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Effect of Longan Leaf Extract (*Dimocarpus longan* L.) on Total Cholesterol and Hepatic Histopathology in Type 2 Diabetes Mellitus Mice

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Abstract
Hypercholesterolemia occurring in type 2 diabetes mellitus can trigger chronic complications, one of which is liver damage. Longan leaves contain metabolites that function as antihyperlipidaemic agents and repair liver damage. This study used 24 male DDY mice divided into six groups: negative control (A), positive control (B), metformin (C), longan leaf extract at 28 mg/kg body weight (D), 42 mg/kg body weight (E), and 56 mg/kg body weight (F). Type 2 DM was induced orally with a high-fat diet (HFD) and alloxan administered intraperitoneally. Longan leaf extract was administered orally. Total cholesterol levels were measured using a cholesterol meter. Liver histological slides were prepared using paraffin methods and evaluated using a light microscope. Total cholesterol levels and liver histopathology were statistically significant. The results showed that the longan leaf extract significantly affected total cholesterol levels and liver histopathology ($p<0.05$). The 56 mg/kgBW dose of longan leaf extract yielded the best results for reducing total cholesterol levels by 17.25 and liver histopathology scores of 1.1. Therefore, longan leaf extract has the potential to be an antihypercholesterolemic agent and to improve liver damage.

Keywords: cholesterol level; diabetes mellitus; hepatic histopathology; longan leaf

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INTRODUCTION

Type 2 diabetes mellitus (DM) is a chronic metabolic disease characterised by high blood glucose levels or hyperglycaemia caused by insulin resistance (Rusdi, 2020). This condition also affects lipid metabolism, which is characterised by increased cholesterol levels in the blood. Diabetes has several types based on its pathologic mechanism, namely: Type 1 DM, Type 2 DM, and gestational DM, or diabetes that occurs during pregnancy (El Qahar, 2020). This disease has become a more significant global health issue with increasing prevalence. According to data from the *International Diabetes Federation* (IDF), Indonesia ranks fifth among countries with 19.5 million people living with diabetes in 2021 and is projected to reach 23.3 million by 2030. The *World Health Organisation* (WHO) predicts an increase in the prevalence of type 2 diabetes in Indonesia, from 8.4 million in 2000 to approximately 21.3 million by 2030 (PERKENI, 2021).

Lifestyle changes continuously influence the consumption patterns of foods containing excessive amounts of sugar. Consuming foods with excessive sugar content can increase blood glucose levels (Hendrawan *et al*., 2023). Excessive glucose levels can lead to the development of diabetes because the body cannot regulate glucose optimally. The process of glucose entering cells is controlled by insulin (Dewi & Asman, 2020). Insulin helps the body absorb glucose from the blood, thereby maintaining normal blood glucose levels. When the body produces insulin, but there is a disruption in the intracellular signalling pathway of the insulin receptor, the process of GLUT-4 translocation to the cell membrane is disrupted. As a result, glucose cannot enter the cell optimally (Decroli *et al*., 2022).

Obesity is one of the risk factors for type 2 diabetes mellitus (Widiasari *et al*., 2021). Obesity can increase the production of proinflammatory cytokines caused by the accumulation of saturated fat in the bloodstream (Syari *et al*., 2019). In addition to type 2 diabetes mellitus, obese individuals are at risk of having high cholesterol levels. An increase in circulating fat results in excess free fatty acids. This condition leads to an increase in the flow of free fatty acids to the liver and fat accumulation in muscle

cells. The accumulation of fatty acids in muscle cells disrupts the translocation of Glucose Transporter 4 (GLUT 4), leading to insulin resistance (van Gerwen *et al*., 2023).

Insulin resistance can trigger type 2 diabetes, causing peripheral adipocytes to undergo increased lipolysis (Guilherme *et al*., 2019). This process results in elevated levels of free fatty acids in the blood, which can lead to triglyceride accumulation in the liver. Fat accumulation in the liver may occur due to the release of free fatty acids into the bloodstream. Elevated levels of free fatty acids can disrupt glucose metabolism and worsen insulin resistance (Oktaviona *et al*., 2023).

