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Original Article

The Effect of Sapodilla Leaf Extract (*Manilkara zapota* L.) on Lipid Profiles of Alloxan-Induced Diabetic Mice

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ABSTRACT

The aim of this study is to examine the effect of sapodilla leaf extract on lipid profiles of alloxan-induced diabetic mice. This research method are 30 male mice were used as experimental animals, which were randomly divided into five groups, each group consisting of 6 mice. The division of the group is as follows: Treatment of non-diabetic mice, diabetic mice, diabetic mice by administering pioglitazone at a dose of 2 mg/kg BW, extracts of manila sapodilla leaf (*M. zapota* L.) dose 100 mg/kg BW and 300 mg/kg BW. Observations were made on the 14th day, after administration of sapodilla leaf extract, mice were given light anesthesia and serum lipid profiles Total Cholesterol (TC), triglycerides (TG), High-Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL) were measured using diagnostic kits (Pars Azmoon Kit) and automatic analyzer (Abbot, model Alcyon 300). The results of this study are in TC, there was a significant difference in pioglitazone and 100 mg leaf extract against all treatment groups. In TG, there was a significant difference in pioglitazone and 300 mg leaf extract against all treatment groups. In LDL, there were significant differences in the 100 mg, 300 mg leaf extract and pioglitazone, against negative control, and diabetes control. In HDL, there was a significant difference in negative control and 300 mg leaf extract, against 100 mg leaf extract, pioglitazone, and diabetes control. The conclusions of this study exhibited the ethanol extract of *M. zapota* leaves contains several phytochemical compounds including alkaloids, flavonoids, saponins, polyphenols, tannins, quinones, and steroids. *M. zapota* leaves extract (100 mg/kg and 300 mg/kg) exhibited a significant effect on improvement in lipid protein.

Key words: Alloxan, Diabetes, Lipid Protein, *Manilkara zapota*.

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INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by increased blood sugar levels due to decreased insulin secretion, weakened insulin activity or both.[1,2] Insulin functions to convert sugar into energy and fat synthesis. Low body insulin conditions result in excess sugar in the blood. Diabetes or Blood glucose levels above normal can potentiate the occurrence of lipidemia by increasing levels of total cholesterol, triglycerides, LDL (Low-Density Lipoprotein), and decreased HDL (High-Density Lipoprotein) levels.[3,4] The Centers for Disease Control and Prevention in 2014 reported that 70-97% of individuals with diabetes experience dyslipidemia.

Hyperlipidemia or hypercholesterolemia is one of the lipid fraction abnormalities in the blood or better known as dyslipidemia. This condition occurs due to disorders of lipoprotein metabolism which is often called the lipid triad that consists of increased concentrations of Very Low-Density Lipoprotein (VLDL) or triglycerides, decreased concentration of HDL, and the formation of LDL which is atherogenic.[5] Insulin resistance that affects metabolism in the body can result in changes in the process of production and disposal of lipoproteins in plasma. Lipoproteins are molecules made up of proteins and lipids. Lipogenesis is reduced and lipolysis increases due to a decrease in the effect of insulin on adipose tissue. An increase in the lipid fraction in plasma is a sign of lipid metabolism disorder due to diabetes mellitus, which is called dyslipidemia.[6]

As a countermeasure for antidiabetic and antihyperlipidemic, many medicines have been developed from natural ingredients that have proven to be effective as alternative therapies.[7-9] Conventional medical therapies such as pioglitazone and oral hyperlipidemic drugs have many side effects, such as weight gain, edema, and increased likelihood of bone fractures.[10] On the other hand, alternative medicine can be used using natural ingredients to overcome the side effects,[11-13] for example, traditional medicine, by processing natural ingredients to be used as medicine.[14] Indonesia has an abundant diversity of plants, one of which is sapodilla (*M. zapota*). Taxonomically, sapodilla comes from the Sapotaceae family and can be used in traditional medicine.

Several previous studies stated that the sapodilla plant has the potential to be used as an antihyperlipidemic drug , including the study conducted by Barbalho *et al.* (2015)[15] which showed that Male rats were given the juice from the leaves or fruit of *M. zapota* for 50 days, and the results showed considerably decreased levels of glycemia, insulin, leptin, cholesterol, and triglycerides and increased levels of HDL-c in the treated rats. Another research that has been conducted by Karle *et al.* (2022)[16] also shows that *Manilkara* fruit doses of 300 and 600 mg/kg showed significant antihyperglycemic effects, improved lipid profiles, increased body weight, and improved glomerulosclerosis.

