Food Research 10 (3) : 119 - 126 (June 2026)
Journal homepage: https://www.myfoodresearch.com

FOOD RESEARCH

RESEARCH PAPER

Investigating *Glycine max* (soybean) seed extract and *Zingiber officinale* (ginger) rhizome as new anti-dyslipidemic agents

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Article history:
Received: 17 April 2025
Revised: 30 May 2025
Accepted: 19 September 2025
Published: 20 May 2026

Keywords:
Anti-dyslipidemia,
Ginger,
Soybean,
Lipid profile

DOI:
https://doi.org/10.26656/fr.2017.10(3).098

Abstract

Dyslipidemia is linked to diabetes mellitus (DM) as a risk factor of cardiovascular disease. Low levels of high-density lipoprotein cholesterol (LDLc) and a rising lipid profile are the main symptoms of dyslipidemia. Functional foods like *Glycine max* and *Zingiber officinale* have been empirically utilized to treat a variety of diseases. However, the effectiveness of herbs to prevent dyslipidemia in DM has not yet been fully established. This study aimed to examine the anti-dyslipidemia effects of *G. max* seed and *Z. officinale* rhizome extract on rats with diabetes. Diabetic rats (Sprague Dawley) were induced by a single dose of 25 mg/kg BW intraperitoneal streptozotocin, high fructose, and high lipid diet. The experimental animals were divided into 6 groups, and each group consisted of 5 rats. *Glycine max* (5000 mg/kg bw), *Z. officinale* (500 mg/kg bw), and their combination with two different doses were administered orally for four weeks. A blood sample was taken, and a spectrophotometer was used to assess the serum lipid profile. One-way ANOVA was used to evaluate the data, and then the LSD test ($p<0.05$) was performed. The administration of *G. max, Z. officinale* and their combination decreased total cholesterol levels up to 20% compared to the control group ($p<0.05$), while triglyceride levels were lowered by 40%–60% ($p<0.05$). LDLc levels dropped by approximately 40%-70% in the test group ($p<0.05$), and non-HDLc levels decreased about 20%-50% ($p<0.05$). Meanwhile, *Z. officinale* could raise HDLc levels only by roughly 10% ($p<0.05$). Polyphenol of *Z. officinale* and isoflavone from *G.max* were implicated in anti-dyslipidemia. The combination *of G. max* seed extract and *Z. officinale* rhizome can reduce LDLc levels, triglycerides, non-HDLc and total cholesterol in diabetic rats; however, *Z. officinale* extract can only raise HDL levels.

1. Introduction

Dyslipidemia in diabetes mellitus is associated with cardiovascular disease. Dyslipidemia is a lipid metabolic disorder characterized by changes in the lipid component of plasma (Soegondo *et al*., 2006). According to the Centers for Disease Control and Prevention (CDC), between 70-97% of people with diabetes have dyslipidemia (Huang *et al*., 2014; Ma'rufi *et al*., 2014). Complications of dyslipidemia are the main cause of mortality in patients with diabetes mellitus (DM). In the era of the COVID-19 pandemic, one of the most prevalent comorbidities in COVID-19 patients is diabetes mellitus, which increases the risk of mortality from COVID-19. Dyslipidemia is increased due to a decrease in insulin secretion caused by DM, leading to lipase activation (Nirosha, 2014). This condition accelerates the lipolysis of adipose tissue (Jonathan *et al*., 2017). Blood glucose regulation is essential for reducing diabetic complications in individuals with diabetes.

Oral anti-diabetes (OAD) medications are commonly used to control blood glucose levels in people with DM and associated complications (Goodman *et al*., 2022). These medications reduce insulin resistance and increase insulin secretion (Huang *et al*., 2014). However, DM patients often experience side effects as a result of taking OAD medications (Goodman *et al*., 2022). Therefore, people are increasingly seeking natural alternative medicinal sources, such as herbs. Herbs are gaining popularity in medicine due to their fewer side effects and holistic therapy benefits.

