RESEARCH ARTICLE AGROBIOLOGICAL RECORDS
ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
Open Access Journal

AMELIORATIVE EFFECTS OF COMBINED CASSIAVERA, MOREL BERRY, AND DAYAK ONION EXTRACTS ON COMPLICATIONS IN HYPERCHOLESTEROLEMIC-HYPERTENSIVE RATS

Fauzan Azima [1]*, Novizar [1], Yusrawati [2], Tuty Anggraini [1], Desniarti [3], Muhammad Iqbal [1] and Dina Intan Rizki [1]

[1]Department of Food Technology and Agricultural Product, Faculty of Agricultural Technology, Universitas Andalas, Padang 25163, Indonesia
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Andalas, Padang 25163, Indonesia
[3]Department of Agricultural Industry Technology, Faculty of Agricultural Technology, Universitas Andalas, Padang 25163, Indonesia

*Corresponding author: fauzandes@yahoo.com; fauzanazima@ae.unand,ac.id

ABSTRACT

Hypercholesterolemia and hypertension are two major and closely related cardiovascular disease risk factors. Concerns about the long-term safety of conventional pharmacotherapy have sparked interest in natural product-based intervention. This study aimed to evaluate the antioxidant, anti-hypercholesterolemic, anti-hypertensive and cardioprotective effects of a combined extract of Cassiavera, Dayak onion, and morel berry (CMD) in Wistar rats with HFD-induced hypercholesterolemia and L-NAME-induced hypertension. The rats were assigned to six groups: normal (H1), hypercholesterolemic (H2), hypertensive (H3), hypercholesterolemic treated with CMD (H4), hypertensive treated with CMD (H5), and hypercholesterolemic-hypertensive treated with CMD (H6). CMD was given by oral gavage at a dose of 90 mg/kg body weight for 3 weeks. The antioxidant activity was measured using the DPPH assay (IC_{50}). Body weight was monitored weekly, whereas total cholesterol and blood pressure were measured periodically using the CHOD-PAP and tail-cuff methods, respectively. At the end of the experiment, organ weights, total leukocytes, and histopathological changes were evaluated. CMD showed strong antioxidant activity (IC_{50} = 82.5 ± 0.02 ppm) and significantly reduced total cholesterol and blood pressure in the treated groups. It also reduced histopathological damage in cardiac, hepatic, and renal tissues. Conclusions: Our results suggest that CMD has potential as a natural adjunct therapy for the management of hypercholesterolemia and hypertension.

***Keywords*:** Antioxidant, Hypercholesterolemia, Hypertension, Plant extract, Rat model.

Article History (ABR-26-185) || Received: 25-May-2026 || Revised: 19-Jun-2026 || Accepted: 22-Jun-2026 || Published Online: 25-Jun-2026

1. INTRODUCTION

Cardiovascular disease (CVD) remains one of the largest health issues globally, impacting over 650 million people, which is about one in every twelve individuals (British Heart Foundation, 2025). Hypercholesterolemia and hypertension are the main risk factors that can increase the morbidity and mortality related to CVD (Zhu et al., 2025). High cholesterol, unhealthy diets, and high blood pressure are projected to be the primary factors contributing to the rise in CVD rates worldwide between 2025 and 2050, as these conditions are often comorbid and they interact to accelerate vascular damage and increase the risk of cardiometabolic complications (Rodriguez-Porcel et al., 2003; Chong et al., 2025). Some of the mechanisms underlying hypercholesterolemia and hypertension include increased oxidative stress, endothelial dysfunction, and activation of the renin-angiotensin-aldosterone system, which promote pro-oxidant, proinflammatory and pro-thrombotic actions, accelerating atherosclerosis (Ivanovic & Tadic, 2015; Li et al., 2026). These overlapping pathways have led to the categorization of the two disorders as "two sides of the same coin" (Ivanovic & Tadic, 2015). Furthermore, epidemiological data suggest the synergistic effect of hypercholesterolemia and hypertension on the risk of cardiovascular problems (Mohseni et al., 2024).

The management of hypercholesterolemia and hypertension usually consists of pharmacological interventions with statins and antihypertensive agents, respectively, which have been demonstrated to effectively modulate lipid levels and blood pressure and to reduce CVD risk. Although these medications have clinically proven efficacy, they have long-term side effects, such as myopathy, liver dysfunction and decreased patient adherence (Nugraha et al., 2024; Li et al., 2025). The above disadvantages have increased interest in the use of natural compounds as safer and

Citation: Azima F, Novizar, Yusrawati, Anggraini T, Desniarti, Iqbal M and Rizki DI, 2026. Ameliorative effects of combined cassiavera, morel berry and dayak onion extracts on complications in hypercholesterolemic-hypertensive rats. Agrobiological Records 24: 202-219. https://doi.org/10.47278/journal.abr/2026.038

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
Open Access Journal

more sustainable. Some bioactive compounds of plants have been reported to possess antioxidant, anti-inflammatory, antihypercholesterolemic, and antihypertensive activities with relatively low toxicity (Iqbal et al., 2023; Anguera-Tejedor et al., 2024). These effects occur through various mechanisms, such as reducing oxidative stress and enhancing endothelial function, which may mitigate blood vessel damage and prevent atherosclerosis, a major instigator of CVD (Butnariu et al., 2023; Gutiérrez-Cuevas et al., 2024).

Cassiavera (*Cinnamomum burmanni*) contains cinnamaldehyde and phenolic compounds that have antioxidant, anti-inflammatory and hypolipidemic activity. Several studies have demonstrated that supplementation of cinnamon can help maintain cardiovascular health by lowering LDL and total cholesterol levels, reducing oxidative stress, and controlling blood pressure (Yazdanpanah et al., 2021; Mohammadabadi & Jain, 2024). Morel berry (*Physalis angulata* L.) has been reported to contain flavonoids and saponins. These have the potential to improve lipid profile, protect the liver, and exert anti-inflammatory effects and help protect the cardiovascular system (Alinnisa et al., 2023; Bestari et al., 2024; Azima et al., 2025). Meanwhile, Dayak Onion (*Eleutherine palmifolia*, an indigenous Indonesian plant that is rich in phenolic compounds and traditionally used to lower blood pressure, has also been reported to exhibit antihypertensive effects in experimental models (Arbain et al., 2022; Sari et al., 2024).

Although the benefits of cinnamon, morel berry and Dayak onion have been widely reported individually, there is limited research on the combined effects of the three extracts in hypercholesterolemia and hypertension. Therefore, the present study was designed to assess the effect of the combined extract of cinnamon, morel berry, and Dayak onion (CMD) on the lipid profile, blood pressure, relative organ weights, and histopathological change in the hypercholesterolemic-hypertensive rat model. These findings are expected to provide experimental evidence supporting CMD as a natural multi-target strategy for reducing cardiovascular risk.

This study was intentionally designed to evaluate the primary outcomes relevant to each experimental disease model. Accordingly, the evaluated parameters were selected based on the specific objectives of each model. In the hypercholesterolemic model, lipid profile and cardiac and hepatic histopathological changes were prioritized because they directly reflect the metabolic disturbances and tissue alterations associated with hypercholesterolemia. Conversely, in the hypertensive model, blood pressure and renal histopathological assessments were prioritized because they represent the principal functional and target-organ outcomes of hypertension. Therefore, blood pressure and renal histopathology were not evaluated in hypercholesterolemic rats, whereas lipid profile and cardiac and hepatic histopathological evaluations were not performed in hypertensive rats, as these assessments were beyond the predefined scope of the present study.

