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Anti-hyperlipidemic effect of mangosteen (*Garcinia mangostana* L.) peel extract in dyslipidemia-induced rats

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ABSTRACT

Dyslipidemia is due to an increase in blood lipid levels, which include cholesterol (CHOL), triglycerides (TG), and low-density lipoprotein (LDL). Since oxidative stress is the primary factor of dyslipidemia, it is strongly recommended that an antioxidant-based therapy be developed. Mangosteen is an antioxidant agent that exhibits free radical scavenging attributes and oxidation of low-density lipoprotein oxidatio's protection. This study focused on determining the anti-hyperlipidemic and antioxidant effects of mangosteen peel extract (MPE) in dyslipidemia rats. Lipid profile: CHOL, TG, LDL, High-Density Lipoprotein (HDL), and Malondialdehyde (MDA) levels of dyslipidemia rats were assessed. High cholesterol was delivered to the rats for 4 weeks to induce dyslipidemia. The high cholesterol administration was stopped after rats encountered dyslipidemia. Subsequently, rats were given MPE 1000; 500; 250 mg/kg body weight (BW) daily for 14 days (initial treatment) and 28 days (subsequent treatment), normal control (normal feed), and negative control (dyslipidemia rats). Hematoxylin Eosin staining was used to observe the histology of liver and vascular endothelial tissue. After 28 days of treatment, the CHOL, TG, and LDL were critically declined by 1000 mg/kg MPE. MDA plasma level showed a decrease in all treatments. Mangosteen peel extract improved histological structure by reducing lipid accumulation in the hepatocyte cytoplasm. In conclusion, MPE showed anti-hyperglycemic and antioxidant activity in dyslipidemia-induced rats.

Keywords: antioxidant, dyslipidemia, hypolipidemic, lipid, mangosteen

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INTRODUCTION

Dyslipidemia is a common illness correlated to declining longevity and rising morbidity from various diseases such as hypertension, obesity, cardiovascular disease and insulin resistance. Dyslipidemia is due to low high-density lipoprotein (HDL) and an increase in blood lipid levels, which include cholesterol (CHOL), triglyceride (TG) and low-density lipoprotein (LDL). The lipoproteins are classified into chylomicrons, intermediate low-density lipoprotein 1 (IDL1), Very Low Density Lipoprotein 2 (VLDL2), LDL3, HDL4, and apolipoproteins (Apo), including Apo A, Apo B, Apo C, and Apo E (Birudu et al., 2015). Over the last few decades, the global prevalence of DM in adults worldwide has increased. According to the International Diabetes Federation (IDF), 1,9% of people worldwide have diabetes mellitus (DM), making it the seventh largest cause of mortality globally (IDF, 2017). The highest prevalence occurs in middle-income countries. India, China and countries with populations over 100 million will have large diabetes cases between 2021 and 2045 due to urbanization and middle age. In 2017, Indonesia got the 6th place in the world's top number of DM sufferers with 10.3 million DM sufferers and is expected to experience an increase in 2045 by 62% to 16.7 million (IDF, 2017).

Tropical countries, like Malaysia, Indonesia, Thailand, Sri Lanka, and Philippines, are where mangosteen fruits (*Garcinia mangostana* L.) grow. In some countries of Southeast Asia, the peel of mangosteen has been used as a medical agent to medicate several illnesses. Mangosteen fruit was consumed to heal metabolic dysfunction. Nevertheless, the chemical principle for the treatment was unclear. Based on several studies, mangosteen fruit has activity of antioxidant (Gondokesumo et al., 2019; Widyowati et al., 2020a; Wathoni et al., 2019), anti-diabetes mellitus (Husen et al., 2017), anti-inflammation (Widowati et al., 2016), anti-obesity (Watanabe et al., 2018), anti aging (Widyowati et al., 2020b) and anti-cholesterol (Liu et al., 2015).

Mangosteen peel has antioxidant activity; it has the capability to free radical scavenging properties and protect the oxidation of LDL (Devalaraja et al., 2011). The predominant compound of antioxidants in mangosteen peel is mangostin, which is derived from xanthone (Gondokesumo et al., 2019). α-mangostin has the effect of protecting tissues by reducing oxidative stress (Gondokesumo et al., 2019). γ-mangostin also presented hydroxyl radical-scavenging activity (Sampath & Vijayaraghavan, 2007). Previous studies revealed that mangosteen peel comprises various bioactive compounds. Those compounds have the potential to be utilized as therapeutic medium or functional food additives, like tannins and phenolic acids (Pothitirat et al., 2009), xanthones, anthocyanins (Palapol et al., 2009) and other bioactive compounds. One of the mangosteen peel compound was xanthone, with showed some potential for anti-oxidant, anti-inflammatory, cardio-protective, and neuro-protective effects (Gondokesumo et al., 2019; Phyu & Tangpong, 2014; Widowati et al., 2016; Widowati et al., 2020a).