Based on some of these studies and considering that there are still very few antihyperlipidemic studies using sapodilla leaves, the researchers would like

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to carry out further research on the effects of the ethanol extract of sapodilla leaves (*M. zapota*) obtained by maceration method on total cholesterol of diabetic mice alloxan induced. In this study sapodilla leaf extract was carried out using the maceration method with the consideration that this method can be carried out on a large scale and is quite easy for the community to do. Ethanol was chosen because it has several advantages, such as being relatively more selective, difficult for mold and germs to grow, non-toxic, neutral, and less heat required for the concentration.

MATERIALS AND METHODS

Tools and materials

The tools and materials used in this study was the leaves of sapodilla manila obtained from Puri District, Mojokerto Regency. The other tools and materials that were used in this study were male Wistar mice strain, saline solution, alloxan, pioglitazone, CMC (Carboxy Methyl Cellulose), glucometer (Accu Chek Instant), Accu Chek Instant blood glucose test strips, blood serum lipid diagnostic kit (Azmoon kit), automatic analyzer abbot (Alcyon 300), centrifuge, strainer, rotary evaporator, beaker glass, stir bar, aluminum foil, 96% ethanol, water, Hi-Pro-Vite Pokphand 511 feed, sawdust, 0.9% NaCl, distilled water, and 70% alcohol.

Animal care

This study uses healthy male Wistar mice, mice aged ± 3 months and have body weights of around 25-35 grams. Mice were placed in a cage with size (50cm x 50cm x 40cm). The bottom of the cage is lined with husk as thick as 1 cm and replaced every two days. Mice cages have good ventilation and humidity of 40-60% with a temperature of 22-25°C, the mice were given feed and drinking water twice a day. Ethical code, institutional, and national regulation of live animals were rigorously followed, and the Health Research Ethical Clearance, Faculty of Veterinary Medicine, Airlangga University, granted ethical clearance for the animals used in this inquiry (No. 2.KEH.068.06.2022).

Extraction of Sapodilla leaves (***M. zapota*** L.)

Sapodilla manila leaves (*M. zapota* L.) were washed with clean water and put in the oven at 60°C, then ground and sieved until a dry powder was obtained. Sapodilla leaf powder was soaked in 96% ethanol with a ratio of 1: 7, stirred several times, and left for 24 hours at room temperature. After 24 hours, it was filtered, the macerate was separated, and the dregs were re-macerated with the addition of 96% ethanol in a ratio of 1: 4. After filtering, all macerate was evaporated at 60°C until a thick extract was obtained.

Enter the thick extract obtained inside the beaker glass, cover it with aluminum foil, and then store it in the fridge to prevent damage extract. The solvent used is a *Carboxymethyle Cellulose* (CMC) concentration of 0.5 % to produce the extract wanted.

Table 1: The phytochemical results of sapodilla leaves.

No	Chemical Substance	Results
1	Alkaloids	Positive
2	Flavonoids	Positive
3	Saponins	Positive
4	Polyphenols	Positive
5	tannins	Positive
6	Quinone	Positive
7	Steroids	Positive
8	terpenoids	Negative

Table 2: Lipid profile of the 14th-day Wistar mice.

Group	Lipid Protein			
	TC	TG	LDL	HDL
Negative control	86,2 ± 3,56[a]	99,8 ± 3,03[b]	30,8 ± 6,57[a]	70 ± 7,9[c]
Diabetes control	149 ± 3,67[d]	185,6 ± 3,78[d]	98,8 ± 6,46[c]	40,4 ± 5,9[a]
Extract 100 mg/kg BW	114,6 ± 6,07[c]	121,6 ± 4,98[c]	57,8 ± 2,05[b]	58 ± 4,47[b]
Extract 300 mg/kg BW	94,8 ± 7,01[b]	92,8 ± 6,22[a]	50,8 ± 7,15[b]	65,6 ± 3,78[c]
Pioglitazone 2 mg/kg BW	118,6 ± 5,81[c]	90 ± 6,52[a]	53,8 ± 6,94[b]	52 ± 5,7[b]

