ORIGINAL RESEARCH ARTICLE

Diponegoro International Medical Journal 2024 July, Vol 5, No.1: 24-30
e-ISSN: 2745-5815

Effects Of *Garcinia Mangostana Linn Pericarp* Extract And Physical Exercise On Renal Atheroembolic Histopathology In Wistar Rats With Metabolic Syndrome

Evangga Yudha Perdana[1], Ika Pawitra Miranti[2], Fathur Nur Kholis[3], Noor Wijayahadi[4], Andreas Arie Setiawan[5]*

[1]*Undergraduate Program, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
[2]*Department of Anatomical Pathology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia, Indonesia*
[3]*Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia*
[4]*Department of Pharmacology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*

Keywords:

Atheroembolic, Atherosclerosis Garcinia Mangostana linn pericarp extract Nanoemulsion.

*) Correspondence to:
andreasarie45@gmail.com

Article history:

Received 07-01-2024
Accepted 04-07-2024
Available online 29-07-2024

ABSTRACT

Background: Renal atheroembolism is an under-recognized cause of renal failure . Atheroembolism is caused by cholesterol crystals from ulcerated atherosclerotic plaques and is influenced by inflammation and endothelial dysfunction. The formation of complicated atherosclerotic lesions is a prerequisite for the development of cholesterol crystal emboli. Non-pharmacological therapeutic management (such as diet and physical exercise) is an important factor in preventing and reducing the risk of atherogenesis. *Garcinia Mangostana Linn pericarp* can inhibit the process of atherosclerosis through the reduction of free radicals and improvement of endothelial function.
Objective: To investigate the effect of *Garcinia Mangostana Linn Pericarp* administration along with Physical Exercise on the histopathologic features of renal atheroembolism in Wistar rats with metabolic syndrome.
Methods: This study is a *true experimental* study with research subjects in the form of male *Rattus norvegicus* Wistar rats which were randomly divided into 3 groups. K (not given therapy), P1 (*garcinia pericarp* extract 800 mg / kg / day with physical exercise), and P2 (*nanoemulsion* 50 mg / kg / *time* of administration with physical exercise).
Results: In the group treated with *garcinia pericarp* extract 800 mg/kg bw/day with physical exercise and the group with *nanoemulsion* 50 mg/kg *bw/day* with physical exercise, there were no *fatty streaks*, inflammation, and impaired myocyte coherence. There was 0-5% fibrous connective tissue, one layer of foam cell layer and myocyte-lipid, no cholesterol crystal embolism was found.
Conclusion: The administration of *Garcinia Mangostana Linn pericarp* extract and/or *nanoemulsion* with physical exercise can have an effect on the histopathological picture of the kidneys of Wistar rats with metabolic syndrome. There was no difference in effect between the two treatments. However, it could not be compared with the group that was not given any treatment because it had died completely before the end of the study period.

DIMJ, 2024, 5(1), 24-30 DOI: https://doi.org/10.14710/dimj.v5i1.21750

1. Introduction

Ateroembolic kidney disease is part of a multisystem disease caused by arterial blockage by cholesterol crystal emboli originating from ulcerated atherosclerotic plaques. Aeroembolic kidney disease is an important, but still underdiagnosed component of renal disease associated with atherosclerosis and an unexplored area of nephrology research[1]. The exact mechanisms underlying ateroembolic are not fully understood. Local tissue necrosis and inflammatory reactions caused by cholesterol crystals (CCs) play an important role in atheroembolic pathogenesis[2].

Histologically, cholesterol crystal emboli are identified in the lumen of arcuate and interlobular arteries as biconvex, *needle-shaped*, and empty gaps, referred to as *ghost cells* because they dissolve during specimen processing. Small crystals rarely lodge in afferent arterioles and glomerular capillaries. Tissue damage caused by these crystal emboli is usually patchy. Glomerular and interstitial changes are mainly ischemic with varying degrees of glomerular damage and interstitial fibrosis. In the early phase, areas of acute tubular necrosis can be identified. Cholesterol crystal emboli are also identified in the skin, gastrointestinal tract and muscles[3,4].