Besides antioxidant activity, mangosteen peel possesses other activities. Mangosteen peel extract, α-mangostin, and γ-mangosteen could reduce the yield of IL-6, NO, COX-2, and IL-1β, hence demonstrating the anti-inflammatory effect (Widowati et al., 2016). α-mangosteen and γ-mangosteen contained in mangosteen peel had the most active anti-aggregations and antioxidant activities (Widowati et al., 2014). Prominent anti-obesity potential was acquired from mangosteen peel ethanolic extract (Abuzaid et al., 2016; Widowati et al., 2020a).

On account of epidemiology studies, the component of mangosteen peel extract (MPE) has activity of protecting oxidation of LDL causing dyslipidemia. This studys purpose is to examine the anti-hyperlipidemic and antioxidant effects of MPE in dyslipidemia rats by measuring the lipid profile, Malondialdehyde (MDA) level, and histological analysis of liver and vascular endothelial tissue.

MATERIALS AND METHODS

Materials

One kilogram of dried mangosteen peel and 70% ethanol was used for extraction. Twenty-five, six weeks old male Sprague-Dawley rats (140-170 gr), a special diet with additional cholesterol 1.25% (Sigma Aldrich, C8867) and cholic acid 0.5% (Sigma Aldrich, G3272) was used for animal

experiment. Cholesterol FS, GPO PAP": enzymatic photometric method (DiaSys Gmbh Germany), Triglyceride FS, "GPO" colorimetric enzymatic method (DiaSys Gmbh Germany), HDL from HDL Precipitant (DiaSys Gmbh Germany) was used for the lipid analysis. 10% buffered neutral formalin, ascending graded alcohol (70, 80, 90, 95 and 100%), xylene, paraffin, aquades, Mayer's Hematoxylin (Merck 1.15938.0025), eosin (Merck 1.15935.0025) was used for histological analysis.

Methods

Extract preparation

Mangosteen peel was obtained from Subang, Indonesia. Determination of the plants was carried out by herbarium personnel of the Department of Biology, Sekolah Ilmu dan Teknologi Hayati (SITH), Bandung Institute of Technology, Bandung, West Java, Indonesia. Mangosteen peel that has been dried, as much as one kilogram, was macerated with distilled 70% ethanol. Dried peel was soaked in ethanol for 24 hours and the supernatant was assembled. Filtration and evaporation using a rotary evaporator at 40^0C were conducted afterwards. The yield of extraction (MPE) was stored at 20^0C (Rusmana et al., 2017; Widowati et al., 2017; Widowati et al., 2016).

Animals and treatment

A total of twenty-five six weeks old male Sprague-Dawley rat with body weight range between 140-170 grams were used in this study. Animal experiments were done at the Animal Research Center, Center of Inter-University, Gadjah Mada University, Yogyakarta, Indonesia. The ethics committee for this research was accomplished from the Faculty of Medicine, Maranatha Christian University and Immanuel Hospital, Bandung, Indonesia (No:007/KEP/II/2017). Separate cage was used to maintain the rats, with a condition of 12-hour darkness/12-hour light cycle, with 25°C temperature and 55% relative humidity. There are five groups of treatment. (I) The normal control group is untreated rats with a normal diet. (II) The negative control group is the dyslipidemic model only administered with a high cholesterol diet. (III) The rats that were given a high cholesterol diet + MPE 1000 mg/kg BW; (IV) a high cholesterol diet + MPE 500 mg/kg BW; (V) a high cholesterol diet + MPE 250 mg/kg BW.

A high cholesterol feed for dyslipidemic modeling was given for two months. Negative control and MPE treatment groups rats were administered with cholesterol for 28 days to induce dyslipidemia. The lipid profiles were checked to prove that the rats suffered dyslipidemia (Widowati et al., 2013). After rats underwent dyslipidemia, the high cholesterol feed was stopped and rats were given MPE 1000; 500; 250 mg/kg BW daily for 14 days (initial treatment) and 28 days (subsequent treatment), (Raharjo & Monica, 2015). Lipid profile analysis was performed on days 14 and days 28 post-treatment (Widowati et al., 2013).

Sample collection

For lipid profile analysis, a total of 1.5 ml of blood was collected from the retro-orbital vein. The centrifugation of the blood was subsequently done for 20 minutes at 3000 rpm. The blood plasma was collected and kept at -80°C until needed for analysis. For histological analysis, rats were sacrificed by cervical dislocation, and then the liver and vascular endothelial were taken. The organ is stored in a 10% buffered neutral formalin fixative solution (BNF 10%) for histological analysis.

Measurement of lipid profiles (CHOL, HDL, TG, and LDL levels)

The total CHOL was determined in accordance with the kit's manufacturer's instructions from DiaSys Gmbh Germany's Cholesterol FS, triglyceride from Triglyceride FS, GPO PAP: enzymatic photometric method, "GPO" colorimetric enzymatic method, HDL from HDL Precipitant, "CHOD-PAP": photometric method, and LDL from LDL Precipitant, "CHOD-PAP": photometric method (DiaSys Gmbh Germany) (Widowati et al., 2013).