Diabetes induction mellitus

Making mice models of diabetes mellitus was carried out after seven days after adaptation. Mice Wistar strain-adapted males were injected with alloxan single dose of 150 mg/kg BW dissolved in NaCl 0.9%.[17] Mice with blood glucose levels ≥ 200 mg/dL were categorized as diabetes mellitus mice and continued with with the next stages of extract therapy.[18]

Antihyperlipidemic test

In this study, 30 male mice were used as experimental animals, which were randomly divided into five groups, each group consisting of 6 mice. The division of the group is as follows:[18] Treatment of non-diabetic mice by administering 1.5 mL of physiological NaCl solution, treatment of diabetic mice by administering 1.5 mL of physiological NaCl solution,treatment of diabetic mice by administering Pioglitazone at a dose of 2 mg/kg BW, extracts of manila sapodilla leaf (*M. zapota* L.) dose 100 mg/ kg BW, and extracts of manila sapodilla leaf (*M. zapota* L.) dose 300 mg/ kg BW.

Observations were made on the 14th day, after administration of sapodilla leaf extract, mice were given light anesthesia and serum lipid profiles (total cholesterol, triglycerides, HDL, and LDL) were measured using diagnostic kits (Pars Azmoon Kit) and automatic analyzer (Abbot, model Alcyon 300).

RESULTS AND DISCUSSION

In TC, there was a significant difference in pioglitazone and 100 mg leaf extract ([c]) against negative control ([a]), 300 mg leaf extract ([b]) and diabetes control ([d]). In TG, there was a significant difference in pioglitazone and 300 mg leaf extract ([a]) against negative control ([b]), 100 mg leaf extract ([c]) and diabetes control ([d]). In LDL, there were significant differences in the 100 mg, 300 mg leaf extract and pioglitazone ([b]), against negative control ([a]), and diabetes control ([c]). In HDL, there was a significant difference in negative control and 300 mg leaf extract ([c]), against 100 mg leaf extract ([b]), pioglitazone ([b]), and diabetes control ([a]).

Diabetes induction in mice was carried out with a single dose of alloxan (150 mg/kg BW) which was injected intraperitoneally. In the body, alloxan is reduced to dialuric acid and then produces superoxide, which damages pancreatic cells, thereby inhibiting insulin production.[19,20] Diabetic hyperglycemia will be achieved in ± 48 hours.[21]

Laboratory test results showed that the lowest TC value was found in negative control group with 86.2 ± 3.56[a], whereas the highest TC value was found in diabetes control group with 149 ± 3.57[d]. Diabetes group had the highest total cholesterol compared to negative control group and treatments group *M. zapota* leaf extract because alloxan damage pancreatic β-cells. Pancreatic β-cells produce insulin which regulates lipase enzymes, such as lipoprotein lipase (LPL) and lipoprotein sensitive hormone (LSH). Lipase enzyme activity will increase when insulin levels decrease, therefore lipid metabolism disorder characterized by an increase total cholesterol levels.[22] The lowest TG value laboratory test results was found in treatment group pioglitazone 2 mg/kg BW with 90 ± 6.52[a], whereas the highest TG value was found in diabetes control group with 185.6 ± 3.78[d]. High TG values in diabetic mice due to increased sensitive hormone lipase enzyme activity, thus

non-esterified fatty acids (NEFA) release from triglycerides stored in adipose tissue. This condition encourages the liver to produce more triglycerides, thus liver has high level cholesterol. Cholesterol rate in liver is regulated by HMG-CoA, when glucagon levels increase HMG-CoA reductase sustain phospholiration and becomes inactive.[23]