2. MATERIALS AND METHODS

2.1. Preparation and Extraction of Cassiavera, Morel Berry and Dayak Onion (CMD)

Cassiavera (*C. burmannii*) was acquired from Sumatera Tropical Spices, Indonesia. Samples of morel berry (*P. angulata L.*) and Dayak onion (*E. palmifolia*) were collected from local farmers in West Sumatera, Indonesia. The dried plant materials were ground separately into powder and sieved through a 40-mesh sieve. Each powder was macerated in 96% food-grade ethanol (1:5, w/v) at room temperature with occasional stirring for 24 h. The mixtures were filtered with Whatman No. 1 filter paper. The filtrates were concentrated to viscous extracts with reduced pressure using a rotary evaporator (Buchi, Swiss) at 40°C (Asmira et al., 2024). The extracts were each mixed in a 6:3:1 ratio (Cassiavera: morel berry: Dayak onion) using a method adapted from a previous study (Azima et al., 2025). The final CMD was stored in amber glass bottles at 4°C until further analysis.

2.2. Antioxidant Activity (IC_{50})

The antioxidant activity was assessed using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay, employing a method from Azima et al. (2025). 0.1 g of CMD was dissolved in methanol and diluted to 100 mL to prepare a stock solution. Dilution series were prepared to obtain concentrations from 2 to 10 ppm. An aliquot of 2 mL from each sample solution was added to 1 mL of 200 µM DPPH solution, and the mixture was incubated for 15 min at room temperature in dark conditions. The absorbance was measured at 517 nm using a UV-Vis spectrophotometer at wavelength 517 nm (Shimadzu 1800, Japan). The absorbance values were calculated to obtain the percentage inhibition (%inhibition). A calibration curve was plotted to obtain the linear regression equation for obtaining the IC_{50} value.

2.3. Experimental Animal Preparation

The current study was conducted on 42 male albino Wistar rats (200-300 g; 2-3 months old). The animals were obtained from the Animal House Facility, Universitas Andalas, Indonesia. They were housed separately in standard cages under controlled environmental conditions (25 ± 2°C, 12-h light/dark cycle) with free access to standard rat feed (CitraFeed RatBio®, PT Citra Ina Feedmill, Jakarta, Indonesia). After a 7-day acclimatization period, the rats were assigned to experimental groups in accordance with metabolic tolerance testing guidelines.

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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Hypercholesterolemia was induced by a high-fat diet (HFD) and oral administration of propylthiouracil (PTU) once daily for 28 days according to a modified protocol. The HFD consisted of 2.5 mL/200g BW of quail egg yolk and 1 mL of lard supplemented with 0,43% cholesterol powder, whereas PTU was given separately as an oral suspension at a dose of 1.8 mg/200g BW (Nofianti et al., 2015; Enika et al., 2021; Huang et al., 2024). HFD and PTU administration were maintained throughout the experimental period to sustain hypercholesterolemic conditions.

Hypertension was induced by daily intraperitoneal injection of N-nitro-L-arginine methyl ester (L-NAME, TCI, N0661) at a dose of 20 mg/kg BW for 4 consecutive days to elevate blood pressure, and the injections were continued throughout the experimental period to maintain hypertension, following a modified method described by Kanthlal et al. (2020). Systolic and diastolic blood pressure were measured using a non-invasive tail-cuff plethysmography system (CODA™ system, Keny Scientific, USA) as previously described (Wang et al., 2017). For the hypercholesterolemia-hypertension model, the protocol involved sequential induction of hypercholesterolemia followed by hypertension, as described above, with treatments maintained throughout the study period. CMD was administered orally by gavage once daily for 3 weeks at a dose of 90 mg/kg body weight, with weekly dose adjustments based on body weight measurements, as previously described (Azima et al., 2025).

The animals were randomly assigned to six groups (n=7) as follows:

H1: untreated healthy rats (normal)
H2: Hypercholesterolemic rats (HFD combined with PTU)
H3: Hypertensive rats (L-NAME 20 mg/kg body weight)
H4: Hypercholesterolemic rats treated with CMD (90 mg/kg body weight)
H5: Hypertensive rats treated with CMD (90 mg/kg body weight)
H6: Hypercholesterolemic-hypertensive rats treated with CMD (90 mg/kg body weight)

2.4. Blood Sampling

Before blood collection, the rats were fasted for 10-12 h (Karam et al., 2018). After the fasting period, animals were anesthetized with diethyl ether via inhalation (Merck, Germany). Blood samples were obtained from the retro-orbital sinus with microhematocrit capillary tubes. Approximately 2 mL of blood was collected in a vacuum tube containing a clot activator gel and inverted gently to mix. Plasma was obtained by centrifugation of the blood at 3,000 rpm for 10 min (Hettich EBA20, Germany). The separated plasma was aspirated and transferred to sterile microtubes (Onemed, Indonesia) and stored at -80°C until further analysis (Parasuraman et al., 2010).

2.5. Lipid Profile Analysis

Biochemical analysis was performed on plasma samples. The effect of CMD treatment was assessed by measuring total cholesterol (TC) weekly. Lipid profile was measured at the end of the third week of CMD treatment. Total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides (TG) were measured by CHOD-PAP and GPO-PAP methods (enzymatic photometric assay), and low-density lipoprotein (LDL) was estimated using the Friedewald formula. Plasma (10 µL) was loaded into the tube, mixed with 1000 µL of reagent (Diasys), and incubated for 20 min at 25°C for TC and for 10 min for TG. Then, the level was measured at a wavelength of 546 nm using a Microlab 300 (Vital Scientific, Germany) (Nirvana et al., 2020; Azima et al., 2025).

2.6. Blood Pressure Analysis

Systolic and diastolic blood pressure were measured non-invasively using a tail cuff plethysmography system (CODA™ High Throughput System, Kent Scientific, USA) based on volume pressure recording (VPR) technology. Measurements were performed in a temperature-controlled room (20-23°C). Before data collection, the system was calibrated according to the manufacturer's instructions. Rats were placed individually in size-appropriate restraints and placed on a heating platform to maintain body temperature at 32-35°C. Rats were allowed to acclimate to the restrainer and warming platform for at least 5 min before cuff placement. An occlusion cuff was placed at the tail base, and a VPR sensor cuff was positioned distally to ensure proper alignment and unobstructed air tubing. After all rats were prepared, an additional 5 min stabilization period was provided. For each session, an acclimatization cycle was performed before data collection. A total of 15 measurement cycles were performed per animal with a 5-second interval between cycles. The first five cycles were disregarded, and the mean systolic (SBP) and diastolic (DBP) pressures from the valid cycles were calculated for statistical analysis (Wang et al., 2017).

2.7. Total Leukocyte Analysis

On the final day of extract treatment, 0.5 mL of fresh blood was collected from each rat using a leukocyte pipette and diluted with Turk solution up to the mark, then homogenized for 3 min to ensure proper dilution. After discarding the first drops, one drop of the diluted sample was placed into a hemocytometer counting chamber (Neubauer, Germany) and allowed to stand for 2 min to allow leukocytes to settle. Total leukocytes were counted in

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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the four corner squares under a light microscope (Olympus CX33, Japan) (Dillasamola et al., 2019).

Total leukocytes = Total number of leukocyte cell × $\frac{20}{0.4}$

2.8. Histopathological Analysis

Histopathological examinations of the heart, liver, and kidney were performed according to the protocols already decided for each organ. On the last day of the experiment, the rats were euthanized and dissected to collect organ tissue. The tissues were then rinsed with 0.9% physiological saline solution (NaCl, Merck) and fixed in 10% buffered formalin (ParaFORM, Indonesia). Tissue samples were then processed by paraffin embedding techniques, sectioned at approximately 3 µm, and stained with hematoxylin-eosin (H&E) for routine histopathological evaluation. The stained preparations were observed under a light microscope (Olympus BX53, Olympus DP21 digital camera) and analyzed by CellSens Standard software. Histopathological changes were performed in a single-blind manner by a pathologist blind to the treatment groups. Heart histopathological damage was evaluated descriptively by examining the tissue morphology under a light microscope (Dhibi et al., 2016). Liver histopathological damage was evaluated using the NASH activity Score (NAS), based on three histological parameters: steatosis (0-3), lobular inflammation (0-2), and hepatocellular ballooning (0-3). A NASH Score ≥4 indicates NASH (Liang et al., 2022). Kidney histopathological damage was evaluated using the EGTI scoring system in four components: endothelial, glomerular, tubular, and tubulointerstitial (Toprak et al., 2020).