Functional foods like *Z. officinale* (ginger) and *G. max* (soybean) have empirically shown efficacy in

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treating various diseases (Kang et al., 2023). Animal experiments have demonstrated that *G. max* has a hypoglycemic effect and improves the lipid profile in diabetic mice (Villegas *et al.*, 2008; Ng, 2011). The main active ingredients in *G. max* are predicted to be isoflavone compounds, such as genistein and daidzein (Mezei *et al.*, 2003). On the other hand, *Z. officinale* rhizome contains gingerol and shogaol, which have antioxidant and anti-hyperlipidemic properties (Nammi *et al.*, 2009; Li *et al.*, 2012). Currently, research predominantly focuses on evaluating the bioactivity of single herbs, with testing of combinations of herbs being uncommon. There is still incomplete research on the use of *Z. officinale* rhizome and *G. max* seed in preventing dyslipidemia in diabetic patients. This study aimed to examine the anti-dyslipidemic properties of *G. max* and *Z. officinale* in diabetic rats.

2. Materials and methods

2.1 Preparation of Glycine max and Zingiber officinale extract

Zingiber officinale and *G. max* rhizome were acquired from Laboratory UPT Herba Materia Medika Batu Malang, Indonesia, with certificate numbers 074.241/102.7/2017 and 074/211/201.7/2017 as a raw material. In brief, *Z. officinale* rhizome powder (50 g) was extracted using an aqueous solvent (250 mL) and the infusion process. Meanwhile, 100 mL of water was used to boil 80 g of *G. max* seeds, and a blender was used to minimize the size of the seeds. For this reason, a filtration process was used to separate the extract from its waste. When a concentrated extract was produced, both extracts were evaporated.

2.2 Animals and treatment

Male Sprague Dawley (SD) rats weighing between 180 and 200 grams were obtained from Gajah Mada University in Yogyakarta, Indonesia. The study was carried out in compliance with ethical principles that were authorized by the Brawijaya University, Malang, Indonesia, Commission of Ethical Research, under certificate number 823-KEP-UB. The SD rats were kept apart in an autonomously regulated environment with a temperature of 25±1°C and a light-dark cycle of 12:12 hours. Prior to the studies, the SD rats were given standard meals and unlimited water, and were fasted for the entire night. Every two days, food for the normal diet (ND) and the high-fructose high-lipid diet (HFHLD) was combined freshly.

Diabetes was induced in rats by feeding them a high-fat and high-lipid diet (HFHLD) combined with a single intraperitoneal injection of streptozotocin 25 mg/kg. Rats were diagnosed with diabetes if their fasting blood glucose level exceeded 126 mg/dL (Alharbi *et al.*, 2022). Rats used in the experiment were divided into six groups, each including five rats. HFHLD was administered for eight weeks to the treatment and diabetes groups, whereas ND was given to the control group. Four treatment groups were assigned; the first received 5000 mg/kg BW of extract from *G. max*, the second received 500 mg/kg BW of extract from *Z. officinale*, the third received their combinations of 2500:250 mg/kg BW (combination 1), and the fourth received their combinations of 5000:500 mg/kg BW (combination 2) for a period of four weeks. The selection of dose was based on Nammi's (2009) and Mustofa *et al.*'s (2010) research studies with slight modifications. Food consumption and body weight were calculated every week. Following an overnight fast, intracardiac blood samples were obtained. A blood sample was immediately centrifuged at 4,500 rpm. After being separated, the serum was kept at -20°C.

2.3 Blood glucose assay

After an overnight fast, blood samples were taken from the tail vein. A glucometer that is sold commercially (Accu Check) was used to measure them right away.

2.4 Total cholesterol level measurement

Total cholesterol was measured using the Cholesterol Oxidase-Peroxidase Aminoantipyrine (CHOD-PAP) method and analyzed using a spectrophotometer. Approximately 10 μL of serum was put into the test tube, and 1 μL of cholesterol test reagent and 10 μL of standard cholesterol were added, then mixed and let stand for 5 min at 37°C. The absorbance value is measured at $\lambda = 500$ nm.

