. https://doi.org/10.20961/plexus.v2i1.219

15. Singh, A., Srinivasan, A. K., Chakrapani, L. N., Kalaiselvi, P. (2019). LOX-1, the Common Therapeutic Target in Hypercholesterolemia: A New Perspective of Antiatherosclerotic Action of Aegeline. Oxidative Medicine and Cellular Longevity, 2019, 1–11. https://doi.org/10.1155/2019/8285730

16. Priadna, A. I., Adiwinoto, B., Handajani, F. (2019). Pengaruh Ekstrak Buah Mengkudu (*Morinda citrifolia*) terhadap Kadar Kolesterol Total Darah pada Tikus Putih (*Rattus novergicus*) Jantan Galur Wistar yang Diberi Diet Tinggi Lemak. Medical and Health Science Journal, 3 (1), 17–24. http://dx.doi.org/10.33086/mhsj.v3i1.922.

17. Nurcahya, V., Nuraida., Ani, N. (2022). Efektifitas Ekstrak Biji Mahoni dan Buah Mengkudu terhadap Mortalitas Larva Kumbang Tanda di Laboratorium. Jurnal Agrofolium, 2 (2), 129–134.

18. Hadi, D. K., Rinidar, Fakhrurrazi, Rosmaidar, Sayuthi, A. (2019). Daya Hambat Ekstrak Etanol Daun Mengkudu (*Morinda citrifolia* L.) terhadap Pertumbuhan *Salmonella* sp. dan *Escherichia coli*. Jimvet, 3 (2), 87–97

19. Suri, L. A., Syamswisna, S., Mardiyyaningsih, A. N. (2023). Etnobotani Tumbuhan Obat oleh Masyarakat Desa Sungai Ulu Kabupaten Natuna. Bioscientist : Jurnal Ilmiah Biologi, 11 (2), 1862–1877. https://doi.org/10.33394/bioscientist.v11i2.9440

20. Sogandi, S., Rabima, R. (2019). Identification of Active Compound Extracts from Noni Fruit (*Morinda citrifolia* L.) and Its Potential as Antioxidants. Jurnal Kimia Sains Dan Aplikasi, 22 (5), 206–212. https://doi.org/10.14710/jksa.22.5.206-212

21. Sogandi, S., Nilasari, P. (2019). Identifikasi Senyawa Aktif Ekstrak Buah Mengkudu (*Morinda citrifolia* L.) dan Potensinya sebagai Inhibitor Karies Gigi. Jurnal Kefarmasian Indonesia, 9 (2), 73–81. https://doi.org/10.22435/jki.v9i2.1289

22. Priamsari, M. R., Rokhana, A. (2021). Uji Aktivitas Antibakteri Ekstrak Etanolik Daun Mengkudu (*Morinda Citrifolia* L.) Terhadap Bakteri *Streptococcus Pyogenes* secara In Vitro. Jurnal Farmasi (Journal of Pharmacy), 9 (2), 15–20. https://doi.org/10.37013/jf.v9i2.105

23. Wulandari, A., Lakiu, D. R., Dewi, N. P. (2022). Uji Efek Ekstrak Daun Mengkudu terhadap Penurunan Glukosa Darah Tikus Putih yang Diinduksi Streptozotocin. Farmakologika Jurnal Farmasi, 19 (1), 1–13.

24. Hindrianingtyas, R. M., Kuswanti, N. (2023). The Effect of Noni Leaf Extract on Diabetic Mice Ulcer Length and Blood Glucose Level. LenteraBio: Berkala Ilmiah Biologi, 12 (2), 204–211. https://doi.org/10.26740/lenterabio.v12n2.p204-211

25. Panjaitan, R. G. P., Novitasari N, N. (2021). Anti-diabetic Activity of the Red Dragon Fruit Peel (*Hylocereus polyrhizus*) in Ethanol Extract against Diabetic Rats. Pharmacognosy Journal, 13 (5), 1079–1085. https://doi.org/10.5530/pj.2021.13.140

26. Panjaitan, R. G. P., Amelia, S. (2022). Antihypercholesterolemic Power of Red Dragon Fruit (*Hylocereus polyrhizus*) Peel Extract. Pharmacognosy Journal, 14 (3), 518–523. https://doi.org/10.5530/pj.2022.14.65

27. Sutjiatmo, A. B., Sukandar, E. Y., Sinaga, R., Hernawati, R., Vikasari, S. N. (2013). Efek antikolesterol ekstrak etanol daun cerme (*Phyllanthus acidus* (L.) Skeels) Pada Tikus Wistar Betina. Kartika Jurnal Ilmiah Farmasi, 1 (1). https://doi.org/10.26874/kjif.v1i1.1

28. Kartikaningrum, V. (2018). Pengaruh Pemberian Air Rebusan Daun Salam (*Syzygium polyanthum*) terhadap Kadar HDL dan LDL Kolesterol Serum Mencit (*Mus musculus* L.) Jantan Hiperlipidemia. Widya Warta, 42 (2), 149–161.