The lowest low-density lipoprotein (LDL) laboratory results data was found in the negative control group with 30.8 ± 6.57^{a}, whereas the highest value was in diabetes control group with 98.8 ± 6.46^{c}. The lowest high-density lipoprotein (HDL) value was found in diabetes control with 40.4 ± 5.9^{a}, whereas the highest value was found in the negative control group with 70 ± 7.9^{c}. Decrease in HDL-cholesterol level of diabetic mice induced with alloxan can be attributed to the mechanism of action of alloxan that reacts with two –SH groups on glucokinase sugar-binding site resulting in the inactivation of enzyme. Reduction of alloxan will form dialuric acid that will get reoxidized, establishing a redox cycle that release free radical in the form of superoxide.[24] Superoxide can release Fe 3+ from ferritin and reduced it to Fe 2+ , as well as HA- that is able to reduce ferric ion. Superoxide radical will be turned into hydrogen peroxide. During redox cycle, alloxan will form reactive oxygen species (ROS) and excessive free radicals.[24] This will cause oxidative stress that ruin pancreatic beta cells function resulting in decrease of insulin production. Decrease in insulin causes an elevation in blood glucose level as insulin mediated glucose transport into cell decreases. Insulin regulates enzyme useful in lipid metabolism such as lipoprotein lipase and hormone-sensitive lipase, hence why a decrease in insulin level will result in the disturbance of lipid metabolism. Lipoprotein lipase is responsible to hydrolyzing tryglyceride in the circulation, whereas hormone-sensitive lipase will hydrolyze triglyceride stored in adipocytes.[25] This will causes an increase of lipid in circulation and decrease of it in the adipocytes. Increased hydrolyzing of triglyceride causes more fatty acids to be found in blood. Free fatty acid will be transported into liver and binds to albumin.

Excess acly CoA in the liver will be turned into Acetyl CoA. Acetyl CoA will form HMG-CoA that will be reduced into mevalonate with the help of HMG-CoA reductase.[26] In the liver mevalonat will be turned into cholesterol.

Elevation of cholesterol level will accelerates HDL uptake from the circulation and decrease Apo-A1 resulting in the lowering of serum HDL-cholesterol level. Alloxan is a diabetogenic agent that can be used in many experimental animals to induces diabetes using various dosages. Based on the previous study by Uddin *et al.* (2021) administration of alloxan 150 mg/kg BW significantly reduces HDL level in induced diabetic mice.[27]

Decrease of LDL-cholesterol level after the administration of sapodilla leaves extract can be attributed to the activity of flavonoid, alkaloid, saponin, tanin, polyphenol, quinon, and steroid. Flavonoid acts as exogenous antioxidant that prevents damage of cell caused by oxidative stress through direct and indirect mechanism. Directly through donating hydrogen ion so that toxic effect of free radicals can be neutralized and indirectly by enhancing expression of antioxidant gene.[28]

Sapodilla leaves contains flavonoid that is able to prevent oxidation of LDL. Flavonoid directly and indirectly inhibit HMG-CoA reductase resulting in the reduction of cholesterol synthesis. Inhibition of HMG-CoA reductase obstructs conversion of Acetyl-CoA into mevalonat in the cholesterol synthesis pathway resulting in subsiding cholesterol synthesis of the liver. Flavonoid is able to improve LCAT which can convert free cholesterol into more hydrophobic cholesterol esther. Cholesterol esther then binds with lipoprotein forming new HDL. Antioxidant will improve HDL-cholesterol by producing Apo-A1 which will be the enzyme cofactor for LCAT.[29] Elevation of Apo-A1 will improve HDL-cholesterol of serum.[30]

Alkaloid works as an antioxidant by donating hydrogen ion just like flavonoid.[31] It also inhibits pancreas lipase activity thereby increasing lipid secretion through feces, consequently absorption of lipid by the liver is inhibited and can not be turned into cholesterol.[32] Reduced pancreatic lipase activity can lower triglyceride deposits from small intestine as those enzyme are responsible in converting triglyceride into two monoglyceride and two free fatty acids that can enter blood vessel.[33]

Tannins can be used to lower blood glucose level by metabolizing glucose and lipid so that excess calorie can be avoided.[34] Tannin prevents absorption of lipid in intestine by interacting with mucosal proteins and intestinal epithelial cells.[35] Furthermore, tannin precipitates mucosal protein on small intestine surface, thus reducing the effectiveness of cholesterol and lipid absorption. Amino acid and protein from feed may be precipitated by tannin from sapodilla leaves resulting in disturbance of lipid absorption. Those process causes cholesterol transport by chylomicron to liver not directly proportional to the concentration of cholesterol in feed.

Polyphenol were reported to be capable to lower total cholesterol and inhibit atherosclerosis through its antioxidant activity.[36] Sapodilla leaves contains saponin that is able to lower cholesterol by hindering the reabsorption of bile acids that were synthesized from cholesterol by intestinal cells, thus causing bile acid to be excreted with feces and to compensate bile acid loss, cholesterol will be converted by liver into new bile acids, resulting in reduced cholesterol level in blood.