Total cholesterol levels are the level of cholesterol in the blood, which consists of high-density lipoprotein (HDL) or unsaturated fat, low-density lipoprotein (LDL) or saturated fat, VLDL, and triglycerides (Fahreza *et al*., 2020). Hypercholesterolemia is a condition where cholesterol levels in the blood exceed normal limits. In hypercholesterolemia, elevated LDL levels can lead to plaque formation, narrowing of blood vessels, and an increased liver workload in processing fats (Meidayanti, 2021). Excessive fat accumulation can trigger an increase in the production of *reactive oxygen species* (ROS). Increased ROS can cause oxidative stress in hepatocyte cells, leading to cell degeneration and necrosis (Pangkahila *et al*., 2019).

Generally, synthetic drugs are used to treat diseases they suffer from, such as metformin, which is used to control diabetes mellitus. Synthetic drugs like biguanides have both short-term and long-term side effects (Susanti *et al*., 2016). Metformin, a synthetic drug, has side effects like digestive issues, insomnia, respiratory tract infections, and urinary tract dysfunction (Pane *et al*., 2021).

Using safer materials, such as natural materials, has fewer side effects, is cheaper, and is easier to obtain. One alternative herbal material that has potential as an antihyperglycaemic and antihyperlipidaemic is longan leaves (*Dimocarpus longan* L.). Longan is a plant belonging to the Sapindaceae family that contains bioactive compounds such as polyphenols, including flavonoids (Salamah and Widyasari, 2015). The highest concentration of these bioactive compounds is found in the leaves. According to research by Hilma *et al*. (2021), longan leaves contain secondary metabolites such as phenols and flavonoids.

Flavonoids are polyphenolic compounds that act as antioxidants, lowering cholesterol levels by inhibiting cholesterol biosynthesis. The process by which flavonoids lower cholesterol levels involves inhibiting the activity of the HMG-CoA enzyme (Ayunda and Malita, 2024). Flavonoids also exhibit antioxidant properties, which can help to repair cellular damage in liver tissue. Flavonoids work by stabilising hepatocyte cell membranes, preventing lipid peroxidation, and inhibiting the activation of inflammatory pathways that can damage liver tissue reductase (Al Amin *et al*., 2023).

Based on previous research, administration of longan leaf extract can reduce total cholesterol levels in male Wistar strain white rats (*Rattus norvegicus*) fed a high-fat diet. The study mentioned that longan leaf extract can influence the reduction of total cholesterol levels in experimental animals. Mice were used as experimental animals because they are closely related to humans and share similar physiology. This study's novelty lies in administering a *high-fat diet* (HFD) to experimental subjects conditioned with type 2 diabetes mellitus (DM) and longan leaf extract on total cholesterol levels and liver histopathology in type 2 DM mice. This study was conducted to determine the effect of longan leaf extract (*Dimocarpus longan* L.) on total cholesterol levels and liver histopathology in type 2 diabetic mice (*Mus musculus*).

MATERIALS AND METHODS

This study is an experimental study with a completely randomised design divided into six groups, namely the negative control group (no high-fat diet (HFD) + alloxan), positive control group (HFD + alloxan), metformin group (HFD + alloxan + metformin), and the treatment group with longan leaf extract (28, 42, and 56 mg/kgBW) with four replicates for each treatment. The study was conducted over 3 months, from February to April 2025, at the Biology Study Programme Laboratory, Faculty of Mathematics and Natural Sciences, Surabaya State University.

Extraction of longan leaves was carried out by collecting leaves with the criteria of being green, undamaged, and fresh, taken from the third node from the base of the stem. The leaves were washed and then drained. The leaves were dried for 7 days, then wrapped in newspaper, oven-dried for 3 days at 60°C, and ground into powder. During the maceration stage, the powdered simplisia was soaked in 96% ethanol solvent for 3 × 24 hours and filtered using filter paper. The maceration filtrate was evaporated using a rotary vacuum at 60°C until a 100% extract was obtained. The extract was weighed according to the 28, 42, and 56 mg/kgBW treatment doses and diluted in 1% sodium carboxymethyl cellulose (NaCMC).

This study used male mice of the Deutchland *Denken Yoken* (DDY) strain, aged 8–10 weeks and weighing 25–30 grams, obtained from PUSVETMA Surabaya. A total of 24 mice were selected based on the following criteria: white fur, clear red eyes, active behaviour, good health, and no physical defects. Before treatment, the mice were first acclimated for 7 days in plastic cages and fed CP511 (5% fat content) at a rate of 5 grams/day/rat and given ad libitum drinking water.