The most important risk factor for atheroembolism is atherosclerosis and most other risk factors, such as diabetes mellitus, hypertension, hyperlipidemia, and smoking are actually also risk factors for atherosclerosis. The severity of atherosclerosis is a determinant of atheroembolic risk[5].

The formation of complicated atherosclerotic lesions is

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj

a prerequisite for the development of cholesterol crystal emboli. The process of atherogenesis begins with inflammation of the endothelial lining of the blood vessels. The endothelial layer that functions to produce vasodilator and vasoconstrictor molecules, such as nitric oxide (NO) and endothelin, will experience an imbalance in the production of these vasoactive substances resulting in impaired function referred to as endothelial dysfunction[6].

If it is related to the current condition, the lower and middle classes tend to believe in the benefits of herbal medicine as an alternative therapy management, both as a complement and alternative[7].

The potential effects of medicinal plants in improving and maintaining human health, low cost, and low side effects, have taken center stage. *Mangosteen* (*Garcinia mangostana*) is a tropical fruit used for centuries in Southeast Asia for medicinal purposes. Mangosteen rind contains *xanthones*, which are bioactive compounds that have potential benefits, such as anti-inflammatory, antioxidant, neuroprotective, cytotoxic, and antiproliferative responses[8].

Non-pharmacological therapeutic management that is easy to do is an effort to control body weight, mainly by exercise (physical exercise). The form of physical exercise in mice includes running on a *treadmill* following an exercise protocol. From previous research, exercise on a *treadmill at* a speed of 12 m/min with a duration of 60 minutes per day, 5 times a week for 6 weeks, prevents the development of atherosclerosis and has a favorable effect on the composition of atherosclerotic plaques[8].

Renal atheroembolism is an underdiagnosed and under-researched clinical disease in the field of nephrology. To date, no studies have been conducted that prove the potential of *Pericarp Garcinia Mangostana Linn* as an anti-inflammatory herbal medicine in renal atheroembolism. So it is necessary to conduct this research.

2. Methods

This study is a *true experimental* with *The Randomized Pre and Post-Test Control Trial* (RCT) design. Maintenance and treatment were carried out at the UNISSULA Biomolecular Laboratory from December 2022 to February 2023. Paraffin block making and preparation processing, including HE painting were carried out at the Anatomical Pathology Laboratory of FK UNDIP-RSND. This study has obtained *ethical clearance* granted by the Ethics Commission for Health Research (KEPK) FK UndipNo.44/EC-H/KEPK/FK=UNDIP/V/2023.

The research subjects were male *Rattus norvegicus* Wistar rats that met the inclusion criteria (healthy male rats, white fur and active appearance, age ± 2 months (6-8 weeks), healthy rats on physical examination characterized by clear eyes, shiny fur, white, clean and thick, agile movements, and feces that are not mushy or watery) and exclusion (defects, appearing sick (standing fur, mushy feces), rats whose conditions decreased and / or died during the study). The sampling method used was *simple random sampling* and 16 rat samples were obtained. All rats were induced with a diet similar to the "*Western*" *purified atherogenic diet* patented by Envigo® with *high fat diet* formulation (20 - 23% BW; 40 - 45% kcal from fat), saturated fatty acids (SFA >60% of total fatty *acids*), and drinking from tap water *ad libitum* for 8 weeks.

Control group rats (K) were not given additional treatment. Rats in treatment group-1 (P1) were supplemented with *Garciana Mangostana Linn Pericarp* Extract at a dose of 800 mg/kgBB/day, divided into 3 doses, per round, for 8 weeks. The average weight of rats is in the range of 300 grams, so the dose used is 240 mg / day divided into 3 doses, which is 80 mg per administration / rat. Accompanied by physical exercise with a *treadmill* speed of 12 m/min, duration of 60 minutes per day, 5 days a week, for 8 weeks. Rats of treatment group-2 (P2) plus the administration of *Nanoemulsion of Garciana Mangostana Linn Pericarp* Extract 50 mg/kgBB once a day, per round, for 8 weeks. Physical exercise with a *treadmill* speed of 12 m/min, duration of 60 minutes per day, 5 days a week, for 8 weeks. Treatment was done individually.