2.5 Triglyceride levels measurement

Serum triglyceride levels were measured using the GPO-PAP method and evaluated using a spectrophotometer. A 10 μL aliquot of serum was transferred into a test tube. Next, 1 mL of Triglyceride test reagent and 10 μL of standard Triglyceride were added, then mixed and let stand for 5 min at 37°C. The absorbance value is measured at $\lambda = 500$ nm.

2.6 Low density lipoprotein cholesterol levels measurement

LDLc levels were determined indirectly using the Friedewald formula involving other lipid parameters such as HDLc, Total Cholesterol (TC), and Triglycerides (TG), with the formula:

$$\text{LDLc (mg/dL)} = \text{TC} - (\text{HDLc} + \text{TG}/5)$$

https://doi.org/10.26656/fr.2017.10(3).098

2.7 High density lipoprotein cholesterol level measurement

Serum HDLc levels were measured using the GPO-PAP method and evaluated using a spectrophotometer. A 0.2 mL serum sample was combined with 0.5 mL of reagent A (Cholesterol HDL kit) in a tube, followed by centrifugation for 10 min at 4000 rpm at room temperature, after which the supernatant was collected. The supernatant was then mixed with distilled water, the HDLc standard (S), and reagent A (HDLc kit) in a tube. The mixture was incubated for 30 min at room temperature, and the absorbance was measured at λ = 500 nm.

2.7 Non-high density lipoprotein cholesterol levels measurement

Non-HDL levels in the serum were calculated as total cholesterol (TC) minus HDL level, as shown in the formulae below:

$$\text{Non-HDLc (mg/dL)} = \text{TC-HDLc}$$

2.8 Statistical analysis

The data were presented as means ± standard deviation (SD). The statistical analysis was performed using One-way ANOVA. When comparing means, the least significant difference (LSD) test was used, and a value of $p < 0.05$ was deemed statistically significant.

3. Results and discussion

3.1 The effect of Glycine max, Zingiber officinale and their combination on body weight, food consumption and glucose level of diabetic rats

After treatment, food consumption decreased for the diabetic group (Table 1). However, there was no significant difference in body weight loss between the test group and the diabetic group. Oral administration of *G. max* and combination-2 significantly reduced fasting blood glucose (FBG) levels compared to the diabetic group ($p \leq 0.05$).

3.2 The effect of Glycine max, Zingiber officinale and their combination on the total cholesterol level of diabetic rats

Administration of 500 mg/kg BW of *Z. officinale* rhizome and 5000 mg/kg BW of *G. max* seed extract effectively decreased serum total cholesterol levels in diabetic rats by 10% and 15%, respectively, when compared to the diabetic group ($p<0.05$) (Figure 1). Meanwhile, the combination of groups 1 and 2 reduced total cholesterol levels more strongly by 25% and 20%, respectively, compared to the diabetic group ($p<0.05$).

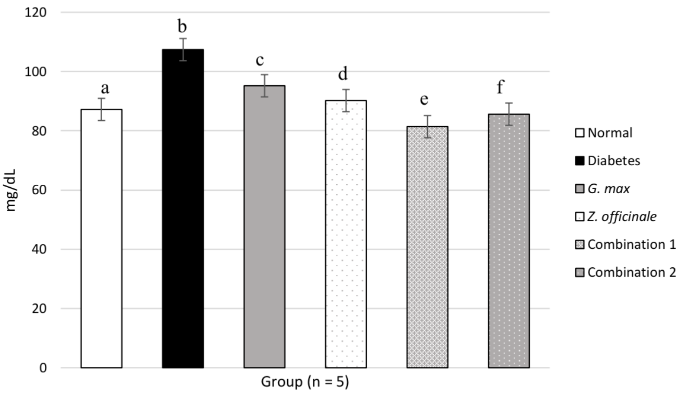

Figure 1. Histogram of total cholesterol levels in DM rats treated with *G. max*, *Z. officinale* extracts and their combination. Bars with different notations are statistically significantly different ($p<0.05$, LSD test).