2.9. Data Analysis

The data were statistically processed using IBM SPSS Statistics 27.0 (IBM Corp, USA). Differences among experimental groups were evaluated using one-way analysis of variance (ANOVA), followed by Duncan's Multiple Range Test (DMRT) for further post hoc comparisons when appropriate. Results were considered statistically significant at $P<0.05$.

3. RESULTS AND DISCUSSION

3.1. Antioxidant Activity (IC_{50})

The concentration of the extract required to inhibit 50% of DPPH free radicals is expressed as the IC_{50} Value (Azima et al., 2025). In this research, the combined extract of cassiavera, morel berry, and Dayak onion (6:3:1) had an IC_{50} of 82.50 ± 0.02 ppm and was classified as a strong antioxidant according to Molyneux (2004), wherein IC50 values of 50-100 ppm are considered strong. This scavenging activity might be due to the different bioactive compounds from each plant extract. Cassiavera is reported to contain cinnamaldehyde and several polyphenolic compounds that exhibit strong free-radical scavenging activity (Hayati et al., 2021; Djarot et al., 2023). Furthermore, reports suggest that the antioxidant and anti-inflammatory effects of cinnamon may help lower cardiovascular risk factors (hypercholesterolemia, hypertension, and diabetes) (Mohammadabadi & Jain, 2024). Morel berry also has an antioxidant profile, as it contains flavonoids and phenolic acids (Waris et al., 2025). On the other hand, Dayak onion contains naphthoquinones such as eleutherine and isoeleutherine, which have been shown to exhibit high antioxidant activity (Silva et al., 2024). The synergistic effect of these phytochemicals may enhance antioxidant activity through mechanisms such as hydrogen atom donation, electron transfer, and stabilization of reactive oxygen species (Shahidi & Ambigaipalan, 2015). This result suggests that the multicomponent extract formulations could enhance antioxidant activity through phytochemical synergy and may help prevent disorders associated with oxidative stress.

3.2. Total Cholesterol Levels (TC)

Weekly monitoring of total cholesterol was performed to evaluate the effect of CMD administration in experimental rats. Hypercholesterolemia was successfully induced as indicated by the significant increase in TC in the hypercholesterolemic groups after disease induction (week 0). Fig. 1 shows the changes in total cholesterol levels during the experimental period. The total cholesterol (TC) values before induction in the range of 56-60 mg/dL, suggesting relatively homogeneous conditions among groups. After induction of hypercholesterolemia, TC increased in groups H2, H4, and H6, reaching a range 103.63 mg/dL-144 mg/d, while the normal group (H2) remained stable. Administration of CMD gradually lowered TC to 58-75 mg/dL by the final day of treatment, while the untreated hypercholesterolemic group maintained high TC. The increase in cholesterol due to an HFD indicates the successful induction of hypercholesterolemia, in which an HFD consistently increased TC through enhanced lipogenesis and hepatic triglyceride accumulation (Munshi et al., 2014; Pinatih et al., 2022).

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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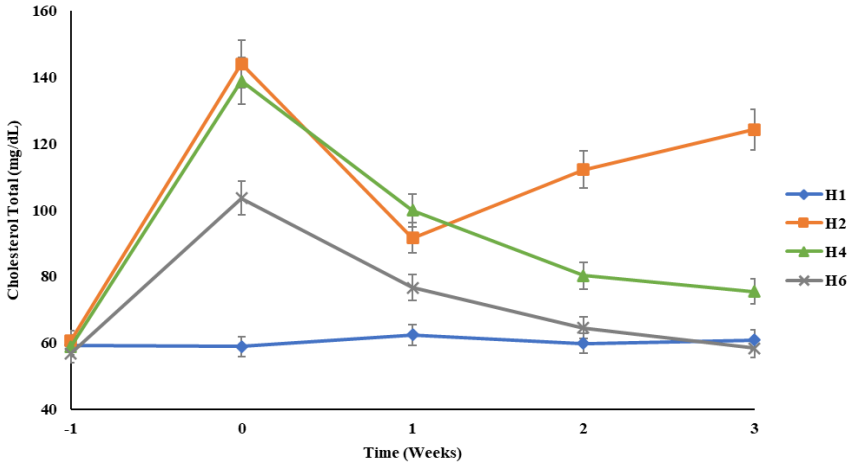

Fig. 1: TC level changes in experimental Rats. Week -1 represents baseline TC before Disease induction. Week 0 represents TC after Disease Induction. Weeks 1-3 represent the CMD treatment period, during which disease induction was maintained. H1: Normal; H2: Hypercholesterolemic Untreated; H4: Hypercholesterolemic + CMD; H6: Hypercholesterolemic-hypertensive + CMD.

In this study, administration of the CMD reduced TC not only in hypercholesterolemic but also in hypercholesterolemic-hypertensive conditions. This reduction in TC is likely related to CMD's antioxidant activity, as indicated by an IC_{50} value of 82.50 ± 0.02 ppm, suggesting strong antioxidant activity. Several studies demonstrated that bioactive compounds, such as polyphenols and flavonoids, inhibit cholesterol biosynthesis by modulating enzymes involved in lipid metabolism and increasing cholesterol via biliary secretion (Gong et al., 2020; Liu et al., 2023). Moreover, the antioxidant activity of these phytochemicals can prevent lipoprotein oxidation and improve lipid metabolism, thereby reducing TC (Mohammadabadi & Jain, 2024; Dahili et al., 2025).

The findings of this study support previous studies, demonstrating that phytochemicals contained in cinnamon, such as cinnamaldehyde and procyanidin, lower both TC and LDL by inhibiting HM-CoA reductase, increasing oxidative capacity, and reducing inflammation (Ismail et al., 2022). Additionally, morel berry contains many bioactive phytochemicals including flavonoids and polyphenols, which inhibit free radicals, promote tissue regeneration, and reduce cholesterol (Djarot et al., 2023; Azima et al., 2025). Whereas Dayak onion contains flavonoids and naphthoquinones, which possess antioxidant properties, leading to a cholesterol-lowering effect through antioxidant mechanisms by increasing lipid metabolism (Susilowati & Setiawan, 2020). In summary, the data indicate that CMD administration can reduce TC to near-normal levels. This suggests that the combination of extracts of these plants has good potential as a lipid-lowering agent, and is capable of correcting hypercholesterolemia through antioxidant mechanisms and by improving lipid metabolism (Gong et al., 2020; Liu et al., 2023).

3.3. Lipid Profile

Total cholesterol (TC) was monitored throughout the entire experimental period, but further assessment of lipid profile in experimental rats was carried out at the end of the treatment period with measurement of plasma lipid profile parameters like total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG). These parameters are known as important indicators of cardiovascular health and lipid metabolism. Elevated LDL and TG levels, with reduced HDL, are generally associated with increased risk of CVD. It is important to evaluate the changes in TC, HDL, LDL, and TG levels. This information is important for evaluation of the possible cardioprotective effect of CMD. The results of the lipid profile analyses are shown in Fig. 2.

The improvement in lipid profile at the end of the treatment period (Fig. 2) showed significant differences between groups for all lipid parameters tested. The untreated hypercholesterolemic group (H2) had significantly higher levels of TC (124.47 ± 17.32mg/dL), TG (60.50 ± 4.78 mg/dL), and LDL (72.10 ± 9.87 mg/dL), than normal group (H1), CMD administration significantly decreased TC in H4 (75.47 ± 7.66 mg/dL) and H6 (58.40 ± 7.95 mg/dL), with reduction in TG and LDL compared to H2.