On day 0 after acclimatisation, total cholesterol levels were measured in all groups using the EasyTouch device. The HFD treatment consisted of a mixture of beef fat oil and duck egg yolk at a dose of 0.75 ml/day/mouse given to all groups. The HFD was administered orally via gavage for 14 days. On day 14, mice were induced with alloxan intraperitoneally at a dose of 110 mg/kg body weight, mixed with 0.1 M sodium citrate buffer. After 3 hours of alloxan induction, mice were given a 10% sugar solution for 3 days to prevent hypoglycaemia.

Blood glucose level measurements were performed to determine whether mice had developed type 2 diabetes mellitus (DM). Each blood glucose measurement is conducted after the mice have fasted for 8–12 hours. The device used to measure blood glucose and total cholesterol levels was the EasyTouch GCU. Blood was collected from the mice's tail veins using a blood lancet. The blood was dropped onto a glucose strip, and the results were recorded. A mouse is considered to have diabetes if its fasting blood glucose level is ≥126 mg/dL (Pasaribu *et al*., 2021). Total cholesterol levels were measured by dropping the blood onto a cholesterol strip, and the results appear on the screen. A mouse is considered to have high cholesterol if the level is >130 mg/dL (Mahmudah *et al*., 2024). Total cholesterol levels were measured on day 0, day 14, and day 30.

The mouse liver specimens were prepared using the paraffin method and stained. The liver was obtained by anaesthetising the mouse with chloroform and excising it. The liver organ was then fixed in 10% Neutral Buffer Formalin (NBF). The liver was trimmed and placed in a tissue cassette. Dehydration was performed by immersing the organ in alcohol at concentrations of 70% in four stages: two stages of 80%, 96%, and absolute alcohol, each for 30 minutes. The clearing process was performed by immersing the organ in xylol for two steps, for 15 minutes and overnight. Next, infiltration was performed by immersing the organ in paraffin-xylol for 30 minutes, followed by three steps of paraffin, each for 1 hour. The embedding process was performed by pouring paraffin into a base mould containing the organ and waiting for it to harden. Sectioning was performed using a microtome with a thickness of ± 4 µm. Lastly, slides were stained using HE staining and mounted using Entellan.

Liver preparations were observed using a light microscope. Histopathological change was evaluated using the Manja Roenigk Histopathology Scoring Model, and the percentage of liver damage was calculated in Table 1.

Table 1. Histopathology scoring based on Manja Roenigk (Soetrisno *et al*., 2019)

Level of Damage	Score
Normal	1
Parenchymatous degeneration	2
Hydrophilic Degeneration	3
Necrosis	4

Total cholesterol levels and liver histopathology data were analysed statistically using the Shapiro-Wilk normality test and the Levene's test for homogeneity of variances. Total cholesterol levels were analyzed using the One-Way ANOVA test ($p<0.05$) and Duncan's post-hoc test. Liver histopathology scores were analyzed using the Kruskal-Wallis test ($p<0.05$) and the Mann-Whitney post-hoc test.

RESULTS

Based on the research conducted, there were differences in total cholesterol levels between the control group and the treatment group. The data obtained consisted of measurements taken before HFD induction (day 0), after HFD (day 14), and after treatment (day 30), and the difference in total cholesterol levels after administration of longan leaf extract (Table 2).

Based on the ANOVA test ($p<0.05$), longan leaf extract has an effect on total cholesterol levels. Table 2 shows that group F, with a longan leaf extract dose of 56 mg/kgBW, was the most effective dose. Evaluation of liver histopathology scores showed differences in the level of damage between treatment groups. The assessment was performed using the Manja Roenigk Histopathology Scoring Model, which can be seen in Table 3.

Table 2. Total cholesterol levels for each treatment group.