Measurement of MDA levels

Plasma samples for measuring MDA were frozen immediately after sampling at -80 °C until further processing. Other groups of rats were sacrificed 10 days after the last administration of saline. The

level of MDA was measured spectrophotometrically (Multiskan Go, Thermo ScientificTM) at 535 nm (Widowati et al., 2013).

Histological analysis

Hematoxylin and eosin (HE) staining was employed to analyze histological analysis of liver and vascular endothelial tissue. The liver and vascular endothelial sample were fixed with 10% buffered neutral formalin for 5 days. Then the samples were dehydrated, cleared and paraffin infiltrated using spin tissue processing (Thermo ScientificTM, STP 120). The dehydration process was carried out with ascending graded alcohol starting from 70% up to 100% for 1 hour each alcohol concentration. After that, the clearing process was using xylene. Then, liquid paraffin infiltration (paraffin I, II, and III) was given into the tissue at 60°C for 30 minutes each paraffin concentration. The embedding process was carried out using an embedding machine (Sakura Tissue TEK III model 4584) to form paraffin blocks. Paraffin blocks were cut using a microtome (Leica BioCut Rotary Microtome, RM2235) with a thickness of 4-5µm. The paraffin sheets were then stained using hematoxylin (Merck 1.15938.0025) and eosin (Merck 1.15935.0025). The slides were then analyzed using a Zeiss microscope (Primo Star 3) and a special Lumenera scientific microscope camera (Infinity1-microscope camera) (Gondokesumo, 2019).

Statistical analysis

SPSS software was operated to perform the statistical analysis. The data analysis used one way ANOVA to know the significantly difference ($p<0.05$) and the difference of each treatment was analyzed using Tukey's post hoc test and T-Test (SPSS 20) for total lipid profile parameters. All experiments were replicated at least three times.

RESULTS AND DISCUSSION

Dyslipidemia occurs when the blood lipid levels increase, including CHOL, TG and LDL. In this study, rats were fed by cholesterol (1.25% w/w) and cholic acid (0.5% w/w) for 2 months. The cholesterol feeding treatment was stopped after rats were proven to have dyslipidemia. In 14 days of post-treatment, there was no significant difference in lipid profiles among different MPE doses.

After testing, rats suffered dyslipidemia because CHOL, TG and LDL were significantly increased. The high level of cholesterol (>1%) and cholic acid (0.25% - 0.5% w/w) can increase TG and LDL. In 14 days of lipid profiles data, the hyperlipidemia rat modeling showed a significant difference from the normal control (Figure 1). In 28 days of post-treatment, the different doses of MPE showed different effects in lipid profile change. 1000 mg/kg BW of MPE showed the highest effect in reducing the blood CHOL, TG, and LDL and also in increasing the blood HDL concentrations after hyperlipidemia conditions.

The abundance of energy sources contributed to the high CHOL level in the positive control groups, which in turn can lead to elevated acetate levels and the buildup of fat within the body. If the total lipid is abundant in a body, it will lead to abnormal fat metabolism and CHOL deposit. The various diseases can happen to abnormal fat metabolism such as hyper TG, hypercholesterolemia, and low HDL that will lead to dyslipidemia (Alves-Bezerra & Cohen, 2017; Husen et al., 2017).