At the end of the 8th week, rats that were still alive until the end were terminated, then the kidney organs were taken. Preparations were taken from the interstitial arteries and histopathologic tissue processing, paraffin blocking, HE staining, and interpretation of the histopathologic images by an anatomic pathologist.

3. Result

Table 1. Study Groups and Number of Mice

	Frequency	%	Presentas Valid	Percentage Cumulative
K	5	31.3	31.1	31.3
P1	6	37.5	37.5	68.8
P2	5	31.3	31.3	100.0
Total	16	100.0	100.0	

All study subjects were given an atherogenic diet to trigger the onset of metabolic syndrome. The diagnostic criteria for metabolic syndrome were the presence of at least three of the following five risk factors; a) obesity with *elevated* waist circumference (≥102 cm or ≥40 inches for men; ≥88cm or ≥35 inches for women); b) elevated triglycerides (>150 mg/dL or 1.7 mmol/L) or being on therapy to lower triglyceride levels; c) decreased HDL (<40 mg/dL or40 mg/dL or 1.03 mmol/L in men; <50 mg/dL or 1.3 mmol/L in women) or on therapy to lower HDL levels; d) elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic or on antihypertensive drug therapy in patients with a history of hypertension); and e) elevated fasting glucose levels (≥100 mg/dL or on drug therapy to lower elevated sugar levels[10].

During the research, the following facts were obtained:

1. K was found that all rats died before the end of the study period, consisting of rat K.3 died on the second day of the fifth week of the study (Tuesday, 3/1/2023), rat K.5 died on the fifth day of the fifth week of the study (Friday, 6/1/2023), rats K.1 and K.4 died on the third day of the sixth week (Wednesday, 11/1/2023). Rat K.2 died on the fourth day of the sixth week (Thursday, 12/1/2023).

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj

2. P1 obtained three rats died before the end of the study period, consisting of rat P1.4 died on the first day of the first week of the study (Tuesday, 6/12/2022). Rats P1.3 and P1.6 died on the first day of the fifth week of the study (Monday, 2/1/2023).
3. P2 obtained one rat died before the end of the study period, which consisted of rat P2.3 died on the first day of the fifth week (Monday, 2/1/2023).

There are various possible causes underlying the death of rats in this study, including the use of solvents in drugs, such as ethanol and aquabides. In this study, aquabides was used to dissolve the mangosteen peel extract and ethanol to dissolve the *nanoemulsion*. The use of ethanol as a solvent is better than aquabides because aquabides only dissolves water-soluble compounds. Meanwhile, compounds that are not water soluble will be wasted which results in compounds that are needed and not water soluble cannot be used. Other studies also show that the use of aquabides gives results that are not better than ethanol.

In addition, the use of drug sachets administered to rats several times a day is also suspected to be the cause of rat deaths. The frequency and method of using the drug sonde that is not appropriate or exceeds the prescribed time can lead to errors.

Therefore, the rats in the control group could not be statistically analyzed and compared with the treatment group because the control rats had all died before the end of the study period.

Table 2. Pre and Post Foam Cell Test Results

Group	Pre Foam Cell	Post Foam Cells		P
		1 layer	>1 layer	
P1	1 layer	6 (100)	0 (0)	1,000†
	>1 layer	0 (0)	0 (0)	
P2	1 layer	4 (100)	0 (0)	1,000†
	>1 layer	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t-test between pre-foam cells and post-foam cells using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 3. Differences in Foam Cells of Groups P1 and P2

	Group	Foam cell		P
		1 layer	>1 layer	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired t test between groups P1 and P2 using the Mann-Whitney alternative test on pre foam cells and post foam cells, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 4. Test Results of Pre Lipid Myocytes and Post Lipid Myocytes

Group	Myocyte lipid pre	Myocyte lipid post		P
		1 layer	>1 layer	
P1	1 layer	6 (100)	0 (0)	1,000†
	>1 layer	0 (0)	0 (0)	
P2	1 layer	4 (100)	0 (0)	1,000†
	>1 layer	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t test between pre lipid myocytes and post lipid myocytes using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 5. Differences in Myocyte Lipids of Groups P1 and P2