Oral administration of *G. max* seed extract, *Z. officinale* rhizome, and their combination decreased serum total cholesterol levels. This effect was related to active substances that worked as anti-hyperlipidemia and antioxidants. Isoflavone, which exists in *G. max* seed extract, can reduce cholesterol levels by blocking the mechanism of the HMG-CoA reductase pathway, which decreases the production of cholesterol in the liver (Lichtenstein, 1998; Ng, 2011; Franz, 2012). Additionally, *G. max* extract can prevent lipolysis by preventing the saponin-regulated hormone-sensitive lipase (HSL) activation in adipose tissue (Lichtenstein, 1998; Ng, 2011).

The rhizome extract of *Z. officinale* has polyphenol chemicals that can raise the enzyme 7-α-hydroxylase and cause alterations in hepatic cholesterol to bile salts, which lowers the production of hepatic cholesterol (Alharbi *et al.*, 2022). In order to prevent oxidative

Table 1. Body weight, food consumption, blood glucose of diabetic rat.

n = 5	Normal	Diabetic	*G. max*	*Z. officinale*	Comb 1	Comb 2
Body Weight (g)	285.4±18.6	246.5±26.5	217.2±19.9	224.3±19.0	254.6±20.7	233±19.3
Food consumption (%)	74.7±8.0	68.3±13.0	894±8.0	87±11.0	72±27.0	78.5±27.0
FBG pre-treat (mg/dL)	105.4±7.5	201.3±35	182.6±43.1	168.5±35.8	205.8±56.5	163.5±11.5
FBG post-treat (mg/ dL)	105.4±7.5^{a}	139.0±14.9^{b}	109.0±13.2^{c}	132.3±17.9^{b}	129.5±9.4^{b}	124.0±12.5^{d}

Values are presented as mean±SD. Values with different superscripts in the same row are statistically significantly different ($p<0.05$, LSD test).

https://doi.org/10.26656/fr.2017.10(3).098

damage to pancreatic β-cells and preserve insulin secretion, phenolic compounds found in ginger, like shogaol and gingerol, have an antioxidant action by removing superoxide anion (Dugasani *et al.*, 2010)

3.3 The effect of Glycine max, Zingiber officinale and their combination on the triglyceride level of diabetic rats

Oral administration of 500 mg/kg BW of *Z. officinale* and 5000 mg/kg BW of *G. max* seed extract effectively decreased blood triglyceride levels in rats with a diabetic model by 40% and 50%, respectively, when compared to the diabetic group ($p<0.05$) (Figure 2). Meanwhile, the combination of groups 1 and 2 lowered triglyceride levels by the same value (60%) compared to the diabetic group ($p<0.05$).

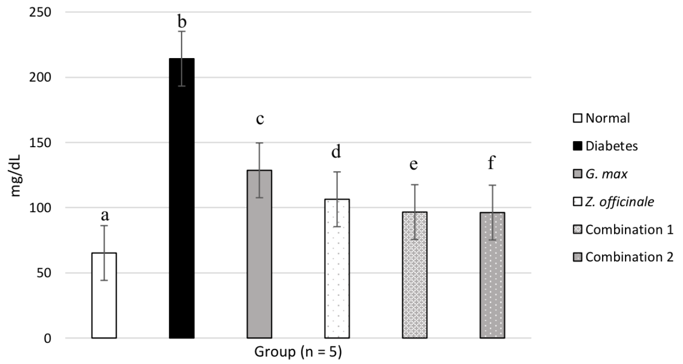

Figure 2. Histogram of triglyceride levels in DM rats treated with *G. max*, *Z. officinale* extracts and their combinations. Bars with different notations are statistically significantly different ($p<0.05$, LSD test).