29. Koban, I. Y. R., Klau, M. E., Rame, M. M. T. (2019). Uji Aktivitas Antihiperkolesterolemia Ekstrak Etanol Daun Kriyuh (*Chromolaena odorata* L.) terhadap Tikus Putih (*Ratus novergicus* L.) Jantan yang Diinduksi Diet Lemak Tinggi. CHMK Pharmaceutical Scientific Journal, 2 (2), 73–82.

30. Syachriyani, S., Firmansyah, F., Mamin, M. L. (2022). Pengaruh Pemberian Ekstrak Buah Pining (*Horntstedtia alllia-cea*) Terhadap Penurunan Kadar Kolesterol Total Darah Tikus Putih (*Rattus norvegicus*). PAPS Journal, 1 (1), 37–42. https://doi.org/10.51577/papsjournals.v1i1.307

31. Budi, A., Sijabat, R. M. (2023). Relationship Between Level of Knowlegde and Accuracy of Using Simvastatin in Hypercholesterolemic Patients at Advent Medan Hospital. Journal of Pharmaceutical and Sciences, 6 (2), 437–444. https://doi.org/10.36490/journal-jps.com.v6i2.111

32. Dewi, A. C., Anggreani, H. (2023). Rasionalitas penggunaan obat pada pasien penyakit jantung koroner dengan komplikasi dislipidemia. Journal of Pharmacy and Tropical Issues, 3 (1), 25–31. https://doi.org/10.56922/pti.v3i1.519

33. Santoso, A., Santoso, P., Tilarso, D. P., Sulastri., Huda, C. (2024). Efektivitas Kapsul Biji Jintan Hitam (*Nigella sativa*) Sebagai Terapi Komplementer Pada Pasien Hyperkolesterolemia. IJOH: Indonesian Journal of Public Health, 2 (1), 178–188.

34. Doja, B. C. D., Rame, M. M. T., Rengga, M. P. E. (2020). Uji Aktivitas Antihiperkolesterolemia Ekstrak Methanol Buah Belimbing Wuluh (*Averrhoa bilimbi* Linn.) pada Tikus Putih (*Rattus novergicus*) Galur Wistar. CHMK Pharmaceutical Scientific Journal, 3 (2), 124–132.

Received 12.08.2025
Received in revised form 20.10.2025
Accepted 15.12.2025
Published 30.12.2025

Ruqiah Ganda Putri Panjaitan*, Professor, Doctor, Master of Science, Bachelor of Science, Department of Biology Education, Tanjungpura University, Jl. Profesor Dokter H. Hadari Nawawi, Bansir Laut, Kec. Pontianak Tenggara, Kota Pontianak, Kalimantan Barat, Indonesia, 78124

Andi Besse Tenriawaru, Master of Pedagogy, Bachelor of Education, Department of Biology Education, Tanjungpura University, Jl. Profesor Dokter H. Hadari Nawawi, Bansir Laut, Kec. Pontianak Tenggara, Kota Pontianak, Kalimantan Barat, Indonesia, 78124

Nurul Hayati, Bachelor of Education, Department of Biology Education, Tanjungpura University, Jl. Profesor Dokter H. Hadari Nawawi, Bansir Laut, Kec. Pontianak Tenggara, Kota Pontianak, Kalimantan Barat, Indonesia, 78124

Hurriah Dewi Sartika Panjaitan, Medical doctor, Basuki Rahmat Primary Health Care Center, Sersan Sani (Basuki Rahmat) str., Kecamatan Kemuning, Palembang, Sumatera Selatan, Indonesia

Dona Fitriawan, Master of Pedagogy, Bachelor of Education, Department of Mathematics Education, Tanjungpura University, Jl. Profesor Dokter H. Hadari Nawawi, Bansir Laut, Kec. Pontianak Tenggara, Kota Pontianak, Kalimantan Barat, Indonesia, 78124

***Corresponding author:** Ruqiah Ganda Putri Panjaitan, e-mail: ruqiah.gpp@fkip.untan.ac.id*