The reduction was associated with the CMD, which contains bioactive compounds such as polyphenols and flavonoids. Several studies have shown that polyphenolic compounds inhibit LDL oxidation, thereby reducing the atherogenic properties of this lipoprotein. Polyphenols are involved in preventing CVD through diminishing the oxidative modification of LDL and improving endothelial function (Susilowati & Setiawan, 2020; Jacobo-Velázquez, 2025). This reduction effect could be due to bioactive compounds of cassiavera cinnamaldehyde and procyanidins, which were reported to have anti-hyperlipidemic activity by reducing TC, TG, and LDL levels through the inhibition of lipid synthesis, inhibition of the HMG-CoA reductase pathway, and increased antioxidant

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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activity (Fateh & Amin, 2024). Flavonoid and phenolic acids in morel berry have been reported to inhibit lipogenesis in the liver and promote fatty acid β-oxidation, thereby reducing TG and TC in the blood. Flavonoids such as quercetin, myricetin, and kaempferol have been reported to reduce the production of Reactive Oxygen Species (ROS) and mediators of inflammation, resulting in improved lipid profiles in dyslipidemia (Bestari et al., 2024; Nugraha et al., 2025). Furthermore, the combination of *C. burmannii and E. palmifolia* extracts has been shown to improve the lipid profile and reduce oxidative stress in the heart of hyperlipidemic rats. Suggesting its potential as a safe antihyperlipidemic agent (Susilowati & Setiawan, 2020). The findings of this study suggest that CMD can serve as a hypolipidemic agent that improves the lipid profile through mechanisms involving enhancedlipid metabolism and antioxidant activity. The decrease in TG and LDL, with an increase in HDL, observed in this study, could be due to the synergistic effects of bioactive compounds in CMD.

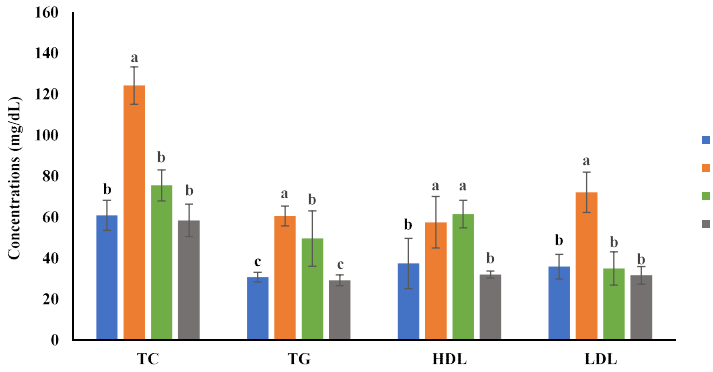

Fig. 2: Lipid profile parameters in experimental rats were measured at the end of the treatment period and presented as mean ± SD. Different superscript letters indicate significant differences (P<0.05). H1: normal; H2: Hypercholesterolemic untreated; H4: Hypercholesterolemic + CMD; H6: Hypercholesterolemic-hypertensive + CMD.

3.4. Blood Pressure

Blood pressure is an important physiological parameter for evaluating cardiovascular function and the development of hypertension in experimental animals. In the present study, SBP and DBP were measured weekly to assess the effect of CMD administration on blood pressure changes in rats induced to hypertension. The time course of the changes in blood pressure (SBP and DBP) during the experimental period.

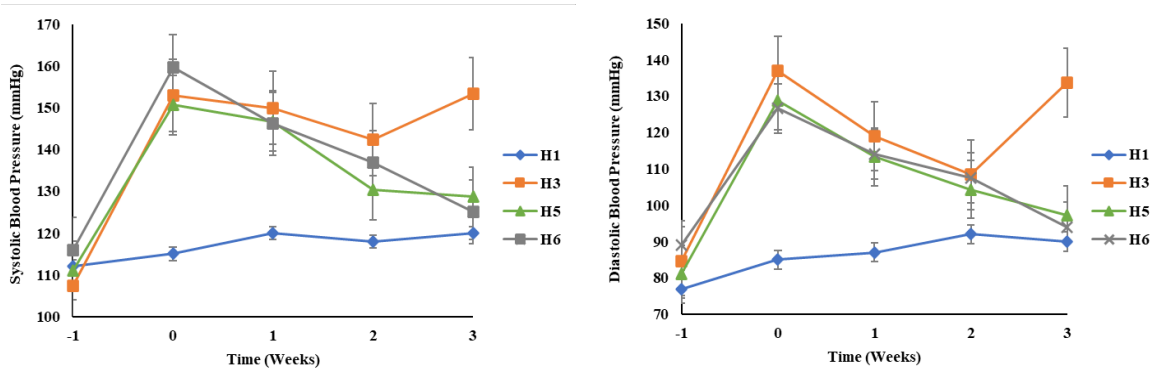

Fig. 3: SBP and DBP changes in experimental rats. Week -1 baseline blood pressure level before induction of disease. Week 0 shows blood pressure levels after 4-day hypertension induction with L-NAME. Weeks 1-3 represent the CMD treatment period, during which disease induction was maintained. H1: normal; H3: Hypertensive untreated; H5: Hypertensive + CMD; H6: hypercholesterolemic-hypertensive + CMD.

Following L-NAME induction, SBP and DBP in the hypertensive groups (H3, H5, and H6) increased significantly compared to baseline and the normal group (H1). At week 0, SBP in H3, H5, and H6 increased to >150 mmHg, while DBP increased to >127 mmHg. During weeks 1-3, a progressive decrease in SBP and DBP was observed in rats treated with CMD (H5 and H6). The untreated hypertensive groups (H3) showed an increase in blood pressure, while the normal group (H1) remained relatively stable throughout the experimental period.

L-NAME-induced hypertensive conditions result from Nitric Oxide Synthase (NOS) inhibition, which reduces endogenous Nitric Oxide (NO) production. Hypertensive conditions are initiated and maintained by decreased NO bioavailability, which induces increased vascular tone, higher peripheral resistance, and

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ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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endothelial dysfunction (Silva et al., 2022). The increase in blood pressure in the complication group (H6) was primarily due to the inhibition of NOS by L-NAME, which reduced the availability of NO and led to prolonged vasoconstriction, and was exacerbated by hypercholesterolemia, which promotes LDL oxidation and oxidative stress (Siti et al., 2015).

Both SBP and DBP were gradually reduced from the first week of treatment in hypertensive rats treated with CMD. This effect may be due to the presence of bioactive compounds in the extracts. Cinnamon is rich in the bioactive compound cinnamaldehyde, which has cardioprotective effects such as stimulation of vasodilation and enhancement of NO activity and ACE inhibition, leading to reduced formation of angiotensin II, a potent vasoconstrictor (Mousavi et al., 2020; Mohammadabadi et al., 2024; Nyulas et al., 2024). Also, *E. palmifolia* is rich in bioactive naphthoquinones, particularly eleutherine, as well as flavonoids and phenolic compounds with antioxidant and anti-inflammatory properties. Administration of *E. palmifolia* extract has also been reported to reduce TNF-α, and VCAM-1 levels, thereby improving endothelial function and lowering blood pressure (Kamarudin et al., 2021; Asmalinda et al., 2026). *P. angulata* contains flavonoids and phenolic compounds having high antioxidant activity, which can increase NO production and decrease oxidative stress in vascular tissues, thus facilitating vascular relaxation and supporting blood pressure regulation in hypertensive models (Febianti et al., 2019). These results indicate that the observed antihypertensive effects are closely related to the bioactive compounds in each CMD component. The observation suggests that the combination of the CMD may have an antihypertensive effect by improving endothelial function, attenuating oxidative stress, and increasing NO bioavailability in the vascular system (Febianti et al., 2019; Gallo et al., 2022; Almasih et al., 2025).