	Group	Lipid myocytes		P
		1 layer	>1 layer	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired t test between groups P1 and P2 using the Mann-Whitney alternative test on pre lipid myocytes and post lipid myocytes, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 6. Test Results of Pre External Lipid Deposition and Post External Lipid Deposition

Group	Pre external lipid deposition	Post external lipid deposition		P
		None	Available	
P1	None	6 (100)	0 (0)	1,000†
	Available	0 (0)	0 (0)	
P2	None	4 (100)	0 (0)	1,000†
	Available	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t-test between pre and post external lipid deposition using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 7. Differences in External Lipid Deposition of Groups P1 and P2

	Group	External lipid deposition		P
		None	Available	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired t test between groups P1 and P2 using the Mann-Whitney alternative test on pre external lipid deposition and post external lipid deposition,

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj

the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 8. Test Results of Pre Cholesterol Crystal Embolism and Post Cholesterol Crystal Embolism

Group	Pre cholesterol crystal embolism	Post cholesterol crystal embolism		p
		None	Available	
P1	None	6 (100)	0 (0)	1,000†
	There is	0 (0)	0 (0)	
P2	None	4 (100)	0 (0)	1,000†
	There is	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t-test between pre cholesterol crystal embolism and post cholesterol crystal embolism using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 9. Differences in Cholesterol Crystal Embolism in Groups P1 and P2

	Group	Cholesterol crystal embolism		P
		None	Available	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired difference test between groups P1 and P2 using the Mann-Whitney alternative test on pre cholesterol crystal embolism and post cholesterol crystal embolism, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 10. Test Results of Pre Atherosclerosis and Post Atherosclerosis

Group	Pre atherosclerosis	Post atherosclerosis		p
		Normal	Inflammation	
P1	Normal	6 (100)	0 (0)	1,000†
	Inflammation	0 (0)	0 (0)	
P2	Normal	4 (100)	0 (0)	1,000†
	Inflammation	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t test between pre atherosclerosis and post atherosclerosis using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 11. Differences in Atherosclerosis in Groups P1 and P2

	Group	Atherosclerosis		p
		Normal	Inflammation	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired t test between groups P1 and P2 using the Mann-Whitney alternative test on pre atherosclerosis and post atherosclerosis, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 12. Fatty Streaks Pre and Fatty Streaks Post Test Results

Group	Fatty streaks pre	Fatty streaks post		p
		None	Available	
P1	None	6 (100)	0 (0)	1,000†
	Available	0 (0)	0 (0)	
P2	None	4 (100)	0 (0)	1,000†
	There is	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t test between pre fatty streaks and post fatty streaks using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 13. Differences in Fatty Streaks of Groups P1 and P2

	Group	Fatty streaks		P
		None	There is	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired difference test between groups P1 and P2 using the Mann-Whitney alternative test on pre fatty streaks and post fatty streaks, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 14. Test Results of Pre Myocyte Coherence and Post Myocyte Coherence

Group	Pre myocyte coherence	Post myocyte coherence		p
		Normal	Distracted	
P1	Normal	6 (100)	0 (0)	1,000†
	Distracted	0 (0)	0 (0)	
P2	Normal	4 (100)	0 (0)	1,000†
	Distracted	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t test between pre myocyte coherence and post myocyte coherence using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 15. Differences in Myocyte Coherence of Groups P1 and P2

	Group	Myocyte coherence		P
		Normal	Distracted	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj

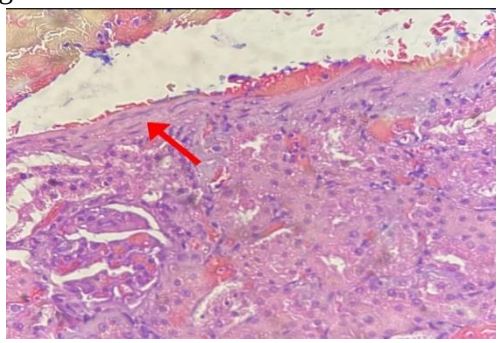
From the results of the unpaired t test between groups P1 and P2 using the Mann-Whitney alternative test on pre myocyte coherence and post myocyte coherence, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