Diabetic mice were treated with single doses of *M. zapota* leaf extract (100 and 300 mg/kg BW) and Pioglitazone (2 mg/kg BW) for 14 days. *M. zapota* leaf extract at a dose of 300 mg/kg was found to be the most effective in maintaining a normal lipid profile. These results indicate that *M. zapota* leaves can improved plasma lipids, as stated in a study by Barbalho *et al.* (2015).[15] Pioglitazone is commonly used to treat type 2 diabetes, although the mechanism is not well understood. This drug lowers total cholesterol levels, triglyceride levels, low-density lipoprotein levels, and can increase high-density lipoprotein levels.[37]

CONCLUSION

From the above discussion it can be concluded that the ethanol extract of *M. zapota* leaves contains several phytochemical compounds including alkaloids, flavonoids, saponins, polyphenols, tannins, quinones, and steroids. *M. zapota* leaves extract (100 mg/kg and 300 mg/kg) exhibited a significant effect on improvement in protein lipid profiles, making it useful in the treatment of antihyperlipidemic.

AUTHORS' CONTRIBUTIONS

All authors conducted the study. Tridiganita Intan Solikhah supervised the experiment. All authors read and approve the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

1. Deepthi B, Sowjanya K, Lidiya B, Bhargavi RS, Babu PS. A modern review of diabetes mellitus: an annihilatory metabolic disorder. J Silico Vitr Pharmacol. 2017;3(1):1-5.
2. Malone JI, Hansen BC. Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite? Pediatr Diabetes. 2019;20(1):5-9.