3.5. Body Weight

Body weight is a measure of general health. Body weight changes may indicate alterations in nutrient metabolism, appetite, or systemic metabolic disorders due to disease. Therefore, body weight monitoring during the experimental period provides further information on the physiological effects of disease induction and on the safety of the administered CMD. The initial and final body weights of the experimental rats, and the body weight gain over the duration of treatment, are shown in Table 1.

Table 1: Body weight in experimental rats

Groups	Body Weight ± SD (g)		Δ Body Weight Gain ± SD (g)	Body Weight Gain (%)
	Baseline Day	Termination Day		
H1	236.54 ± 2.34	239.50 ± 3.30	2.97 ± 5.34^{ab}	1.25
H2	274.19 ± 8.40	293.91 ± 10.66	19.73 ± 8.82^{a}	7.19
H3	202.48 ± 15.89	180.20 ± 19.44	-16.71 ± 3.56^{c}	-9.25
H4	248.68 ± 2.00	257.93 ± 10.84	9.29 ± 9.22^{a}	3.85
H5	239.89 ± 21.14	225.67 ± 13.41	-14.23 ± 7.74^{bc}	-5.93
H6	220.9 ± 7.80	226.50 ± 1.44	5.6 ± 6.46^{ab}	2.54

Data are presented as mean ± SD. Significant differences are indicated by different superscript letters ($P<0.05$). H1: Normal group; H2: Hypercholesterolemic untreated; H3: Hypertensive untreated; H4: Hypercholesterolemic + CMD; H5: Hypertensive + CMD; H6: Hypercholesterolemic-hypertensive + CMD.

On termination day, the groups showed different changes in body weight, indicating the metabolic effect of disease induction and CMD administration. Weight gain was significant in hypercholesterolemic rats (H2), and weight loss in L-NAME-induced hypertensive rats (H3). It is worth noting that the CMD-treated groups showed moderated changes in body weight, suggesting that the extract may have a regulatory role in both single and combined pathological states. The weight gain in the H2 and H4 groups indicates that an HFD not only increases TC, but also enhances the accumulation of adipose tissue and increases body weight (Nurmawati, 2016). These results are consistent with the model of diet-induced obesity, where an HFD increases energy storage as fat, leading to insulin resistance and impaired lipid metabolism (Buettner et al., 2007; Hariri & Thibault, 2010). These conditions can lead to a state of dyslipidemia characterized by increased TC, TG, and LDL levels, which contribute to lipid accumulation in tissues, the onset of atherosclerosis, and progressive weight gain during the experimental period (Marques et al., 2016; Prabhu et al., 2025). Besides, PTU treatment may also impair thyroid hormone function, leading to a decreased basal metabolic rate and an increased tendency toward lipid accumulation, as reported in the relevant study (Jin et al., 2024). In contrast, the L-NAME-induced hypertensive (H3) had significant weight loss, which may be related to NO deficiency. Inhibition of NOS by L-NAME can lead to endothelial dysfunction, decreased tissue perfusion, and increased oxidative stress, which can disturb metabolic homeostasis and contribute to energy imbalance and weight loss (Li et al., 2020; Silva et al., 2022).

Interestingly, CMD administration appears to modulate alterations in body weight under pathological conditions. The hypercholesterolemic group treated with CMD (H4), presented an increase in body weight, but

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this increase was smaller compared to untreated hypercholesterolemic rats (H2), suggesting a possible regulatory effect of CMD. Cassiavera (*C. burmannii*) has been reported to reduce adipose tissue accumulation and improve insulin sensitivity through modulating the GLUT-4 and AMPK pathways (Qin et al., 2010). In the same way, *P. angulata* and *E. palmofolia* are rich in bioactive compounds, including flavonoids, physalin, and naphthoquinones, with antioxidant, anti-inflammatory, and cardioprotective effects (Fauzi et al., 2019). These compounds are thought to improve lipid metabolism, inhibit adipogenesis, and attenuate pro-inflammatory production, possibly reducing the inflammatory pathways associated with cachexia, thereby improving appetite, enhancing endothelial function and tissue perfusion, which may support transport to tissue (Susilowati & Setiawan, 2020; Wang et al., 2021).

The CMD decreased metabolic disturbances in hypertensive rats treated with CMD (H5) and in the combined hypercholesterolemic-hypertensive group (H6), and body weight changes were moderate. This pattern, along with improvements in lipid profiles, glucose levels, and markers of inflammation and oxidative stress, suggests a partial restoration of metabolic conditions (Hussain et al., 2021; Gutiérrez-Cuevas et al., 2024). Within the hypercholesterolemic-hypertensive groups (H6), the observed weight gain may be due to improved energy utilization associated with decreased inflammation, oxidative stress and enhanced vascular function and lipid metabolism, resulting from phenolic compounds (Tuzcu et al., 2017; Rahmatullah et al., 2025).

3.6. Relative Organ Weight

Relative organ weight was measured to assess the effect of disease induction and CMD administration on vital organs in experimental rats. The relative organ weights of the heart, liver, kidney, pancreas, spleen, and lungs are shown in Table 2.

Table 2: Relative Organ Weight in Experimental Rats

Groups	Relative Organ Weight (%)					
	Heart	Liver	Kidney	Pancreas	Spleen	Lungs
H1	0.31 ± 0.03	3.57 ± 0.49	0.40 ± 0.02	0.31 ± 0.09^{bc}	0.28 ± 0.07	0.69 ± 0.02
H2	0.45 ± 0.29	3.80 ± 0.33	0.34 ± 0.03	0.38 ± 0.12^{b}	0.31 ± 0.08	0.92 ± 0.47
H3	0.33 ± 0.03	4.20 ± 0.46	0.41 ± 0.03	0.16 ± 0.01^{c}	0.49 ± 0.21	0.76 ± 0.20
H4	0.28 ± 0.03	3.57 ± 0.46	0.37 ± 0.06	0.35 ± 0.13^{b}	0.34 ± 0.08	0.84 ± 0.24
H5	0.33 ± 0.02	3.56 ± 0.50	0.42 ± 0.07	0.18 ± 0.04^{c}	0.37 ± 0.04	0.74 ± 0.14
H6	0.32 ± 0.03	3.70 ± 0.53	0.40 ± 0.07	0.57 ± 0.09^{a}	0.52 ± 0.06	1.10 ± 0.26

Data are presented as mean ± SD. Significant differences are indicated by different superscript letters ($P<0.05$) H1; Normal group; H2: Hypercholesterolemic untreated; H3: Hypertensive untreated; H4: Hypercholesterolemic + CMD; H5 Hypertensive + CMD; H6: Hypercholesterolemic-hypertensive + CMD.

These results showed no significant differences in relative organ weights (heart, liver, kidneys, spleen, and lungs) between treatment groups. However, the pancreas displayed significant differences, indicating more specific and progressive alterations. Statistically significant changes were found in almost all organs. However, in some groups, there was a tendency toward increased organ weight of vital organs, mainly the heart, liver, and lungs, when compared with the control group fed a standard diet. This is consistent with metabolic syndrome models induced by HFD, in which experimental animals exhibit structural and functional alterations in organs, including inflammation, oxidative stress, cardiac hypertrophy, and hepatic lipid accumulations. In previous studies in HFD Wistar rats. Increased liver and heart weight, as well as pancreatic and renal alterations resembling pathological changes observed in human metabolic syndrome, have been reported (Panchal et al., 2011; Jin et al., 2024). The L-NAME-induced hypertensive group (H3) also showed increased heart and liver weights. This pattern is consistent with the L-NAME hypertension model, in which NOS inhibition decreases NO bioavailability, leading to endothelial dysfunction, increased afterload, cardiac remodeling (hypertrophy) and vascular hepatic modifications, possibly associated with liver weight (Khaliq et al., 2024).