In a diabetic rat model, triglyceride levels were reduced by *G. max* seed extract*, Z. officinale* rhizome, and their combination. Herbs that function as insulin sensitizers, insulin secretagogues and anti-hyperlipidemia agents may have an active ingredient that regulates this effect (Dugasani *et al.*, 2010; Purnomo *et al.*, 2021; Alharbi *et al*., 2022). *G. max* extract stimulates pancreatic insulin β-cell release, which is regulated by the active ingredient isoflavones (Villegas *et al*, 2008; Mezei, 2003). The production of insulin, which is sufficient to activate lipoprotein lipase (LPL) to catabolize chylomicrons and very low density lipoprotein (VLDL), however, did not increase triglyceride levels (Guyton, 2014). Triglycerides can also be bound by the isoflavone in soybean extract, which reduces their absorption in the intestines (Ng, 2011; Purnomo *et al*, 2022). Isoflavones are also able to reduce insulin resistance by increasing the expression of glucose transporter type 4 (GLUT-4), glucose uptake into cells can be increased, therefore lipolysis is prevented (Ng, 2011).

The antioxidant activity of *Z. officinale* rhizome extract is regulated by phenolic active ingredients such as shogaol and gingerol. Phenolic acids have a function as antioxidants by absorbing superoxide anions from free radicals, preventing oxidative damage to pancreatic β-cells, and preserving their functionality (Dugasani *et al.*, 2010). The phenolic content in *Z. officinale* rhizome extract increases insulin secretion through inhibition of DPP-4 and alpha-glucosidase (Purnomo *et al.*, 2021). Moreover, LPL in the endothelium of blood vessels remains active in catabolizing triglycerides in VLDL and chylomicron (Rani *et al.*, 2011). Furthermore, phenolic compounds can lower blood sugar by enhancing the absorption of glucose into cells through an increase in GLUT-4 expression (Yiming *et al.*, 2012).

3.4 The effect of Glycine max, Zingiber officinale and their combination on the low-density lipoprotein cholesterol level of diabetic rats

The administration of 500 mg/kg BW *Z. officinale* rhizome extract and 5000 mg/kg BW *G. max* seed extract successfully decreased the LDLc serum levels of diabetic rats by approximately 60% and 70%, respectively, compared to the diabetic group ($p<0.05$) (Figure 3). The combination of 1 and 2 lowered the LDLc levels of DM rats by approximately 40% and 65%, respectively, in comparison to the diabetic group ($p<0.05$).

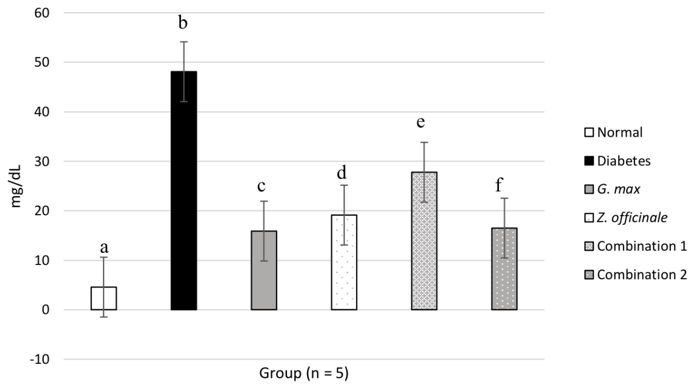

Figure 3. Histogram of LDLc Levels in DM Rats Treated with *G. max, Z. officinale* Extracts and their Combination. Bars with different notations are statistically significantly different ($p<0.05$, LSD test).

The active components in *G. max* extract have the ability to lower LDLc levels by acting as insulin secretagogues and antioxidants. Soybean isoflavone chemicals have antioxidative properties, which means they can shield pancreatic β-cells against apoptotic and pro-inflammatory cytokines (Lafuente *et al*, 2009; Terashima *et al.*, 2012). Sufficient insulin levels can inhibit lipolysis; therefore, LDLc levels do not increase. Furthermore, isoflavones have the ability to activate PPAR-α (Peroxisome Proliferator-activated Receptor-α), which is involved in lipid metabolism. Furthermore, they can control LDLc levels by lowering the production of VLDL (Mezei *et al.*, 2003). Saponin in soybeans increases insulin levels by regenerating damage to β-