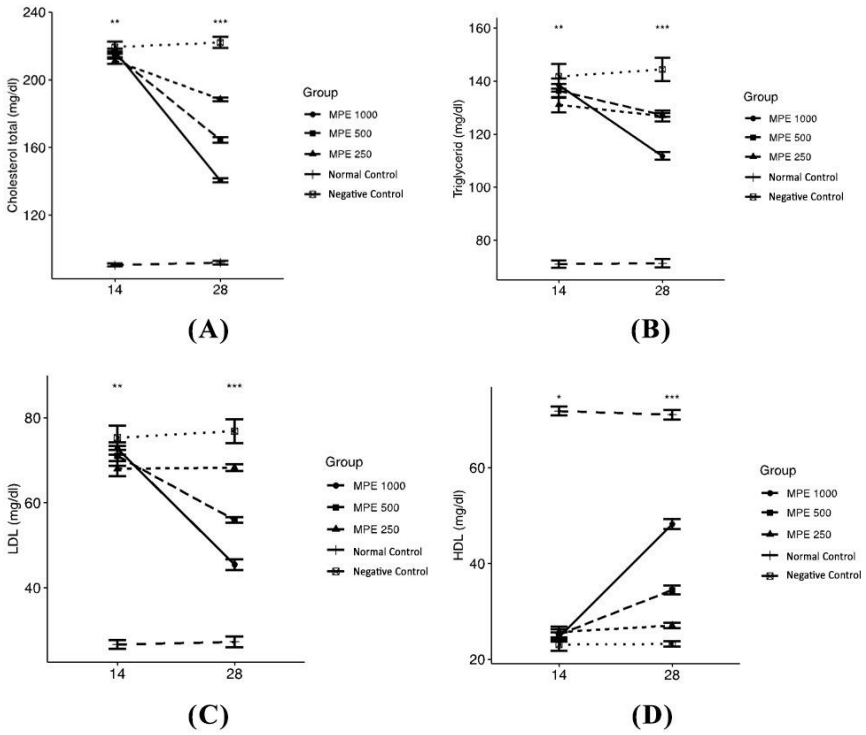

Figure 1. Effect of MPE towards lipid profiles levels in dyslipidemic rats in 14 and 28 days post-treatment. Cholesterol (A), Triglyceride (B), Low Density Lipoprotein (C), High Density Lipoprotein (D). Data was presented as mean±standard deviation with three replications. (ns: non significant $p>0.05$, *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$)

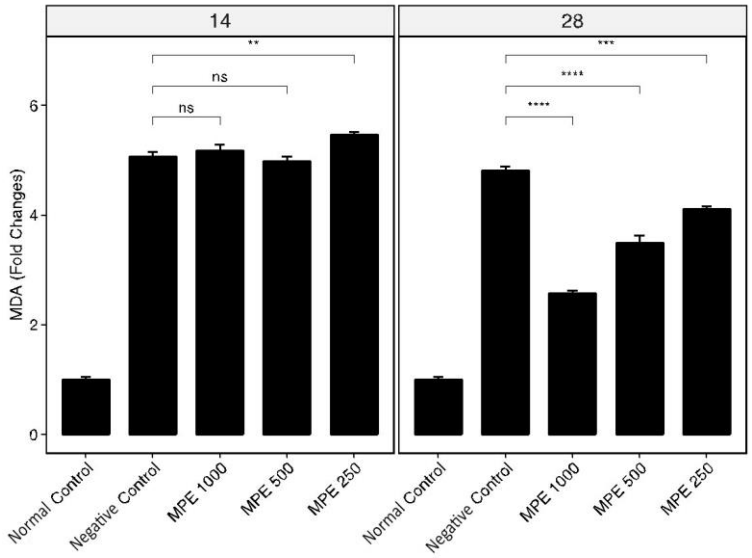

Figure 2. Effect of MPE towards plasma MDA level in dyslipidemia-induced rats in 14 and 28 days post-treatment. Data was presented as mean±standard deviation, with three replications. (ns: non significant $p>0.05$, *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$)

In MDA plasma level analysis, all treatments of the sample a showed low concentration compared to the negative control after 28 days. Different doses of MPE showed different effects in reducing the MDA concentration in plasma, especially MPE 1000 mg/kg BW showed the most effective treatment to reduce MDA level in hyperlipidemia models. Meanwhile, MDA level in 14 days of post-treatment did not show any significant difference between different MPE doses (Figure 2). This result is consistent with previous study which stated that the lower the concentration of mangosteen extract, had higher MDA level. Because lipid peroxidase is active at higher concentration in damaged cells or tissues, the concentration of MDA may be a sign of oxidative stress (Husen et al., 2017).

Interestingly, increasing the MPE dose did not affect the structure in the liver and vascular endothelial, as shown by histopathological examination. The liver and vascular endothelial in all doses of MPE group and normal control group did not show any significant lesion related to the treatment in which all liver was in good condition and there was no plaque found in nucleus and cytoplasm, no injury and inflammation signal. The only treatment that affected the liver structure was in the negative control group, where there is an accumulation of lipids (Figure 3). The accumulation of lipids in the liver induces lipid peroxidation resulting in endothelial dysfunction (Li et al., 2023). Endothelial dysfunction is linked to dyslipidemia (Higashi, 2023). Endothelial dysfunction is the first step in the progression of atherosclerosis, which leads to cardiovascular problems (Le Master & Levitan, 2019). In contrast, the treatment of MPE did not affect both histological analyses. Based on Figure 3, in MPE-treated groups, there is no lipid accumulation in the liver which causes no lesions/damage to the vascular endothelium structure. These data revealed that up to 1000 mg/kg bw had no significant hepatotoxicity and vascular effect. This condition is due to a natural compound in MPE that can protect from liver injury and lipid peroxidation. Prolonged lipid peroxidation effectively destroys cells by breaking the cell membrane and causes apoptosis (Rusman et al., 2021).

This present study showed strong negative correlation between MPE doses and CHOL total, TG, LDL, and MDA level. On the other hand, a strong positive correlation between MPE doses and HDL was seen in 28 days of post-treatment (Figure 4). This data indicated that MPE could give efficacy more than 14 days of treatments.