CMD administration to the treatment group did not result in significant changes in organ weight, but rather tended to maintain organ weights close to that of the normal group. These results are corroborated by the literature, which has shown that cinnamaldehyde and polyphenols from cassiavera significantly reduce liver weight and improve lipid profile in HFD models through the reduction of lipid accumulation and liver inflammation (Tuzcu et al., 2017; Mohammadabadi & Jain, 2024). The protective effects of CMD on organ hypertrophy and morphological changes may be due to the antioxidant, anti-inflammatory, antihyperlipidemic, and antihypertensive activities of its bioactive components (Yuliandra et al., 2018; Nugrahenny et al., 2023; Mohammadabadi & Jain, 2024). The properties are related to decreased oxidative stress, better vascular function, and prevention of organ damage, supporting the potential of CMD as an adjunct therapy to reduce tissue injury in both conditions (Mohammed et al., 2023; Mohammadabadi & Jain, 2024).

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3.7. Total Leukocytes

Total leukocyte count is an important hematological parameter for assessment of immune status and inflammatory responses. The results of leukocyte counts in all experimental groups are shown in Table 3.

Table 3: Total Leukocytes

Groups	Total Leukocyte Count in Blood (× 10^3/µL)
H1	11.00 ± 1.56[a]
H2	7.00 ± 0.28[a]
H3	9.35 ± 0.64[a]
H4	10.70 ± 2.40[a]
H5	9.35 ± 2.19[a]
H6	6.80 ± 4.81[a]

Data are presented as mean ± SD. Significant differences are indicated by different superscript letters (P< 0.05). H1; Normal group; H2: Hypercholesterolemic untreated; H3: Hypertensive untreated; H4: Hypercholesterolemic + CMD; H5 Hypertensive + CMD; H6: Hypercholesterolemic-hypertensive + CMD.

The number of leukocytes in rats ranged from 6.8×10^3/µL to 11.00×10^3/µL of blood. The leukocyte in the normal group (H1) was 11.00×10^3/µL, indicating normal leukocyte values in test rats, which is the benchmark for a healthy immune system (Yapo, 2018). Induction of disease triggered changes in the untreated hypercholesterolemic (H2) and hypertensive (H3) groups, with leukocyte counts decreasing to 7.00×10^3/µL and 9.35×10^3/µL, respectively, but not significantly differing. This reduction is due to a systemic inflammatory response as a result of endothelial dysfunction due to massive migration of leukocytes to target tissue damaged by the accumulation of fats or high blood pressure, resulting in fewer circulating and detectable cells in the peripheral blood (Gisterå & Hansson, 2017; Griendling et al., 2021). Furthermore, literature indicated that hypercholesterolemia does not always lead to significant changes in total leukocyte count but has a more prominent role in promoting leukocyte activation and function in the inflammatory process (Collado et al., 2019; Motkowski et al., 2022).

CMD exerts protective effects with the synergistic activity of bioactive compounds such as cinnamaldehyde, physalin, and eleutheroside, which act as antioxidants and reduce the expression of vascular adhesion molecules, thereby reducing excessive leukocyte migration into tissues (Bastos et al., 2008; Kamarudin et al., 2021). Previous studies have also shown that compounds in cinnamon, morel berry, and Dayak onion exhibit immunomodulatory activity that can prevent leukocyte depletion and help restore leukocyte and neutrophil counts to near normal physiological levels (Abd El-Raouf et al., 2015; Novitasari et al., 2024; Fauzi et al., 2024). The most interesting dynamics were obtained in hypercholesterolemic-hypertensive rats treated with CMD (H6); most strikingly, their leukocyte count fell to 6.80×10^3/µL. In fact, this dramatic reduction actually indicates the powerful suppression of inflammation by CMD. All rats had total leukocyte counts in the normal physiological range of 5.0×10^3/µL to 13.0×10^3/µL, and there was no significant difference among treatment groups (Putri et al., 2022).

3.8. Cardiac Histopathology

Histopathological examination of heart tissue was performed to evaluate structural changes in the myocardium and arterial wall, as shown in Fig. 4.

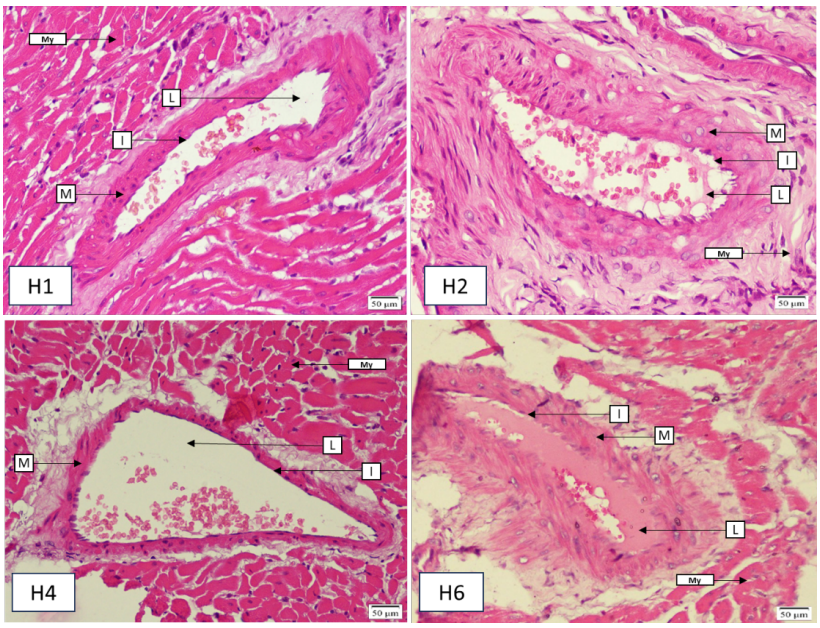

Fig. 4: Cardiac histopathology in experimental rats. H1: Normal; H2: Hypercholesterolemic untreated; H4: hypercholesterolemic +CMD; hypercholesterolemic-hypertensive + CMD. The arterial lumen (L), tunica media (M), tunica intima (I), and myocardium (My) are indicated by arrows. Hematoxylin–eosin (H&E) stained section observed at 400× magnification, scale bar 50 µm.

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Microscopic examination of heart tissue sections stained with hematoxylin-eosin revealed structural differences in the arterial walls among the various treatment groups. In the normal group (H1), the arterial walls remained relatively normal, with a homogeneous tunica media, regularly arranged smooth muscle cells, and a wide lumen showing no narrowing. The myocardium appeared neatly arranged with well-organized muscle fibers. These results are consistent with previous studies indicating that under normal conditions, myocardial tissue is homogeneous without cellular damage or pathological changes in arterial tissue (Reyzov et al., 2023; Shevchuk, 2023). In the hypercholesterolemic group (H2), thickening of the wall (intima-media) and lumen narrowing were observed. This is consistent with reports that hypercholesterolemia increases carotid intima-media thickness as an early indicator of atherosclerotic remodeling (Khan et al., 2013). It has been reported to trigger smooth muscle hypertrophy, collagen and elastic fiber proliferation, and an increase in tunica media thickness, thereby reducing lumen diameter. Additionally, this diet also induces oxidative stress, inflammation, and apoptosis in cardiac tissue, contributing to cardiac remodeling and cardiac dysfunction (Momot et al., 2024; Ahmadi et al., 2025).