Table 16. Test Results of Fibrous Tissue Pre and Fibrous Tissue Post

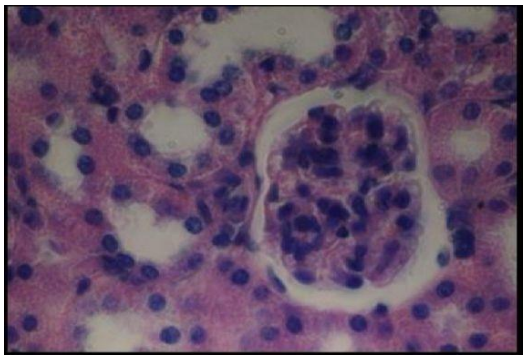
Group	Fibrous pre	Fibrous post		P
		0-5%	5-25%	
P1	0-5%	6 (100)	0 (0)	1,000†
	5-25%	0 (0)	0 (0)	
P2	0-5%	4 (100)	0 (0)	1,000†
	5-25%	0 (0)	0 (0)	

Description: † Wilcoxon

From the results of the paired t-test between pre fibrous connective tissue and post fibrous connective tissue using the Wilcoxon alternative test in groups P1 and P2, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.



Figures 1. Histopathology of Fibrous Tissue of the Treatment Group (HE staining, 100x magnification)



Figures 2. Normal Histopathology of the Treatment Group (HE staining, Magnification 400x)

Table 17: Differences in Fibrous Tissue of Groups P1 and P2

	Group	Fibrosa		p
		0-5%	5-25%	
Pre	P1	6 (100)	0 (0)	1,000‡
	P2	5 (100)	0 (0)	
Post	P1	6 (100)	0 (0)	1,000‡
	P2	4 (100)	0 (0)	

Description: ‡ Mann-Whitney

From the results of the unpaired t test between groups P1 and P2 using the Mann-Whitney alternative test on pre fibrous connective tissue and post fibrous connective tissue, the p value> 0.05 was obtained, so it can be concluded that there is no significant difference.

4. Discussion

The use of herbal medicines in recent times has begun to increase in the world, especially in various countries, such as Indonesia, China, and India. The use of herbal medicine has increased because it has pharmacological effects on almost all diseases with mild side effects. Common problems in herbal medicines are low bioavailability, solubility, absorption of active substances, and stability. To overcome these problems, the technology used for herbal medicine formulation is being developed. One example is nano technology. Nano technology is a technology in which drug particles are made on a nano scale (10 nm - 1000 nm). The use of nano technology is expected to overcome the problems in herbal medicine as well as improve therapeutic effects and reduce toxicity[14].

The nanoemulsion form was chosen because it can increase the physical stability of a bioactive component, protect chemical damage and interactions with food ingredients, and can be well dispersed in aqueous systems. The use of *nanoemulsion* form in this extract can improve and maximize the work of the extract. The increase is due to the large surface area of nanoemulsion which can allow penetration of the active ingredients quickly so that it can be a drug carrier with a small size that will not damage normal human or animal cells[15].

Based on the data obtained, for the number of foam cell layers, 100% of the number of rats in group P1 had 1 layer of foam cell layer. Similarly, 100% of the P2 group also obtained 1 layer of foam cell layer.

The main abnormalities in the lipid fraction are increased LDL, total cholesterol, and decreased HDL. Blood that contains too much cholesterol will easily stick to the inner wall of the blood vessels. After entering the intima, LDL will undergo oxidation and produce oxidized LDL which eventually leads to the synthesis of materials that can attach and attract monocytes through the endothelial layer, then into the intima. Furthermore, oxidized LDL produces chemicals that can convert monocytes into macrophages that can then "eat" LDL through *scavenger receptors*. This phagocytosis will produce foam cells as a by-product[11].