Our previous study evaluated mangosteen peel and xanthones on HepG2 cells. The study displayed mangosteen and xanthones' potential for decreasing CHOL and TG level. Mangosteen peel showed 100% CHOL inhibition activity (Darsono et al., 2015). According to the previous research, *G. mangostana* peel extract significantly reduced LDL levels in rats fed high lipids. Furthermore, *G. mangostana* peel extract increased HDL levels (Adiputro et al., 2013). Rats fed by high lipids can have a higher proportion of lipids than protein, thus the amount of lipoprotein in the blood was lower, meaning the LDL level was higher than HDL level. Additionally, the increasing TG initiated the rise of (VLDL) and chylomicron levels (McLaren et al., 2011).

G. mangostana peel extract can reduce blood CHOL level by inhibiting CHOL formation. The cause of inhibition is the stage of squalene synthesis before becoming CHOL, thus, the formation of CHOL does not happen. The merger between two molecules of farnesyl pyrophosphate and pyrophosphate radicals' eradication happens at this point. The merger of two molecules of farnesyl pyrophosphate is indicated by the combination of two farnesyl pyrophosphate radicals. Squalene formation could be inhibited by inhibition of combination that has been previously mentioned. The inhibition of the combination was done by mangosteen peel ethanolic extract's antioxidant activity (Adiputro et al., 2013). This result showed that mangosteen peel extract at high doses could decrease the oxidative stress, improved lipid profiles, and prevented cells and tissue from damage.

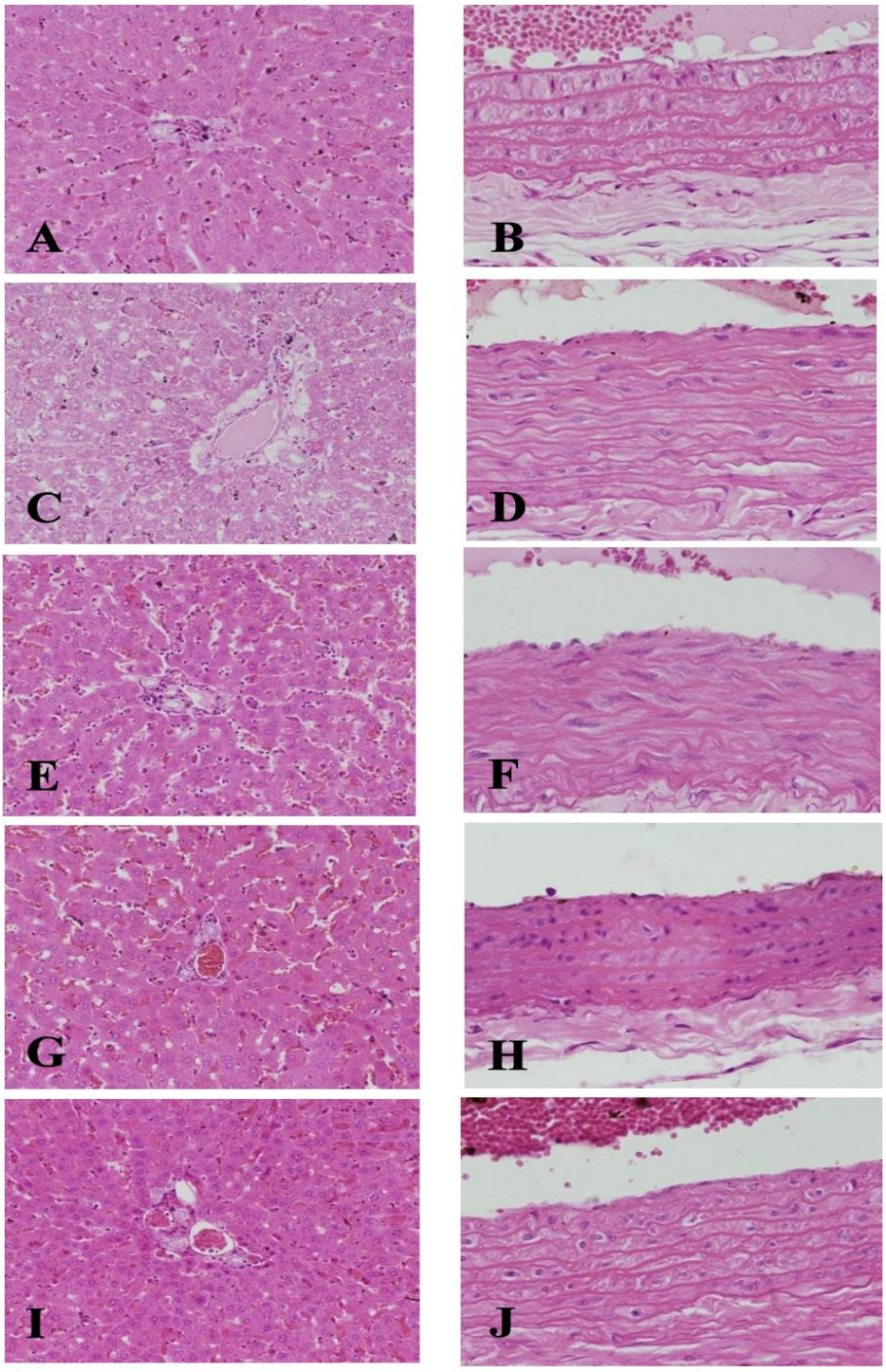

Figure 3. Effect of MPE towards histopathology liver and vascular endothelial in dyslipidemia-induced rats in 14 and 28 days of post treatment.Significant differences were not seen in liver lesion between normal control (A), MPE 1000 mg/kg bw (E), MPE 500 mg/kg bw (G) and MPE 250 mg/kg bw treatment (F) and there was no lesion difference in vascular endothelial in all group (B, D, F, H and J). The negative control group (C)'s liver is the only one that exhibited lipid accumulation in the hepatocyte cytoplasm

