Antihyperlipidemic Activity of Kratom Leaves (*Mitragyna speciosa*) in Metabolic Syndrome Induced-Rats

Sintia Karina Putri[1], Yuandani[2], Pipit Pitriani[3], Said Haikal Alfajar[4], Rony Abdi Syahputra[5]
[1,2,5]Universitas Sumatera Utara, Medan, Indonesia
[3]Universitas Pendidikan Indonesia, Bandung, Indonesia
[4]Institut Kesehatan Helvetia, Medan, Indonesia
Email: yuandani@usu.ac.id

Abstract

Obesity and hyperlipidemia are metabolic problems that can trigger various comorbid diseases. Kratom leaves (*Mitragyna speciosa*) are one of the herbal-based medicines containing alkaloid compounds that have the potential to improve lipid profiles. This study aims to analyze the antihyperlipidemic activity of kratom leaves in vivo and in silico. Extraction of kratom leaves was carried out by maceration using 96% ethanol (1:10 w/v) for 3 days, then concentrated using a rotary evaporator. Compound identification was performed using LC-HRMS. The in vivo study was conducted on rats (n=6 per group) for 14 days, including a negative control, positive control, and three treatment groups with doses of kratom leaf extract of 100, 300, and 500 mg/kg BW. The parameters assessed included body weight, LDL cholesterol, HDL cholesterol, triglycerides, and total cholesterol. The results showed that kratom leaf extract at doses of 100, 300, and 500 mg/kg BW exhibited significant antihyperlipidemic activity compared to the negative control ($p<0.05$), characterized by reductions in triglyceride, total cholesterol, and LDL levels, as well as an increase in HDL and a decrease in body weight. The 500 mg/kg BW dose showed the best pharmacological effect compared to the 100 mg/kg BW and 300 mg/kg BW doses ($p<0.05$).

Keywords: *Hyperlipidemia, In vivo, Kratom leaf, Rat.*

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A. INTRODUCTION

Obesity and hyperlipidemia are two interrelated metabolic conditions and major risk factors for various cardiovascular diseases (Chen et al., 2025; Denisenko et al., 2020). Hyperlipidemia itself is characterized by abnormal blood lipid levels, including elevated low-density lipoprotein (LDL) cholesterol, triglycerides (TG), and decreased high-density lipoprotein (HDL) cholesterol (Lin et al., 2019). This lipid profile imbalance not only accelerates the process of atherosclerosis but also increases global morbidity and mortality (Nabrdalik et al., 2024). The prevalence of both conditions continues to increase worldwide and in Indonesia, thus requiring serious attention in their management.

According to the World Obesity Atlas, (2025), in 2015 there were 205 million men and 261 million women worldwide living with obesity, and this number is predicted to increase to 417 million men and 505 million women by 2030, with the highest prevalence occurring in low- to middle-income countries. Meanwhile in Indonesia, data from UNICEF, (2024) show that the prevalence of obesity in the population aged >18 years reaches 14.4%, with a predominance in women (15.3%) and

a higher obesity rate in urban areas (15.1%) compared to rural areas. The persistently high and increasing incidence of obesity demands the availability of effective, safe, and affordable pharmacological therapies to reduce the prevalence of obesity and prevent metabolic complications such as hyperlipidemia.

Currently, various synthetic chemical drugs such as statins, fibrates, and niacin are available as the main antihyperlipidemic therapies due to their ability to significantly reduce LDL and triglycerides. However, long-term use of these drugs often causes adverse side effects, including myopathy, hepatotoxicity, impaired glucose tolerance, and dyspeptic complaints that can reduce patient compliance (Mumthaj.P et al., 2021; Stewart et al., 2020). These limitations have encouraged a large portion of the population to switch to and choose herbal-based treatments, which are considered more natural, have relatively fewer side effects, and are easily accessible both culturally and economically (Welz et al., 2018).