https://doi.org/10.26656/fr.2017.10(3).098

cells in the pancreas. Through LPL inhibition, increasing insulin hormone output will lower blood levels of free fatty acids (Mezei *et al.*, 2003; Terashima *et al.*, 2012). The reduction in free fatty acids results in a decrease in LDL levels in the blood (Ilha *et al.*, 2020). Phytosterols in soybeans have anti-lipemic action by preventing the formation of HMG CoA reductase; cholesterol synthesis is inhibited, and there is a decrease in the conversion from VLDL to LDL (Samuel *et al.*, 2012; Ilha *et al.*, 2020). This process is responsible for the blood's decreased LDL level. Furthermore, according to earlier studies, the phytosterol components in ginger, particularly stigmasterol, have the ability to inhibit the Dipeptidyl Peptidase-4 (DPP-4) enzyme, maintaining insulin secretion (Purnomo *et al.*, 2021). Adequate insulin levels will reduce the breakdown of adipose tissue and LDL (Hey *et al.*, 2006; Terashima *et al.*, 2012; Ilha *et al.*, 2020).

Antioxidants, insulin sensitizers, and anti-lipemic active ingredients found in the two herbs regulate this action (Handayani *et al.*, 2018; Purnomo *et al.*, 2023). *Z. officinale* has a gingerol molecule that functions as an antioxidant to shield the pancreatic β-cells from damage caused by free radicals. This also allows for the maintenance of insulin hormone secretion (Dugasani *et al*, 2010; Alharbi *et al*, 2022). When hormone-sensitive lipase (HSL) is inhibited by enough insulin, the blood's supply of free fatty acids decreases (Jaworski *et al.*, 2007; Sears *et al.*, 2015). Reducing blood levels of free fatty acids will lessen the liver's production of TG, which will lower LDLc synthesis (Zhang *et al.*, 2012; Brown *et al.*, 2017). In addition, the polyphenol compounds in ginger also have anti-lipemic properties, which can reduce LDLc levels by increasing the activity of the 7-α-Hydroxylase enzyme in bile acid biosynthesis; most of the cholesterol is converted into bile acids (Yiming *et al.*, 2012).

3.5 The effect of Glycine max, Zingiber officinale and their combination on high density lipoprotein cholesterol level of diabetic rats

The treatment of 500 mg/kg BW of *Z. officinale* rhizome extract significantly increased HDLc levels by about 10% ($p<0.05$) (Figure 4). In contrast, the administration of 5000 mg/kgBW of *G. max* seed extract and the combination of the two reduced HDLc levels by approximately 6% and 10%, respectively ($p<0.05$).

The rhizome extract of *Z. officinale* elevated serum HDLc levels in diabetic rats. Ginger's active ingredient, which has antioxidant and insulin-sensitizing properties, regulates this action (Purnomo, 2018). *Z. officinale* has a gingerol molecule that acts as an antioxidant to shield pancreatic β-cells from harm, hence preserving insulin output. Sufficient amounts of insulin will reduce levels of free fatty acids in the blood, thereby increasing the activation of the LCAT, which plays a role in the HDL maturation process. The shogaol compound in ginger can reduce blood glucose levels by enhancing insulin sensitivity through the mechanism of decreasing TNF-α levels in obesity or hyperlipidemia (Dugasani *et al.*, 2010). Increasing insulin sensitivity will inhibit HSL, resulting in a decrease in free fatty acids in the blood circulation; moreover, the process of HDLc formation is not disturbed (Kang *et al.*, 2009; Yiming *et al.*, 2012).

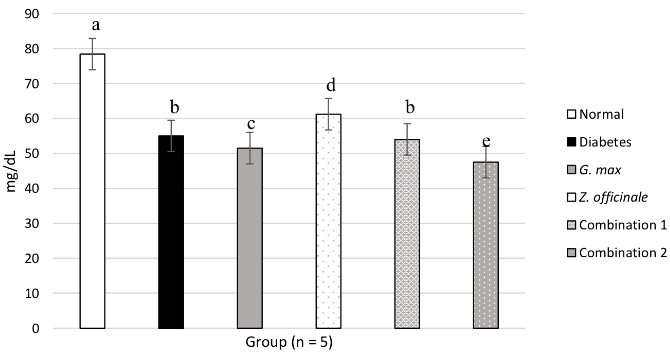

Figure 4. Histogram of HDLc levels in DM rats treated with *G. max*, *Z. officinale* extracts and their combinations. Bars with different notations are statistically significantly different ($p<0.05$, LSD test).