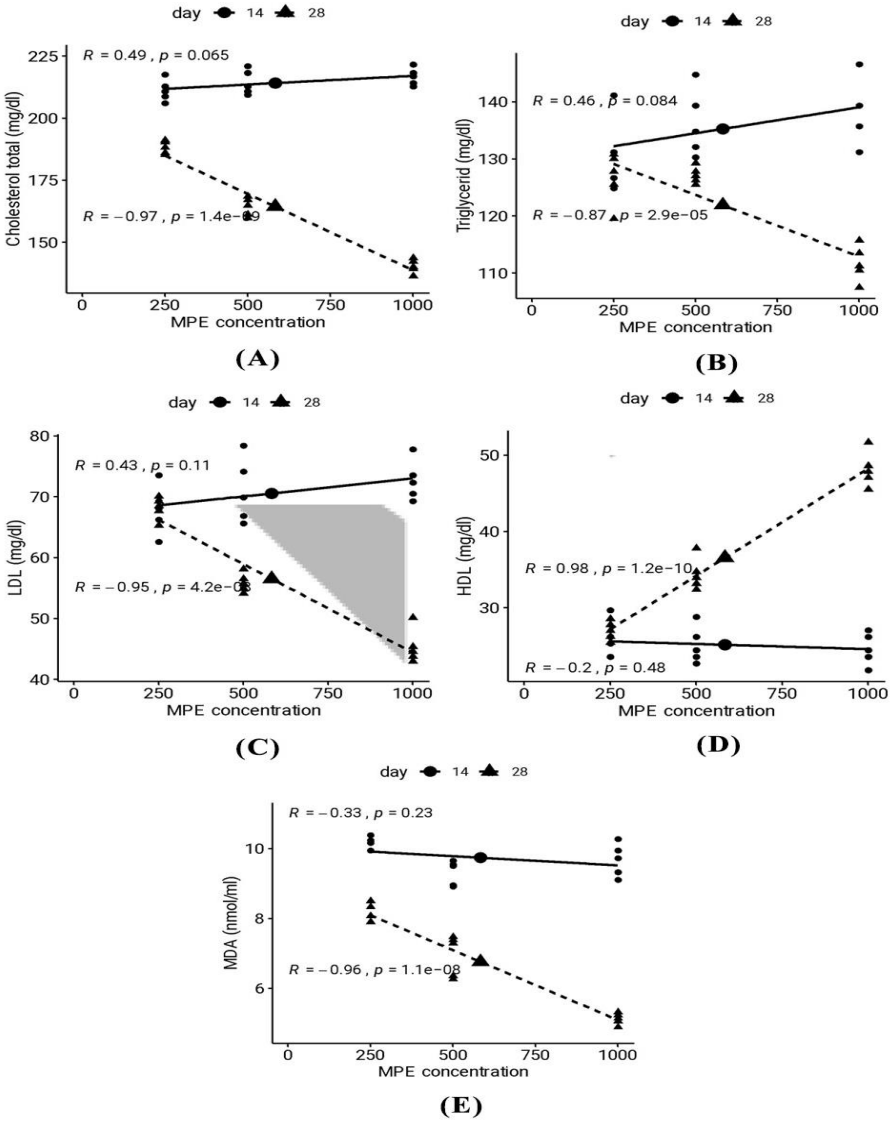

Figure 4. Correlation analysis by "Pearson'' method in different doses of MPE and lipid profiles. CHOL level **(A),** TG level **(B),** LDL level **(C),** HDL level **(D) MDA level (E). Data was presented as mean±standard deviation with three replications.**

CONCLUSION

The dyslipidemia rats treated with mangosteen peel extract showed hypolipidemic activity according to decreased levels of lipid profile, including CHOL, TG, and LDL. Meanwhile, HDL increased at 14 days and 28 days treatments. CHOL, TG, and LDL decreased at 28 days treatments. The MDA level was also decreased by mangosteen peel extract. Mangosteen peel ectract improved histological structure by reducing lipid accumulation in the hepatocyte cytoplasm. Therefore, MPE showed its anti-hyperglycemic and antioxidant activity in dyslipidemia-induced rats.