Developing effective and nontoxic therapeutic strategies is essential to address obesity and the hyperlipidemia. Kratom with the name latin is *mytragyna speciosa* leaves have been traditionally utilized by communities in Thailand and Malaysia for treating diabetes and inflammation (La-up et al., 2021). In Indonesia, Kratom is cultivated and commercially traded due to its potential as an alternative therapy for diabetes management, cholesterol reduction and pain relief (Budiarti et al., 2025). A limited number of studies have suggested that Kratom use may influence serum lipid profiles. In study involving 58 Kratom users and 19 healthy controls, Kratom consumprion were associated woth increased serum cholesterol and High Density Lipoprotein (HDL) levels among both short term and long term users (Singh et al., 2018). In a more recent study involving 100 Kratom users and 100 healthy controls, Kratom users were found to have slightly lower levels of Low Density Lipoprotein (LDL) and total cholesterol (Leong Bin Abdullah et al., 2020). These findings suggest that Kratom may play a role in regulating lipid profiles.

To further explore the molecular mechanism underlying the potential antihyperlipidemic activity of Kratom, an in silico molecular docking approach can be employed targeting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme, which plays a key role in the rate-limiting step of cholesterol biosynthesis. Various bioactive compounds found in kratom leaves, such as mitragynine, paynantheine, speciogynine, and other alkaloids, can be docked into the active site of HMG-CoA reductase to predict their binding affinities and interaction patterns compared to a standard statin drug (e.g., simvastatin or atorvastatin).

Based on the background described above, it is hypothesized that Kratom leaf extract possesses antihyperlipidemic activity by improving the lipid profile and reducing body weight in an in vivo animal model. Therefore, this study aims to identify the effect of Kratom leaf extract on body weight, LDL, HDL, TG, and total cholesterol levels in experimental rats.

B. METHODS

1. Materials and Equipment

Fresh leaves of *Mitragyna speciosa* (UMKL-1 variant) were used. Ethanol 96% (Ab Clonal®) was employed for extraction. Analytical-grade solvents, including acetonitrile (Ab Clonal®) and 0.1% formic acid (LC-MS grade, Ab Clonal®), were used for chromatographic analysis. Filtration was performed using Whatman No. 1 filter paper (Ab Clonal®). For biochemical analysis, commercial assay kits were used to determine the lipid profile (cholesterol, HDL, LDL, and triglycerides). Blood samples were collected into vacuum tubes containing EDTA (Ab Clonal®). Additional materials included alcohol swabs (Ab Clonal®), 23 G needles (Ab Clonal®), and Easy Touch® glucose test strips for blood glucose measurement.

2. Animals

Male Sprague–Dawley rats (200–250 g) were used as experimental animals and maintained under standard laboratory conditions.

3. Plant Collection and Identification

Fresh Kratom leaves collected from Pontianak, Indonesia, underwent rigorous taxonomic verification to confirm species authenticity. Morphological and anatomical analyses—focusing on leaf structure, color, texture, and venation patterns—were performed by a qualified botanist and systematically compared with standard botanical descriptions and taxonomic keys. Species identity was further validated against authenticated herbarium specimens. This identification process was conducted at the Medanense Herbarium, University of North Sumatra, ensuring research reproducibility and accurate plant material confirmation. The identification of Kratom was confirmed through an official plant examination report (Letter No. 676/MEDA/2025), with the verification performed by Prof. Dr. Etti Sartina Siregar, S.Si., M.Si.

4. Drying and Extraction of Kratom Leaves

Fresh Kratom leaves (2 kg) were dried in a drying cabinet for one day and ground into powder (1.2 kg). Extraction was carried out by macerating the powder in 96% ethanol at a 1:10 ratio (500 g powder : 5 L ethanol) for three days (Chumsri et al., 2008). The filtrate (Whatman No. 1 paper) was concentrated using a rotary evaporator, and the ethanol extract was stored away from light.

5. Characterization Test of Kratom Simplicia

a. Water Content Determination

Toluene (200 mL) and distilled water (2 mL) were distilled for 2 hours, then cooled for 30 minutes, and the water volume was recorded (accuracy 0.1 mL). Simplicia powder (5 g) was added to the toluene, heated carefully for 15 minutes, and distillation continued at 2 drops/sec, then 4 drops/sec. The condenser was rinsed with toluene, distillation continued for 5 minutes, and after cooling, the water volume was

read again. The difference in water volume represented the water content, calculated as a percentage (Handayani et al., 2019).

b. Total Ash Content Determination

A total of 2 g of accurately weighed powder was put into a porcelain crucible that had been previously ignited and tared. The powder was evenly flattened inside the crucible. The crucible was then ignited until a constant weight was obtained. The ash content was calculated as a percentage relative to the air-dried sample (Handayani et al., 2019).

c. Acid-Insoluble Ash Content Determination

The ash from the total ash determination was boiled in 25 mL of 2 N HCl for 5 minutes. The insoluble matter was collected, filtered through ash-free filter paper, and washed with hot water. The residue and filter paper were ignited to constant weight, cooled, and weighed. The acid-insoluble ash content was calculated relative to the air-dried sample (Handayani et al., 2019).