From the results of blood laboratory examinations of Wistar rats in this study, an increase in GDP, a decrease in HDL, a decrease in LDL, a decrease in total cholesterol was obtained in the group given the extract. Meanwhile, the group given *nanoemulsion* experienced a decrease in GDP, an increase in HDL, a decrease in LDL more, an increase in total cholesterol, a decrease in triglycerides more.

The main compound found in *mangosteen* rind is *α-mangosteen*. In ripe, mangosteen fruits have about twice the *α- mangosteen* than young mang*osteen* fruits. Recent studies have noted that mangosteen peels have antilipemic properties, lowering total cholesterol, triglycerides, and LDL, possibly increasing HDL cholesterol levels by increasing *Peroxisome Proliferators-Activated Receptors* (PPAR) activity[16].

Based on the interpretation results for the number of myocyte-lipid layers, 100% of the number of rats in group P1 had 1 layer of myocyte-lipid layer. Similarly, 100% of the P2 group also obtained 1 layer of myocyte-lipid layer.

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj

Based on the results obtained from the research that has been carried out regarding the presence or absence of extracellular lipid core deposition, in group P1 no extracellular lipid core deposition was found in 100% of the total number of treated rats. Similarly, group P2 also found 100% no extracellular lipid core deposition.

Based on the examination of the presence or absence of cholesterol crystal embolism, the P1 group found 100% no cholesterol crystal embolism. Likewise, in group P2, 100% were found to have no cholesterol crystal embolism.

Based on the results obtained, all rats in groups P1 and P2 were normal, no inflammation or atherosclerosis was found. There was no significant difference between groups P1 and P2.

The α-mangosteen compound found in this peel has also been shown to have better anti-inflammatory effects than anti-inflammatory drugs available in the market. *Mangosteen* is known to inhibit the release of cytokines involved in inflammatory responses, such as *interleukin-1 beta* (IL-1β), *interleukin-6* (IL-6), and *tumor necrosis factor-alpha* (TNF-α). By inhibiting the release of these cytokines, *mangosteen* can help reduce inflammation that occurs in the body. In addition, *mangosteen* may also have antioxidant activity that can keep cells protected from damage or defects caused by free radicals and oxidative stress associated with inflammation12.

Based on the results obtained, it can be seen that all rats in groups P1 and P2 did not have *fatty streaks*. There was no significant difference between groups P1 and P2.

The main pathological lesion associated with atherosclerosis is *fatty streaks* which are yellow-colored areas on arterial blood vessels, forming patches <1 mm or lines 1-2 mm wide, and up to one mm long[13].

No disturbed myocyte coherence was found in group P1. Likewise in group P2. After statistical analysis, the difference has a p value> 0.05 which can indicate there is no significant difference.

Based on the examination of the presence or absence of fibrous connective tissue, it was found that 100% of the number of P1 treatment rats were included in score 0, which is based on the classification of 0-5% fibrous connective tissue. The same thing was found in group P2.

Inflammation has been shown to be key in the process of atherogenesis, which can result in atheroma plaque rupture. Therefore, therapeutic modalities for atheroembolic kidney disease can also be directed to address the inflammatory response.

5. Conclusion

Both treatment combinations produced evidence of renal histopathology in Wistar rats with metabolic syndrome, namely in the group with the administration of *Garcinia Mangostana Linn Pericarp* Extract *and Nanoemulsion* together with physical exercise, no disturbed myocyte coherence was found. All rats were found to have 0-5% fibrous connective tissue, no *fatty streaks, no* inflammation, a single layer of foam cell layer and lipid myocytes, no external lipid deposition, and no cholesterol crystal emboli.

When associated with the use of nanoparticles in this study, but there is no difference in effect between the administration of extract preparations and *nanoemulsion* which should be nanoemulsion better effect when compared with extracts. This may be influenced by several things, including particle size, dosage regimen, exposure route, surface chemistry, degree of aggregation, transmembrane diffusivity, excretion pathways, and immunogenicity. By controlling these factors, the interaction of nanomaterials with biological tissues, penetration, diffusivity, absorption, distribution, immune recognition, duration of deposition into various body tissues, and clearance from the body can be controlled to prevent unwanted nanotoxicity.