Thickening of tunica media and narrowing of the arterial lumen were milder in the hypercholesterolemic group that received the extract (H4) than in the (H2) group. The observed structural improvement can be attributed to the antihypercholesterolemic, antioxidant, and anti-inflammatory effects of these three plants. Several studies have shown that cinnamon extract has been tested in hypercholesterolemic rats on a high-fat diet (HFD), where the extract reduced blood lipid levels, decreased oxidative stress, and improved histopathological damage of the heart, such as inflammation and fibrosis (Afrose et al., 2018; Elmongy et al., 2022; Handayani et al., 2023). *C. burmannii* is known to reduce TC and LDL in HFD-fed animals due to its phenolic compounds, especially cinnamaldehyde, which inhibits HMG-CoA reductase and suppresses lipid peroxidation (Ismail et al., 2022; Handayani et al., 2023). In another study, Dayak onion exhibited cardioprotective effects by reducing cardiac hypertrophy and enhancing myocardial histopathology (Rahman et al., 2024; Abdullah-Al-Mamun et al., 2025). The phenolic and flavonoid content of Dayak onion has also been reported to reduce TC, and TG in dyslipidemic rats and increase HDL (Susilowati & Setiawan, 2020). This pattern is consistent with reports indicating that interventions with polyphenolic plant extracts may improve lipid profiles and prevent hyperplasia and excessive vascular remodeling in hypercholesterolemic animal models.

However, the lumen of the blood vessel still appeared relatively narrow in the hypercholesterolemic group with hypertension treated with CMD (H6). Hypertension is known to cause thickening of the vessel wall and narrowing of the lumen through mechanisms of media thickening and increased hemodynamic pressure (Schiffrin, 2012; Zeng & Yang, 2024). The coexistence of hypercholesterolemia and hypertension has been shown to aggravate media thickening, increase the adventitial area and induce vascular wall hypoxia, thereby accelerating atherosclerosis and decreasing vascular compensatory capacity (Kai et al., 2002). CMD generally provides only partial protection against dual-pathway damage, reducing oxidative stress and inflammation but not preventing media thickening and lumen narrowing caused by high hemodynamic stress. The protective effects of the CMD are limited by the complexity of these conditions (Avci et al., 2006; Garjani et al., 2011).

3.9. Hepatic Histopathology

Histopathological examination of liver tissue was performed to evaluate structural changes related to NASH, including steatosis, inflammatory cell infiltration and hepatocyte ballooning. The observed hepatic histopathological changes (Fig. 5) and the corresponding NASH-like hepatocyte histopathology score (Table 4).

Table 4: NASH-like Hepatic Histopathological Score

Groups	Steatosis	Inflammation	Ballooning	NASH Score
H1	0.05 ± 0.07^{a}	0.07 ± 0.12^{a}	0.69 ± 0.38^{a}	0.79 ± 0.15^{a}
H2	1.47 ± 0.33^{c}	1.01 ± 0.52^{c}	2.01 ± 0.01^{c}	4.36 ± 0.25^{c}
H4	0.20 ± 0.15^{b}	0.11 ± 0.12^{a}	1.89 ± 0.15^{b}	2.18 ± 0.03^{b}
H6	0.19 ± 0.13^{b}	0.31 ± 0.47^{b}	2.00 ± 0.00^{c}	2.50 ± 0.25^{b}

Data are presented as mean ± SD. Significant differences are indicated by different superscript letters ($P<0.05$). H1: Normal group; H2: Hypercholesterolemic untreated; H4: Hypercholesterolemic + CMD; H6: Hypercholesterolemic-hypertensive + CMD.

Results of this study showed differences in the degree of liver damage across groups as assessed by steatosis, inflammation and hepatocyte ballooning. The normal group (H1) showed a relatively normal hepatocyte structure, clear sinusoids, and a low histopathological score, suggesting that lipid metabolism was within the physiological range, with no excessive fat accumulation in hepatocytes. In contrast, the hypercholesterolemic group (H2) showed increased scores for steatosis, inflammation and ballooning, suggesting liver damage due to altered lipid metabolism. Hypercholesterolemia can cause triglyceride accumulation in hepatocytes, inducing oxidative stress and an inflammatory response that can lead to hepatocyte degeneration and lipid vacuole formation. This increased damage is also associated with lipotoxicity and ROS production, which can damage hepatocyte membranes and activate Kupffer cells, thus exacerbating inflammation and tissue injury.

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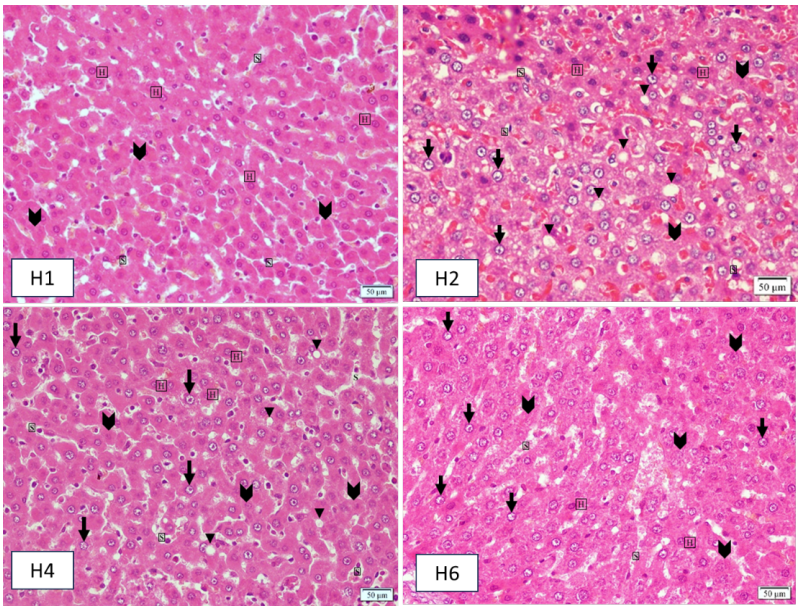

Fig. 5: Hepatic histopathology in experimental rats. H1: normal; H2: hypercholesterolemic untreated; H4: hypercholesterolemic + CMD; H6: Hypercholesterolemic-hypertensive+ CMD. Hepatocytes (H) are arranged in hepatic plates separated by sinusoids (S). The sinusoids contain inflammatory cells (leukocytes), observed both clustered around vessels and scattered within the parenchyma. Hepatocytes exhibit degenerative changes (Chevron), along with steatosis and Ballooning/enlargement. Hematoxylin-eosin (H&E) stained section observed at 400× magnification, scale bar 50 µm.

CMD administration reduced steatosis and inflammation scores compared with the hypercholesterolemic group (H2), suggesting a protective effect on liver tissue. This reduction in damage may be associated with the presence of bioactive compounds such as polyphenols and other compounds with antioxidant and lipid-lowering properties (Li et al., 2021; Nugraha et al., 2025). These compounds are reported to reduce hepatic fat accumulation, increase antioxidant activity, and inhibit the production of pro-inflammatory cytokines, thereby improving steatosis and inflammation in the liver (Alahdal et al., 2025; Ye et al., 2025). Also, various bioactive compounds from natural sources are known to maintain lipid metabolism and minimize oxidative stress, thereby acting as hepatoprotective agents that help protect against liver damage in metabolic disease (Parthasarathy et al., 2020). Histologically, CMD administration showed a more significant protective effect on steatosis and inflammation, while improvement in hepatocyte ballooning was slower. Because ballooning indicates more advanced hepatocyte damage, such as cytoskeletal disruption, endoplasmic reticulum (ER) stress, and activation of the pathway, it requires a more complex recovery process (Tsai et al., 2024). This pattern is consistent with reports that plant extracts improve lipid accumulation and inflammation generally more rapidly than hepatocyte structural damage in NASH (Park et al., 2024).

3.10. Renal Histopathology

Histopathological study of renal tissue was carried out to evaluate structural alterations in the glomerulus, proximal tubules, distal tubules, and interstitial areas in experimental rats (Fig. 6) (Table 5).