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REFERENCES

Abuzaid, A. S., Sukandar, E. Y., Kurniati, N. F., & Adnyana, I. K. (2016). Prevention of obesity and development of metabolic syndrome by mangosteen (Garcinia mangostana L.) pericarp ethanolic extract in male wistar rats fed with High-Fat diet. *International Journal of Pharmacy and Pharmaceutical Sciences*, *8*(5), 372–378.

Adiputro, D. L., Widodo, M. A., Romdoni, R., & Sargowo, D. (2013). Extract of mangosteen increases high density lipoprotein levels in rats fed high lipid. *Universa Medicina*, *32*(1), 37–43.

Alves-Bezerra, M., & Cohen, D. E. (2017). Triglyceride metabolism in the liver. In *Comprehensive Physiology* (pp. 1–22). Wiley. https://doi.org/10.1002/cphy.c170012

Birudu, R. B., Naik, M. J., & M, J. (2015). Anti-dyslipidemia effect of ethanol etract of passiflora foetida on dextrose induced diabetic rats. *Pharmaceutical and Biosciences Journal*, *4*(1), 13–19. https://doi.org/10.20510/ukjpb/4/i1/87840

Darsono, L., Hidayae, M., Maesaroh, M., Fauziah, N., & Widowati, W. (2015). Ex vivo study of garcinia mangostana L. (Mangosteen) peel extract and xanthones as anti-adipogenesis in HepG2 cell model. *International Journal of Medical Research & Health Sciences*, *4*(3), 566. https://doi.org/10.5958/2319-5886.2015.00109.5

Devalaraja, S., Jain, S., & Yadav, H. (2011). Exotic fruits as therapeutic complements for diabetes, obesity and metabolic syndrome. *Food Research International*, *44*(7), 1856–1865. https://doi.org/10.1016/j.foodres.2011.04.008

Gondokesumo, M. E. (2019). Garcinia Mangostana extract enhances skin epithelialization in Rat induced burn injury. *Pakistan Veterinary Journal*, *39*(03), 365–370. https://doi.org/10.29261/pakvetj/2019.059

Gondokesumo, M. E., Pardjianto, B., Sumitro, S. B., Widowati, W., & Handono, K. (2019). Xanthones analysis and antioxidant activity analysis (Applying ESR) of six different maturity levels of mangosteen rind extract (Garcinia mangostana Linn.). *Pharmacognosy Journal*, *11*(2), 369–373. https://doi.org/10.5530/pj.2019.11.56

Higashi, Y. (2023). Endothelial function in dyslipidemia: roles of LDL-cholesterol, HDL-cholesterol and triglycerides. *Cells*, *12*(9), 1293. https://doi.org/10.3390/cells12091293

Husen, S. A., Winarni, D., Khaleyla, F., Kalqutny, S. H., & Ansori, A. N. M. (2017). Activity assay of mangosteen *(Garcinia mangostana L.)* pericarp extract for decreasing fasting blood cholesterol level and lipid peroxidation in type-2 diabetic mice. 020026. https://doi.org/10.1063/1.5004303

IDF. (2017). IDF diabetes atlas 2017 *(8th Edition)*. In IDF Diabetes Atlas, 8th edition. https://www.idf.org/aboutdiabetes/type-2-diabetes.html

Le Master, E., & Levitan, I. (2019). Endothelial stiffening in dyslipidemia. *Aging*, *11*(2), 299–300. https://doi.org/10.18632/aging.101778

Li, Y.-Q., Xin, L., Zhao, Y.-C., Li, S.-Q., & Li, Y.-N. (2023). Role of vascular endothelial growth factor B in nonalcoholic fatty liver disease and its potential value. *World Journal of Hepatology*, *15*(6), 786–796. https://doi.org/10.4254/wjh.v15.i6.786

Liu, Q.-Y., Wang, Y.-T., & Lin, L.-G. (2015). New insights into the anti-obesity activity of xanthones from Garcinia mangostana. *Food & Function*, *6*(2), 383–393. https://doi.org/10.1039/C4FO00758A

McLaren, J. E., Michael, D. R., Ashlin, T. G., & Ramji, D. P. (2011). Cytokines, macrophage lipid metabolism and foam cells: Implications for cardiovascular disease therapy. *Progress in Lipid Research*, *50*(4), 331–347. https://doi.org/10.1016/j.plipres.2011.04.002

Palapol, Y., Ketsa, S., Stevenson, D., Cooney, J. M., Allan, A. C., & Ferguson, I. B. (2009). Colour development and quality of mangosteen (Garcinia mangostana L.) fruit during ripening and after harvest. *Postharvest Biology and Technology*, *51*(3), 349–353.