6. LC-HRMS Analysis of Kratom Leaves

LC-HRMS was used to identify bioactive compounds in Kratom extract. Separation was performed on a C18 column (150 mm × 2.1 mm, 1.7 μm) with a gradient mobile phase of water and acetonitrile (both with 0.1% formic acid) at 0.3 mL/min and 30°C. Injection volume was 5–10 μL. Anthocyanins, flavonoids, and organic acids were analyzed in MRM mode. Data were processed using software and matched against METLIN, MassBank, and HMDB databases. Fragmentation patterns supported structural confirmation, with authentic standards used when available. This method enabled sensitive and specific profiling of known and potential novel bioactive compounds in Kratom leaves.

7. Preparation of Experimental Animals

A total of 30 male Sprague-Dawley rats (200–250 g) were allocated into two diet groups: a normal diet group (n=6) and a high-fat diet (HFD) group (n=30) to induce obesity with metabolic syndrome (MetS). The MetS obesity model was induced over 12 weeks. During this period, changes in body weight, food intake, and water consumption were recorded weekly until the end of the induction phase.

a. HFD + no treatment (0.5% Na CMC, orally) – G Negative
b. HFD + Kratom extract 100 mg/kg, orally – G 100
c. HFD + Kratom extract 300 mg/kg, orally – G 300
d. HFD + Kratom extract 500 mg/kg, orally – G 500
e. HFD + simvastatin 50 mg/kg, orally – G Positive

All treatments were administered for 14 days.

8. Biochemical Analysis

Blood samples collected in EDTA-containing vacuum tubes were centrifuged at 4000 rpm for 15 minutes at 4°C to separate the serum. The serum was stored and

transported to the main laboratory for analysis. The assessed parameters included lipid profile (cholesterol, HDL, LDL, triglycerides) and body weight of the rats.

9. Body Fat Analysis Using DXA Scanner

DXA was used to measure body composition and fat distribution in rats. Rats were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) intraperitoneally or sodium pentobarbital (50 mg/kg), then placed in a prone position. Whole-body scanning was performed using a Discovery QDR Wi DXA system (Hologic, Marlborough, USA) for about 4 minutes (Ekeuku et al., 2024). Body weight was the parameter obtained from the DXA scanner.

C. RESULT AND DISCUSSION

1. Results of Kratom Leaf Extraction

In this study, the maceration method was used as the extraction method, with 96% ethanol as the solvent, by soaking 500 grams of kratom simplicia. The ethanol extract of kratom leaves obtained was 84 grams, with a yield of 16.8%. The yield obtained is considered good because it is >10% (Aristyawan et al., 2023). A study conducted by Aristyawan et al., (2023) using the maceration method with methanol as the solvent produced a methanol extract of kratom leaves weighing 53.12 grams. The solvent is the most important factor affecting the amount of extract obtained. This is due to the polarity level of the compounds contained in the sample. In addition, temperature, light, and humidity are also factors that influence the extraction results (Zebua et al., 2024).

Ethanol is a solvent capable of extracting polar, semi-polar, and non-polar compounds due to the presence of a hydroxyl group (polar) and an ethyl group (non-polar). This ability makes ethanol a universal solvent (Agustini et al., 2023). In addition, ethanol has antibacterial effects, which can help preserve samples for a longer period (Dyrda et al., 2019). Maceration extraction is used for compounds that are thermolabile (heat-sensitive). During this process, the container is tightly closed to minimize solvent loss due to evaporation (Bitwell et al., 2023). Therefore, researchers need to adjust the solvent, concentration, extraction method, and storage temperature according to the research objectives. Proper selection is an important effort to maintain good and stable sample quality throughout the process.