Table 5: EGTI-Based Renal Histopathological Score

Groups	Glomerulus	Endotel	Intestitial	Tubulus
H1	0.15 ± 0.21^{a}	0.29 ± 0.11^{a}	0.43 ± 0.20^{a}	0.64 ± 0.89^{a}
H3	2.19 ± 0.17^{c}	0.35 ± 0.25^{a}	2.36 ± 0.40^{c}	3.20 ± 2.27^{c}
H5	0.53 ± 0.18^{a}	0.22 ± 0.14^{a}	1.34 ± 0.14^{b}	2.29 ± 0.14^{b}
H6	1.00 ± 0.40^{b}	1.33 ± 0.23^{b}	1.73 ± 0.18^{b}	2.88 ± 0.18^{c}

Data are presented as mean ± SD. Significant differences are indicated by different superscript letters ($P<0.05$). H1: Normal group; H3: Hypertensive untreated; H5: Hypertensive+ CMD; H6: Hypercholesterolemic-hypertensive + CMD.

Renal histopathology revealed varying degrees of damage in the endothelial, glomerular, tubular, and interstitial compartments across treatment groups. The hypertension group had higher damage scores than the normal group (H1), suggesting that both hypertension and hypercholesterolemic-hypertension can induce structural changes in renal tissue. The enhanced glomerular, tubular, and interstitial damage observed in the L-NAME-induced hypertensive groups reflects structural renal damage associated with NO deficiency and endothelial dysfunction. L-NAME is a nitric oxide synthase inhibitor, which decreases the bioavailability of NOS, causes vasoconstriction, and decreases renal perfusion. Such changes may result in glomerular ischemia, tubular epithelial degeneration, and inflammatory interstitial infiltration. Such pathological alterations are frequently observed in experimental hypertension and are closely associated with oxidative stress and inflammatory activation within renal

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ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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tissue (Arendshorst et al., 2024; Zhao et al., 2025). Hypercholesterolemia is known to aggravate hypertension-induced kidney damage via increased oxidative stress. Inflammation and impairment of renal vascular endothelial function. Increased levels of mediators of inflammation, such as TNF-α, IL-6 and IL1β also contribute to accelerated renal tissue damage under these conditions (Abdel-Zaher et al., 2020).

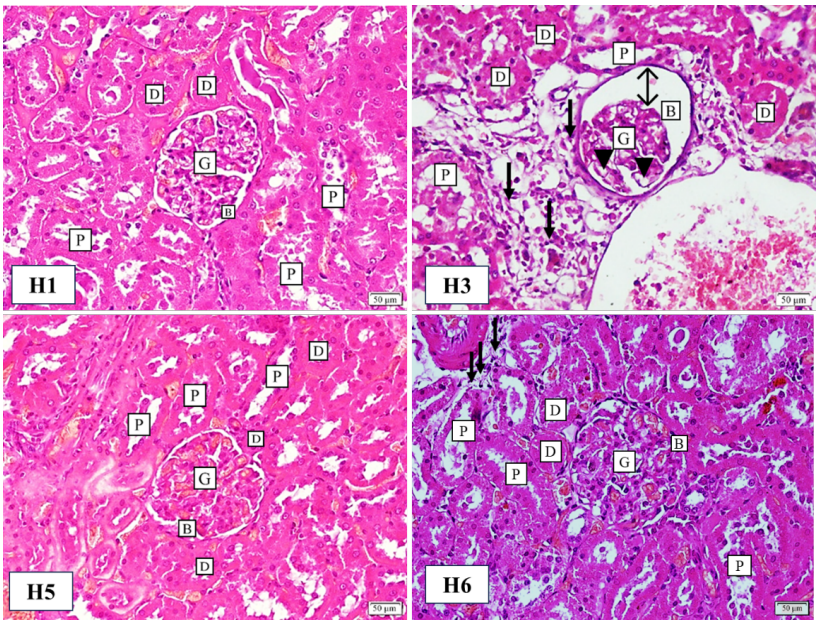

Fig. 6: Renal histopathology in experimental rats. H1: Normal; H3: hypertensive untreated; H6: Hypercholesterolemic-hypertensive + CMD. The renal structure includes the Glomerulus (G), Bowman's Capsule (B), Distal Tubule (D), Proximal Tubule (P). In L-NAME-induced hypertensive rats, tuft retraction was observed along with dilatation of Bowman's Capsule (↕), partial collapse, and hypocellularity were observed in the glomerular capillary loop (▼), consistent with ischemic change. Infiltration of inflammatory cells (↓) in the interstitium, indicating tissue damage related to inflammation and oxidative stress. Hematoxylin–eosin (H&E) stained section observed at 400× magnification, scale bar 50µm.

CMD administration reduced renal damage scores, particularly in glomerular structure and interstitial inflammation, in the hypertensive treatment group (H5). This decrease in histological lesions is probably associated with the presence of bioactive compounds such as polyphenols, flavonoids, and phenolic compounds in the plant extract, which exhibit antioxidant and anti-inflammatory activities that can reduce oxidative stress and inflammatory responses in renal tissue, while improving lipid metabolism, thus protecting the nephron structures from further damage (Rahajeng et al., 2024; Sulistyowati et al., 2024; Dragoș et al., 2025). However, the persistent moderate tubular damage in both treatment groups and the comparatively higher endothelial and tubular damage scores in H6 indicated that renal damage was not entirely reversed. Hypercholesterolemia may worsen endothelial dysfunction and oxidative stress by lipid accumulation and inflammatory activation, thereby reducing the renoprotective effects of CMD (Ye et al., 2023; Kim et al., 2025). Thus, although CMD has protective potential against hypertensive-induced renal damage. It has not completely restored renal structural integrity, especially under hypercholesterolemic conditions combined with other factors, and a longer treatment duration may be needed.

4. CONCLUSION

In conclusion, oral administration of CMD at 90 mg/kg body weight to rats with hypercholesterolemia, hypertension, and hypercholesterolemia-hypertension complications improved physiological parameters, total leukocyte counts, and histopathology. This kind of treatment can decrease cholesterol, improve lipid profiles, decrease blood pressure, maintain body weight, and leukocyte count. Improve the histological condition of the heart, liver, and kidneys. These findings suggest antihypercholesterolemic, antihypertensive, and cardioprotective effects of CMD. Future studies may involve controlled clinical trials with standardized formulations and investigate synergistic effects with conventional therapies to optimize its therapeutic potential in the treatment of hypercholesterolemia and hypertension, thereby supporting its potential as a natural therapeutic agent in the development of functional food.

Declarations

Funding: This research was funded by the Directorate of Research and Community Service, Directorate General of Research and Development, Ministry of Higher Education, Science, and Technology, through the Fundamental

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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Research Scheme (regular) in the form of Research Contract Number 060/C3/DT.05.00/PL/2025 for Fiscal Year 2025.

Acknowledgement: The authors are highly grateful to the Directorate of Research of Community Service, Directorate General of Research and Development, Ministry of Higher Education, Science, and Technology, Republic of Indonesia, for the financial support of this research.

Conflicts of Interest: The authors declare that there are no conflict of interest in this research.

Data Availability: The article includes all data used to support the findings of this research.

Ethics Statement: This research procedure was conducted based on the guidelines and approval of the Research Ethics Committee of Universitas Perintis Indonesia, with the protocol No. 25-10-1821.

Author's Contributions: Fauzan Azima: Supervision, project administration, conceptualization, methodology, and investigation; Novizar: analytical support, methodology, and review; Yusrawati: data curation, investigation, and review; Tuty Anggraini: methodology, validation, and review; Desniarti: sampling and sample preparation, and validation; Muhammad Iqbal: investigation, visualization, data curation, and statistical analysis. Dina Intan Rizki: writing the original draft, investigations, visualization, statistical analysis, and editing.

Generative AI Statements: The authors declare that no Gen AI/DeepSeek was used in the writing/creation of this manuscript.

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ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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Citation: Azima F, Novizar, Yusrawati, Anggraini T, Desniarti, Iqbal M and Rizki DI, 2026. Ameliorative effects of combined cassiavera, morel berry and dayak onion extracts on complications in hypercholesterolemic-hypertensive rats. Agrobiological Records 24: 202-219. https://doi.org/10.47278/journal.abr/2026.038