Treatment	Total cholesterol level (mg/dL)			Difference (mg/dL)
	H0	H14	H30	
A	104 ± 1.22	106 ± 2.28[a]	110.75 ± 1.79[a]	↑ 4 ± 1.63
B	102.25 ± 1.09	156.25 ± 3.27[b]	151.25 ± 3.03[c]	↓ 5 ± 0.82
C	104.25 ± 1.92	151.75 ± 5.40[b]	139 ± 4.77[b]	↓ 12.25 ± 0.96
D	103.75 ± 1.48	157 ± 5.10[b]	151 ± 5.52[c]	↓ 6 ± 0.82
E	103.25 ± 1.48	156 ± 5.61[b]	143.5 ± 4.72[c]	↓ 12.5 ± 1.29
F	102.5 ± 1.66	152.25 ± 5.31[b]	135 ± 5.79[b]	↓ 17.25 ± 1.50

Note: Different subscript letters indicate significant differences ($p<0.05$). The ↑ symbol indicates an increase, while ↓ indicates a decrease. H0 = day before HFD, H14 = day after HFD, H30 = day after extract. A = negative control, B = positive control (HFD+alloxan), C = Metformin group (HFD + alloxan + metformin), D = HFD + alloxan + 28 mg/kg body weight longan leaf extract, E = HFD + alloxan + 42 mg/kg body weight longan leaf extract, F = HFD + alloxan + 56 mg/kg body weight longan leaf extract).

Table 3. Evaluation of histopathological scores of the liver for each treatment.

Treatment	Liver histopathology score
A	1.25 ± 0.10[ab]
B	2.8 ± 0.16[c]
C	1.35 ± 0.10[ab]
D	1.5 ± 0.12[b]
E	1.25 ± 0.25[ab]
F	1.1 ± 0.12[a]

Note: Different subscript letters indicate significant differences ($p<0.05$). A = negative control, B = positive control (HFD+alloxan), C = Metformin group (HFD+alloxan+metformin), D = HFD+alloxan+longan leaf extract 28 mg/kgBW, E = HFD + alloxan + longan leaf extract 42 mg/kgBW, F = HFD + alloxan + longan leaf extract 56 mg/kgBW.

Based on the Kruskal-Wallis test ($p<0.05$), there was a significant effect of various treatments on the histopathological condition of the liver of type 2 DM mice. Based on Table 3, it can be concluded that there was a significant difference in the 56 mg/kgBW (F) dose group compared to other treatment groups. The F treatment group with a dose of 56 mg/kgBW was the optimal dose for the average histopathological score of the liver, with a score of 1.1 ± 0.12. The histopathological observations of the livers of type 2 diabetic mice can be seen in Figure 1.

Based on Figure 1, the results of histopathological observations of the livers of type 2 DM mice in the negative control (A), metformin group (C), longan leaf extract at a dose of 42 mg/kgBW (E), and a dose of 56 mg/kgBW (F) showed low levels of cell degeneration and necrosis. In the group treated with 28 mg/kg body weight of longan leaf extract (D), moderate levels of cellular degeneration and necrosis were observed. Meanwhile, in the negative control group (B), high levels of cellular degeneration and necrosis were observed. Additionally, in the positive control group (B), there was a high degree of cell degeneration and necrosis.

DISCUSSION

Based on this study, induction of HFD for 14 days and alloxan 110 mg/kgBW can increase total cholesterol levels in positive control mice (B) and treatment groups (C, D, E, and F), with an average increase of 51.45 mg/dL. This increase was caused by the administration of an HFD at a dose of 0.75 ml/g body weight, consisting of beef fat oil and duck egg yolk. The elevated total cholesterol levels were due to the accumulation of cholesterol and saturated fat from the 14-day HFD administration. Excessive consumption of saturated fat can lead to increased total cholesterol levels and result in hypercholesterolemia (Yuningrum *et al*., 2022).

Intraperitoneal injection of alloxan at a dose of 110 mg/kgBW caused damage to pancreatic beta cells, resulting in the mice developing type 2 diabetes mellitus. Diabetes mellitus is characterised by fasting blood glucose levels >126 mg/dL. In this study, alloxan induction was performed on day 15 in groups B, C, D, E, and F. Fasting blood glucose levels were measured on day 17, showing an average of 149 mg/dL. These results indicated that the mice had developed type 2 diabetes mellitus. During induction, alloxan enters the cytosol, where it is recognised as glucose by GLUT2, triggering a redox reaction that produces hydroxyl groups (OH). These hydroxyl groups then cause depolarisation of the pancreatic beta cell membrane and increase Ca+ ion levels, leading to damage to pancreatic beta cells (Adhitama *et al*., 2023).