2. LC-HRMS Analysis Results of Kratom Leaves

The active compounds of kratom leaves were analyzed using LC-HRMS. The analysis results showed the typical compounds of kratom leaves, including 7-Hydroxymitragynine (1.19 min), Corynantheidine (1.19 min), Mitragynine (0.818 min), Paynantheine (0.848 min), Speciociliatine (0.818 min), and Speciogynine (0.818 min) (Figure 2). The alkaloid profile of kratom leaves depends on the maturity level and growing environment. Approximately 66% of the alkaloid content in kratom leaves consists of Mitragynine (Fields et al., 2026). According to Permatasari et al., (2025), the alkaloid composition found in kratom leaves includes mitragynine (60%),

7-hydroxymitragynine (2%), speciogynine (15%), paynantheine (15%), and speciociliatine (15%). These findings indicate that these compounds belong to the group of alkaloids that dominate the phytochemical composition of kratom leaves.

However, the differences in the results obtained compared to previous studies are due to differences in sampling locations. Each region has varying altitudes and rainfall levels. The geographical location of a plant is a factor that causes the active compounds of a plant to differ (Wang et al., 2024). Changes and modifications in membrane structure serve as a natural mechanism of plants, thereby modulating the plant's defense system. In addition, photosynthetic activity can affect plant growth and metabolism (Reshi et al., 2023). Therefore, differences in sampling locations will affect the types and quantities of compounds in the sample.

3. Results of Simplicia Characterization of Kratom Leaves

The study examined the characteristics of kratom leaf simplicia. This testing ensures the quality of kratom leaves as the sample used in this study. The results of the simplicia characterization test of kratom leaves are shown in Table 1.

Tabel 1. Results of the Simplicia Characterization Test of Kratom Leaves

No.	Characterization	Result (%) ± SD		Specification standards (%)
		Simplisia	**Ekstract**	
1.	Moisture content	5,9983 ± 0,00	4,1016 ± 0,06	≤ 10 %
2.	Total ash content	3,7433 ± 0,16	1,845 ± 0,03	≤ 16 %
3.	Acid-insoluble ash content	1,7466 ± 0,07	1,2073 ± 0,02	≤ 7 %
4.	Ethanol-soluble extractive content	28,6667 ± 1,54	-	≥ 10 %
5.	Water-soluble extractive content	24,27 ± 0,05	-	≥ 18 %

Note: SD = Standard Deviation

The moisture content of kratom leaf simplicia was 5.9983 ± 0.00%, and that of kratom leaf extract was 4.1016 ± 0.06%. These results met the moisture content requirement of ≤ 10%. The moisture content results that met the requirements indicate that the potential growth of fungi, molds, and bacteria becomes suboptimal (Handayani et al., 2019). However, there are factors that can cause the moisture content results to not meet the requirements, such as non-optimal drying processes, drying times that are too short, or suboptimal temperatures. Other factors that can cause high moisture content include poor storage conditions, which allow the simplicia to reabsorb water vapor from the environment due to relatively high ambient humidity. In addition, slices that are too thick can make it difficult for the inner part of the leaves to evaporate water completely. Samples with high moisture content tend to become an ideal medium for the growth of fungi, molds, and bacteria (Maryam et al., 2020).

The total ash content of the simplicia and kratom was 3.7433 ± 0.16%, and that of the kratom leaf extract was 1.845 ± 0.03%. These results met the requirement of ≤

16.6% (Fatimawali et al., 2020). This indicates that the simplicia and kratom leaf extract are nearly free from inorganic contaminants such as sand, dust, and metal particles that may have been carried over during the collection and drying of kratom leaves. Furthermore, the low total ash content minimizes the risk of spectral interference when analyzing the compounds contained in kratom leaves using an instrument (Noureen et al., 2019).

The acid-insoluble ash content obtained from kratom leaf simplicia was 1.7466 ± 0.07%, and from kratom leaf extract was 1.2073 ± 0.02%. These results did not meet the requirement of ≤ 0.70% (Fatimawali et al., 2020). The acid-insoluble ash content results that did not meet the requirements indicate that the simplicia and kratom leaf extract still contain contaminants such as sand, soil, and dust that are typically carried over during the harvesting or drying process. This is important because contaminants such as sand or soil can interfere with the extraction and analysis processes (Nurlela et al., 2023).

The ethanol-soluble extractive content of kratom leaf simplicia was 28.6667 ± 1.54%, and this result met the requirement of ≥ 10%. Meanwhile, the water-soluble extractive content of kratom leaf simplicia was 24.27 ± 0.05%, and this result met the requirement of ≥ 18% (Najib et al., 2018). The ethanol-soluble extractive content was greater than the water-soluble extractive content. This indicates that the number of compounds dissolved in ethanol is higher than those dissolved in water. This can provide an overview of the amount of compounds dissolved between water and ethanol as solvents from a given simplicia (Handayani et al., 2019).