https://doi.org/10.1016/j.postharvbio.2008.08.003
Phyu, M. P., & Tangpong, J. (2014). Neuroprotective effects of xanthone derivative of Garcinia mangostana against lead-induced acetylcholinesterase dysfunction and cognitive impairment. *Food and Chemical Toxicology*, *70*, 151–156. https://doi.org/10.1016/j.fct.2014.04.035
Pothitirat, W., Chomnawang, M. T., Supabphol, R., & Gritsanapan, W. (2009). Comparison of bioactive compounds content, free radical scavenging and anti-acne inducing bacteria activities of extracts from the mangosteen fruit rind at two stages of maturity. *Fitoterapia*, *80*(7), 442–447. https://doi.org/10.1016/j.fitote.2009.06.005
Raharjo, L. H., & Monica. (2015). Pengaruh ekstrak kulit buah manggis terhadap total kolesterol, LDL, dan HDL serum pada tikus yang diberi minyak jelantah. *Jurnal "Ilmiah Kedokteran"*, *4*(2), 45–53. http://eprints.undip.ac.id/44756/
Rusman, J. R. A., Sundari, S. A., Nuriliani, A., & Saragih, H. T. (2021). Ameliorative effect of Mangosteen (Garcinia mangostana L.) peel infusion on the histopathological structures of the liver and kidney of rats (Rattus norvegicus Berkenhout, 1769) after H2O2 induction. *Veterinary World*, 1579–1587. https://doi.org/10.14202/vetworld.2021.1579-1587
Rusmana, D., Wahyudianingsih, R., Elisabeth, M., Balqis, B., Maesaroh, M., & Widowati, W. (2017). Antioxidant activity of *Phyllanthus niruri* extract, rutin and quercetin. *The Indonesian Biomedical Journal*, *9*(2), 84–90. https://doi.org/10.18585/inabj.v9i2.281
Sampath, P.D., & Vijayaraghavan, K. (2007). Cardioprotective effect of α-mangostin, a xanthone derivative from mangosteen on tissue defense system against isoproterenol-induced myocardial infarction in rats. *Journal of Biochemical and Molecular Toxicology*, *21*(6), 336–339. https://doi.org/10.1002/jbt.20199
Watanabe, M., Gangitano, E., Francomano, D., Addessi, E., Toscano, R., Costantini, D., Tuccinardi, D., Mariani, S., Basciani, S., Spera, G., Gnessi, L., & Lubrano, C. (2018). Mangosteen extract shows a potent insulin sensitizing effect in obese female patients: a prospective randomized controlled pilot study. *Nutrients*, *10*(5), 586. https://doi.org/10.3390/nu10050586
Wathoni, N., Yuan Shan, C., Yi Shan, W., Rostinawati, T., Indradi, R. B., Pratiwi, R., & Muchtaridi, M. (2019). Characterization and antioxidant activity of pectin from Indonesian mangosteen (Garcinia mangostana L.) rind. *Heliyon*, *5*(8), e02299. https://doi.org/10.1016/j.heliyon.2019.e02299
Widowati, W., Darsono, L., Suherman, J., Fauziah, N., Maesaroh, M., & Erawijantari, P. P. (2016). Anti-inflammatory effect of Mangosteen (*Garcinia mangostana* L.) peel extract and its compounds in LPS-induced RAW264.7 Cells. *Natural Product Sciences*, *22*(3), 147. https://doi.org/10.20307/nps.2016.22.3.147
Widowati, W., Darsono, L., Suherman, J., Yelliantty, Y., & Maesaroh, M. (2014). High performance liquid chromatography (HPLC) analysis, antioxidant, antiaggregation of mangosteen peel extract (*Garcinia mangostana* L.). *International Journal of Bioscience, Biochemistry and Bioinformatics*, *4*(6), 458–466. https://doi.org/10.17706/ijbbb.2014.4.6.458-466
Widowati, W., Darsono, L., Suherman, J., Afifah, E., Rizal, R., Arinta, Y., Mozef, T., & Suciati, T. (2020a). Regulation of adipogenesis by mangosteen peel extract and xanthones in 3T3-L1 cells. *Biotropia*, *27*(1). https://doi.org/10.11598/btb.2020.27.1.932
Widowati, W., Ginting, C. N., Lister, I. N. E., Girsang, E., Amalia, A., Wibowo, S. H. B., Kusuma, H., & Rizal, R. (2020b). Anti-aging effects of mangosteen peel extract and its Phytochemical compounds: antioxidant activity, enzyme inhibition and molecular docking simulation. *Tropical Life Sciences Research*, *31*(3), 127–144. https://doi.org/10.21315/tlsr2020.31.3.9
Widowati, W., Rani, A. P., Hamzah, R. A., Arumwardana, S., Afifah, E., Kusuma, H. S. W., Rihibiha, D. D., Nufus, H., & Amalia, A. (2017). Antioxidant and antiaging assays of *Hibiscus sabdariffa* extract and its compounds. *Natural Product Sciences*, *23*(3), 192. https://doi.org/10.20307/nps.2017.23.3.192
Widowati, W., Ratnawati, H., Mozefi, T., Pujimulyani, D., & Yelliantty, Y. (2013). Hypolipidemic

and antioxidant effects of black tea extract and quercetin in atherosclerotic rats. *World Academy of Science, Engineering and Technology International Journal of Medical Science and Engineering*, *7*(10), 64–67.