However, these results could not be compared with the untreated group as all the rats died before the end of the study.

Ethical Approval

This study has obtained ethical clearance granted by the Ethics Commission for Health Research (KEPK) FK UndipNo.44/EC-H/KEPK/FK=UNDIP/V/2023.

Conflicts of Interest

The authors declare that there was no conflict of interest.

Funding

No specific funding was provided for this article.

Acknowledgments

This research was supported by RSND and Faculty of Medicine, Diponegoro Univerisity, Semarang.

References

1 Scolari F, Ravani P, Gaggi R, Santostefano M, Rollino C, Stabellini N, et al. The challenge of diagnosing atheroembolic renal disease: clinical features and prognostic factors. Circulation. 2007 Jul;116(3):298–304.

2 Li X, Bayliss G, Zhuang S. Cholesterol Crystal Embolism and Chronic Kidney Disease. Int J Mol Sci. 2017 May;18(6):1120.

3 Scolari F, Tardanico R, Zani R, Pola A, Viola BF, Movilli E, et al. Cholesterol crystal embolism: A recognizable cause of renal disease. Am J kidney Dis Off J Natl Kidney Found. 2000 Dec;36(6):1089–109.

4 Lie JT. Cholesterol atheromatous embolism. The great masquerader revisited. Pathol Annu. 1992;27 Pt 2:17–50.

5 Ozkok A. Cholesterol-embolization syndrome : current perspectives. Viscular Heal Risk Manag. 2019;15:209–20.

6 Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004 Jun;109(23 Suppl 1):III27-32.

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj

7 Welz AN, Emberger-Klein A, Menrad K. Why people use herbal medicine: insights from a focus-group study in Germany. BMC Complement Altern Med. 2018 Mar;18(1):92.
8 Huang TH-W, Kota BP, Razmovski V, Roufogalis BD. Herbal or natural medicines as modulators of peroxisome proliferator-activated receptors and related nuclear receptors for therapy of metabolic syndrome. Basic Clin Pharmacol Toxicol. 2005 Jan;96(1):3–14.
9 Kadoglou NPE, Kostomitsopoulos N, Kapelouzou A, Moustardas P, Katsimpoulas M, Giagini A, et al. Effects of exercise training on the severity and composition of atherosclerotic plaque in apoE-deficient mice. J Vasc Res. 2011;48(4):347–56.
10 Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005 Oct;112(17):2735–52.
11 Yurista SR, Safithri F, Djunaedi D, Sargowo D. Effect of Extract from Pericarp of Mangosteen (Garcinia Mangostana Linn) as Anti-Inflammatory Agent in Rat Models with Atherosclerosis Efek Ekstrak Kulit Manggis (Garcinia Mangostana Linn) sebagai Anti Inflamasi pada Tikus Model Aterosklerotik. J Kardiol Indones. 2012;33(1):4–9.
12 Septiana UL, Pramudita OP, Retfiliastuti I, Sholikhah LA. Analisis Potensi Senyawa Mangostin dalam Ekstrak Kulit Manggis (*Garcinia mangostana L.*) sebagai Agen Antiinflamasi. J Jendela Inov Drh. 2023;6(2):72–86.
13 Japardi I. Patofisiologi Stroke Infark Akibat Tromboemboli. In 2002. Available from: https://api.semanticscholar.org/CorpusID:73028578.
14 Hanutami BNP, Budiman A. Review Artikel: Penggunaan Teknologi Nano pada Formulasi Obat Herbal. Farmaka. 2017;15(2):29–41.
15 Yuliani SH, Hartini M, Stephanie, Pudyastuti B, Istyastono EP. Perbandingan Stabilitas Fisis Sediaan Nanoemulsi Minyak Biji Delima dengan Fase Minyak Long-Chain Triglyceride dan Medium-Chain Tryglyceride. Tradit Med J. 2016;21(2):93–8.
16 Anna M, Andi W. Peroxisome Proliferator–Activated Receptors and The Metabolic Syndrome. Indones Biomed J. 2009;1(1):4–31.

Published by Universitas Diponegoro.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Available online at: https://ejournal2.undip.ac.id/index.php/dimj