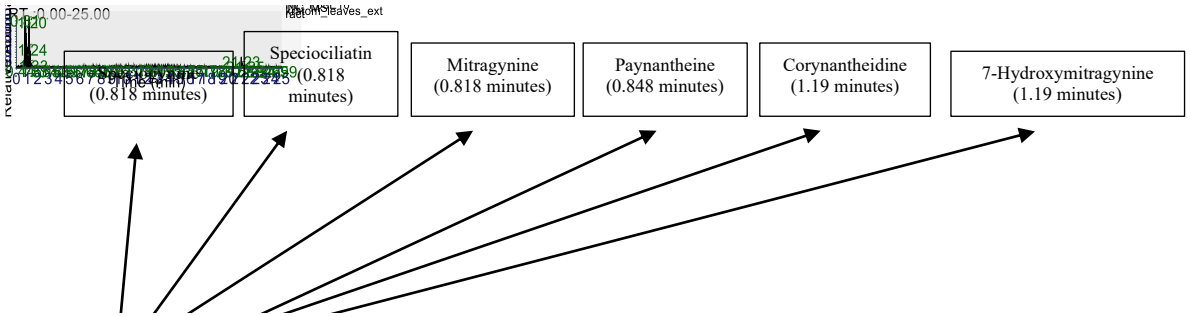

Figure 1. Identification Kratom Leaves with LC-HRMS

4. Activity of Kratom Leaves on Glycemic Profile

Figure 2 shows the glycemic profile of rats. The parameter tested was random Blood Glucose Level (BGL). In addition, HbA1c was also tested in this study. Random BGL is considered high if > 200 mg/dL, and HbA1c is considered high if > 6.5% (Martina et al., 2024).

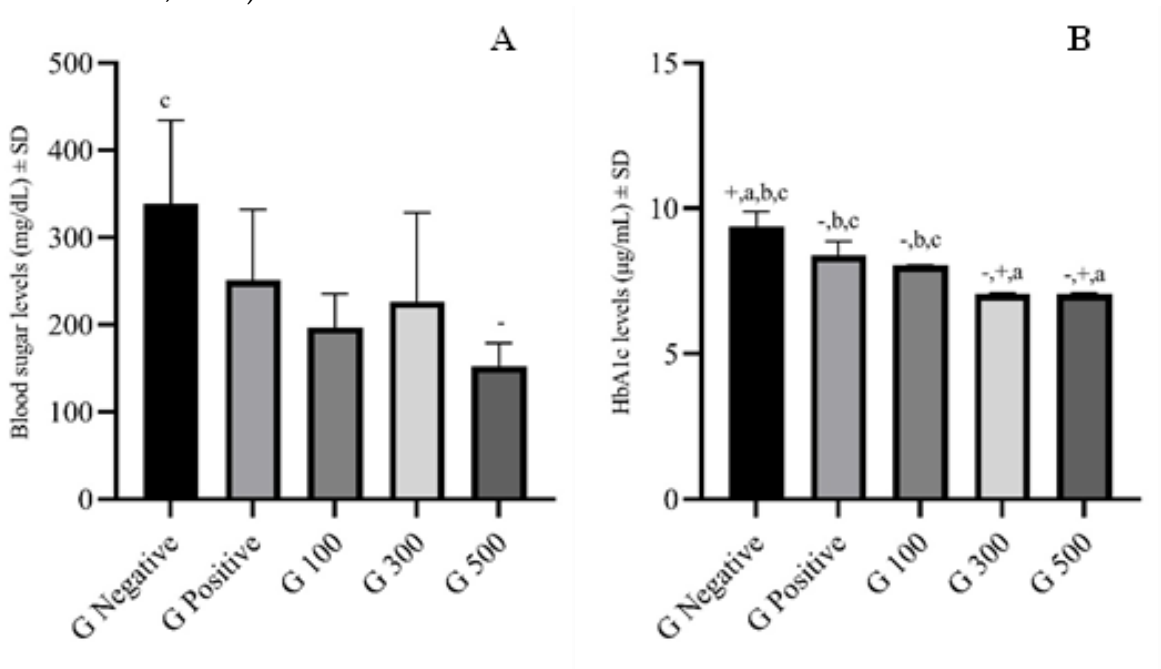

Figure 2. Hyperglycemic profile. (A) Blood glucose level (BGL); (B) HbA1c level. (–) Significantly different from the negative control ($p < 0.05$); (+) significantly different from the positive control ($p < 0.05$); (a) significantly different from G 100 ($p < 0.05$); (b) significantly different from G 300 ($p < 0.05$); (c) significantly different different from G 500 weight ($p < 0.05$).