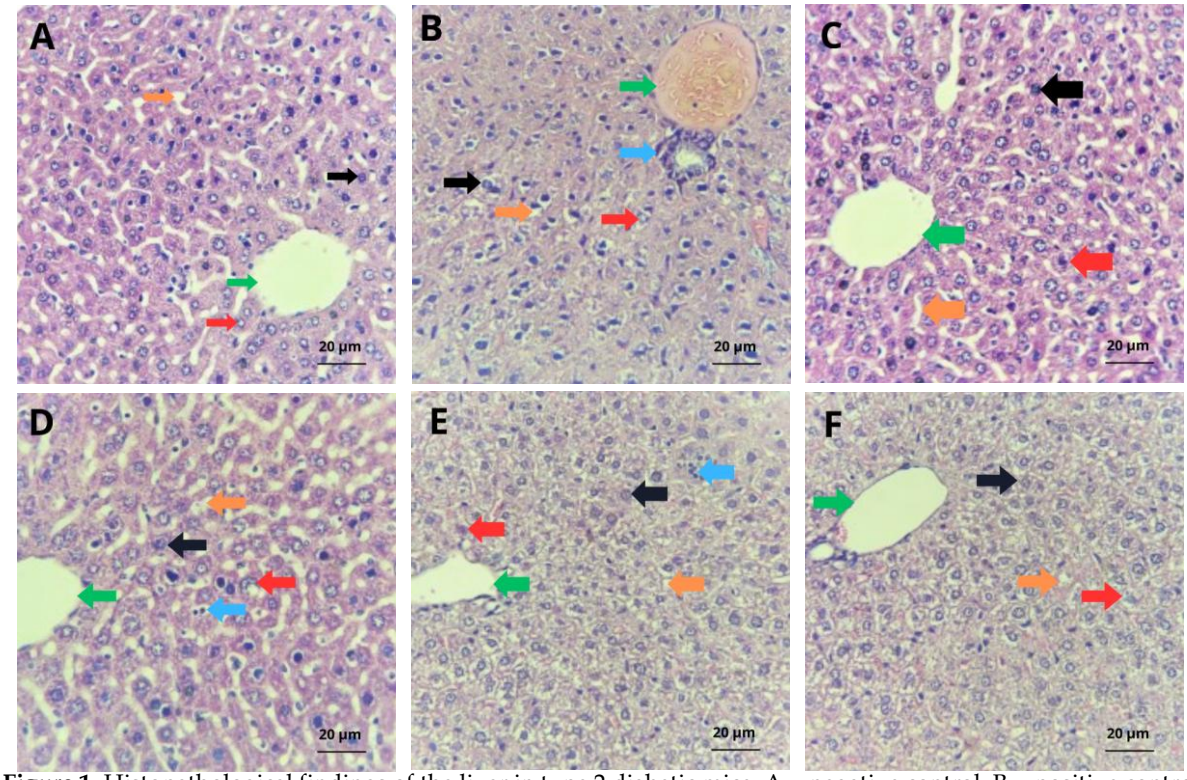

Figure 1. Histopathological findings of the liver in type 2 diabetic mice. A = negative control, B = positive control (HFD + alloxan), C = Metformin group (HFD + alloxan + metformin), D = HFD + alloxan + 28 mg/kg body weight of longan leaf extract, E = HFD + alloxan + longan leaf extract 42 mg/kgBW, F = HFD + alloxan + longan leaf extract 56 mg/kgBW). Green arrow = central vein, yellow arrow = sinusoid, black arrow = normal cell, red arrow = cellular degeneration, blue arrow = cellular necrosis.

Increased total cholesterol levels in DM patients are associated with increased gluconeogenesis. This condition causes dysfunction in the conversion of acetyl-CoA to malonyl-CoA in the liver, resulting in the accumulation of free fatty acids (Murray *et al*., 2003). The amount of free fatty acids is related to the intake of cholesterol and saturated fat consumed. High intake of cholesterol and saturated fats leads to fat accumulation in the liver and increased acetyl-CoA, which directly results in elevated total cholesterol levels in the blood (Yuningrum *et al*., 2022).