3. Zhao F, Pan D, Wang N, Xia H, Zhang H, Wang S. Effect of chromium supplementation on blood glucose and lipid levels in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Biol Trace Elem Res. 2022;200:516-25.
4. Trautwein EA, Koppenol WP, De Jong A. Plant sterols lower LDL-cholesterol and triglycerides in dyslipidemic individuals with or at risk of developing type 2 diabetes; a randomized, double-blind, placebo-controlled study. Nutr Diabetes. 2018;8(1):1-13.
5. Pebriani R, Jafar N, Wahiduddin, Hidayanti H, Burhanuddin, Salamah U. The effect of extract of canarian nuts on reduction of total cholesterol levels of hyperglicemic rat. J Sci Res Med Biol Sci. 2021;2(1):19-29.
6. Cífková R, Krajčoviechová A. Dyslipidemia and cardiovascular disease in women. Curr Cardiol Rep. 2015;17(7):1-10.
7. Solikhah TI, Rani CA, Septiani M, Putra YA, Rachmah Q, Solikhah GP. Antidiabetic of Hylocereus polyrhizus peel ethanolic extract on alloxan induced diabetic mice. Iraqi J Vet Sci. 2022;36(3):797-802.
8. Solikhah TI, Setiawan B, Ismukada DR. Antidiabetic activity of papaya leaf extract (Carica Papaya L.) isolated with maceration method in alloxan-induces diabetic mice. Syst Rev Pharm. 2020;11(9):774-8.
9. Solikhah TI, Solikhah GP. Effect of Muntingia calabura L. leaf extract on blood glucose levels and body weight of alloxan-induced diabetic mice. Pharmacogn J. 2021;13(6):1450-5.
10. Charbonneau MS, Capoccia KL. Pioglitazone: Reviewed and renewed. ADCES Pract. 2022;10(4):30-5.
11. Khairullah AR, Solikhah TI, Ansori ANM. Medicinal importance of Kaempferia galanga L. (Zingiberaceae): A comprehensive review. J Herbmed Pharmacol. 2021;10(3):281-8.
12. Khairullah AR, Solikhah TI, Ansori ANM. A review of an important medicinal plant : Alpinia galanga (L.) willd. Syst Rev Pharm. 2020;11(10):387-95.
13. Rafif KA, Intan ST, Muhammad AAN, Mulyo RH. A review on phytochemistry and pharmacology of Eclipta alba L.: A valuable medicinal plant. Res J Biotechnol. 2022;17(3):134-9.
14. Safira A, Widayani P, An-najaaty D. A review of an important plants: Annona squamosa leaf. Pharmacogn J. 2022;14(2):456-63.
15. Barbalho SM, Bueno PCDS, Delazari DS. Antidiabetic and antilipidemic effects of manilkara zapota. J Med Food. 2015;18(3):385-91.
16. Karle PP, Dhawale SC, Navghare V V. Amelioration of diabetes and its complications by Manilkara zapota (L) P. Royen fruit peel extract and its fractions in alloxan and STZ-NA induced diabetes in Wistar rats. J Diabetes Metab Disord. 2022;7(1):1-10.
17. Balamurugan K, Nishanthini A, Mohan VR. Antidiabetic and antihyperlipidaemic activity of ethanol extract of Melastoma malabathricum Linn. leaf in alloxan induced diabetic rats. Asian Pac J Trop Biomed. 2014;4(Suppl 1):S442-8.
18. Jaiswal YS, Tatke PA, Gabhe SY, Vaidya AB. Antidiabetic activity of extracts of Anacardium occidentale Linn. leaves on n-streptozotocin diabetic rats. J Tradit Complement Med. 2016;7(4):421-7.
19. King A. Animal Models of Type 1 and Type 2 Diabetes Mellitus. Animal Mod. 2017.
20. Sanad FAA, Ahmed SF, El-Tantawy WH. Antidiabetic and hypolipidemic potentials of Solidago virgaurea extract in alloxan-induced diabetes type 1. Arch Physiol Biochem. 2022;128(3):716-23.
21. Ighodaro OM, Adeosun AM, Akinloye OA. Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. Medicina (B Aires). 2017;53(6):365-74.
22. Dunn FL. Management of dyslipidemia in people with type 2 diabetes mellitus. Rev Endocr Metab Disord. 2010;11(1):41-51.
23. Sung MH, Liao FH, Chien YW. Medium-chain triglycerides lower blood lipids and body weight in streptozotocin-induced type 2 diabetes rats. Nutrients. 2018;10(8):963.
24. Treviño S, González-Vergara E. Metformin-decavanadate treatment ameliorates hyperglycemia and redox balance of the liver and muscle in a rat model of alloxan-induced diabetes. New J Chem. 2019;43(45):17850-62.
25. YP, SS. Biochemistry, Lipase. StatPearls Publishing; 2022.
26. Gesto DS, Pereira CM, Cerqueira NM, Sousa SF. An atomic-level perspective of HMG-CoA-reductase: The target enzyme to treat hypercholesterolemia. Molecules. 2020;25(17):3891.
27. Uddin Zim AI, Khatun J, Khan MF, Hossain MA, Haque MM. Evaluation of in vitro antioxidant activity of okra mucilage and its antidiabetic and antihyperlipidemic effect in alloxan-induced diabetic mice. Food Sci Nutr. 2021;9(12):6854-65.
28. Guven H, Arici A, Simsek O. Flavonoids in our foods: a short review. J Basic Clin Heal Sci. 2019;3(2):96-106.
29. Yang Y, Trevethan M, Wang S, Zhao L. Beneficial effects of citrus flavanones naringin and naringenin and their food sources on lipid metabolism: An update on bioavailability, pharmacokinetics, and mechanisms. J Nutr Biochem. 2022;104:108967.
30. Cochran BJ, Ong KL, Manandhar B, Rye KA. APOA1: a protein with multiple therapeutic functions. Curr Atheroscler Rep. 2021;23(3):1-10.
31. Krishnamoorthy V, Chuen LY, Sivayogi V. Exploration of antioxidant capacity of extracts of Perna viridis, a marine bivalve. Pharmacogn Mag. 2019;15(Suppl 3):S402-9.
32. Liu TT, Liu XT, Chen QX, Shi Y. Lipase inhibitors for obesity: A review. Biomed Pharmacother. 2020;128:110314.
33. Bency TB, Murali R, Suriyaprakash TNK, Srinivasan N. A review on pancreatic lipase inhibitors from natural sources: A potential target for obesity. Curr Enzym Inhib. 2021;17(2):83-97.
34. Ajebli M, Eddouks M. The promising role of plant tannins as bioactive antidiabetic agents. Curr Med Chem. 2019;26(25):4852-84.
35. Morzel M, Canon F, Guyot S. Interactions between salivary proteins and dietary polyphenols: potential consequences on gastrointestinal digestive events. J Agric Food Chem. 2022;70(21):6317-27.
36. Zeb A. Concept, mechanism, and applications of phenolic antioxidants in foods. J Food Biochem. 2020;44(9):e13394.
37. Chait A, Goldberg I. Treatment of dyslipidemia in diabetes: recent advances and remaining questions. Curr Diab Rep. 2017;17(11):1-10.

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