The administration of *G. max* extract on diabetic rats actually decreased serum HDL levels. The decrease in HDL levels may occur due to the inadequate dose and duration of administration of herbal extracts. Another factor is the herbal extraction process, which cannot optimally extract the active substance. Based on the previous study, the solvent used to extract the active substance in soybeans is methanol 80%. The solvent is semi-polar, and it is effective at taking both polar and non-polar active compounds. Whereas in this study, the extraction used water as a polar solvent, some non-polar compounds were not extracted well (Mustofa *et al.*, 2010; Kuligowski *et al.*, 2017).

3.6 The effect of Glycine max, Zingiber officinale and its combination on non-high density lipoprotein cholesterol level of diabetic rats

The oral administration of *G. max* 5000 mg/kg bw, *Z. officinale* 500 mg/kg bw and their combination decreased non-HDLc level by 20%, 40% and 50%, respectively, compared to the diabetic group ($p<0.05$). In contrast, non-HDLc levels in diabetic groups were elevated approximately 6-fold compared to the normal group ($p<0.05$) (Figure 5).

Glycine max contains an active compound, isoflavone, that reduces cholesterol level through inhibition of HMG CoA reductase, decreasing the synthesis of hepatic cholesterol (Nammi *et al.*, 2009;

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Purnomo *et al.*, 2021). *Glycine max* also inhibits lipolysis through decreasing Hormone-sensitive lipase (HSL) activation on adipose tissue, which is regulated by active compound saponin (Nammi *et al.*, 2009; Mustofa *et al.*, 2010). It prevents an increase in FFA level; therefore, the hepatic cholesterol synthesis and non-HDLc level also could be reduced. They contribute to inhibiting atherosclerosis or anti-atherogenesis (Purnomo *et al.*, 2021). *Zingiber officinale* contains polyphenol substances that could increase the enzyme 7-α hydroxylase and stimulate the conversion of hepatic cholesterol into bile acid. Moreover, the synthesis of hepatic cholesterol will be reduced through the mechanism (Purnomo *et al.*, 2022). The administration of herbs increases HDLc level as explained above, therefore it contributes to the decrease of non-HDLc involved in the atherogenesis process.

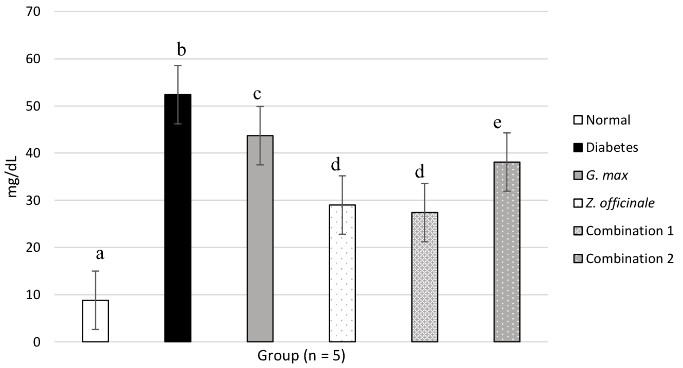

Figure 5. Histogram of non-HDLc levels in DM rats treated with *G. max*, *Z. officinale* extracts and their combination. Bars with different notations are statistically significantly different ($p<0.05$, LSD test).

4. Conclusion

The application of *G. max* seed extract, *Z. officinale* rhizome and its combination can reduce total cholesterol, triglyceride, LDLc and non-HDLc in diabetic rats; HDLc levels only increased after administration of *Z. officinale* extract. For the next study, fractionation and subfractionation should be done to determine the lead compound that acts as an anti-dyslipidemic.

Conflict of interest

The authors declare no conflict of interest.

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