Hypercholesterolemia accompanied by hyperglycaemia can cause liver damage, characterised by changes in its histological structure (Setiadi *et al*., 2020). In the negative group (A), many normal liver cells with round nuclei and uniformly red cytoplasm were found. In contrast, the positive control group (B) exhibits a high degree of cellular damage, with many liver cells showing parenchymal degeneration (blurred boundaries between the nucleus and cytoplasm, swollen cells, cloudy cytoplasm), hydropic degeneration (presence of water vacuoles in the cytoplasm), and cell necrosis (swelling and rupture of cells) caused by the administration of HFD without treatment. If hyperglycaemia and hypercholesterolaemia persist, there will be an increase in reactive oxygen species (ROS). These ROS can cause damage that begins with parenchymal degeneration, hydropic degeneration, and necrosis. Cell degeneration and necrosis can reduce the liver cells' ability to regenerate (Fitriani *et al*., 2020).

On day 18, mice in groups C, D, E, and F were each given treatment. Group C was given metformin, group D was given longan leaf extract at a dose of 28 mg/kgBW, group E was given longan leaf extract at a dose of 42 mg/kgBW, and group F was given longan leaf extract at a dose of 56 mg/kgBW. The treatment was administered over 14 days, with results showing a decrease in total cholesterol levels. Group F exhibited the greatest reduction, with an average decrease from 152.25 ± 5.31 mg/dL to 135 ± 5.79 mg/dL.

The decrease in total cholesterol levels after treatment with ambarella leaf extract was suspected due to its flavonoid content. Flavonoids are polar, making them more soluble in 96% ethanol, which is also polar (Wu *et al*., 2023). The flavonoid content in longan leaves can inhibit the cholesterol synthesis process. Flavonoid compounds lower cholesterol levels by inhibiting the activity of HMG-CoA reductase, which reduces cholesterol synthesis and increases the number of LDL receptors in liver cell membranes, thereby lowering total cholesterol levels in the blood (Mahdavi *et al*., 2020).

The repair of liver cell damage occurs as a result of a decrease in blood cholesterol levels due to a reduction in the number of free radicals in the liver. Longan leaf extract contains flavonoids, which act as antioxidants. Flavonoids can capture and neutralise free radicals by breaking the free radical reaction by donating hydrogen atoms, thereby forming antioxidant radicals with more stable properties. In addition to flavonoids, longan leaf extract contains tannin compounds that act as hepatoprotective agents by enhancing antioxidant activity and inhibiting the cell death pathway caused by oxidative stress (Gonfa *et al*., 2025).

Metformin is a drug commonly used to treat type 2 diabetes mellitus by increasing the activity of *AMP-activated protein kinase* (AMPK), thereby improving insulin sensitivity and reducing gluconeogenesis in the liver (Kristófi and Eriksson, 2021). The reduction in blood glucose levels, cholesterol levels, and free radicals can suppress oxidative stress in liver tissue. This condition ameliorated damage to liver tissue. On the other hand, longan leaf extract (*Dimocarpus longan* L.) contains bioactive compounds such as flavonoids, saponins, and tannins, which provide important antihyperglycaemic, antihypercholesterolemic, and antioxidant effects for patients with type 2 diabetes (Odama *et al*., 2025). Although metformin and longan leaf extract affected total cholesterol levels and liver histopathology, metformin is known to have side effects on the body. Longan leaf extract serves as an alternative, offering cellular protection and being safer than metformin. A dose of 56 mg/kg body weight of longan leaf extract was the most effective for total cholesterol levels and liver histopathology. Therefore, further research on the use of longan leaf extract as an alternative treatment for type 2 diabetes is highly recommended to find more effective treatment solutions.

CONCLUSION

Longan leaf extract affects total cholesterol levels and histopathology of the liver in mice with type 2 diabetes mellitus. A dose of 56 mg/kgBW of longan leaf extract was the most effective dose for reducing total cholesterol levels and improving liver histopathology in mice with type 2 diabetes mellitus. Therefore, longan leaf extract has potential as a treatment for hypercholesterolemia and for improving liver histopathology in type 2 diabetes mellitus.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest during the writing of this study.

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