In the negative control group, the mean random BGL of rats before induction was 114.67 mg/dL, which increased to 264.33 mg/dL (130.51%) after induction, and further rose to 338.83 mg/dL (195.48%) after 14 days of testing, indicating that this group remained hyperglycemic throughout the study. In the positive control group, the mean BGL before induction was 105.67 mg/dL, rose to 328.17 mg/dL (210.56%) post-induction, and then decreased to 250.83 mg/dL (23.56%) after 14 days of simvastatin treatment, although the group still remained hyperglycemic; this reduction is consistent with the findings of Tian & Zhang, (2026), who reported that simvastatin administration alongside a high-fat diet improves glucose tolerance and reduces fasting blood glucose via activation of the LPS-TLR4 pathway, which suppresses the LXR/SREBP-1c pathway, thereby reducing PPAR-α-dependent gluconeogenesis. In the G 100 the mean BGL before induction was 104.17 mg/dL, increased to 292 mg/dL (180.31%) post-induction, and then decreased to 196.75 mg/dL (32.61%) after 14 days, bringing the group back to normal BGL levels. Meanwhile, in the group treated with G 300, the mean BGL before induction was 105.83 mg/dL, rose sharply to 397.67 mg/dL (275.76%) after induction, and then decreased to 226.60

mg/dL (43.01%) after 14 days of treatment, yet this group remained hyperglycemic at the end of the study.

The G 500 showed a significant reduction in BGL compared to the negative control ($p < 0.05$). However, there was no significant difference in BGL reduction compared to the G EEDK 100 and G EEDK 300 (Figure 4.2A). This reduction is likely due to the effect of kratom leaf extract, which can competitively inhibit alpha-glucosidase activity. This finding is supported by previous studies (Limcharoen et al., 2022; Zhang et al., 2023) that reported the antidiabetic effects of kratom leaves through alpha-glucosidase inhibition assays. The mechanism of alpha-glucosidase in lowering BGL is by inhibiting the breakdown of complex glucose structures into simpler ones, thereby hindering absorption in the small intestine and preventing an increase in BGL. This mechanism is similar to that of acarbose (Lu et al., 2023).

In the negative control group, the mean HbA1c level of rats before induction was 4.52%, which increased to 9.04% (100%) after induction and further rose to 9.24% (104.42%) after 14 days, indicating that this group remained hyperglycemic throughout the study. In the positive control group, the mean HbA1c level before induction was 4.43%, rose to 9.14% (106.32%) post-induction, and then decreased to 8.25% (9.73%) after 14 days of simvastatin treatment, yet the group still remained hyperglycemic. In the G 100, the mean HbA1c level before induction was 4.52%, increased to 9.05% (100.22%) after induction, and then decreased to 8.04% (11.16%) after 14 days of treatment, but this group also remained hyperglycemic. Meanwhile, in the G 300, the mean HbA1c level before induction was 4.43%, rose to 9.05% (104.28%) post-induction, and then decreased to 7.05% (22.09%) after 14 days, though the group remained hyperglycemic. Similarly, in the G 500, the mean HbA1c level before induction was 4.52%, increased to 9.05% (100.22%) after induction, and then decreased to 7.03% (22.32%) after 14 days of treatment, yet this group also remained hyperglycemic at the end of the study. Overall, while all treatment groups showed reductions in HbA1c levels compared to the negative control, none of the groups achieved normal HbA1c levels (< 6.5%) after 14 days of testing.

HbA1c is an important marker for blood glucose control, and regular monitoring can help prevent complications (Orozco-beltran et al., 2026). HbA1c is formed from the non-enzymatic binding of glucose to hemoglobin. The higher the blood glucose level over a period of 3 months, the more HbA1c is formed. Thus, a consistent reduction in BGL during the treatment period will be directly reflected as a decrease in HbA1c (Leonel et al., 2023). The G 300 and G 500 mg/kg BW groups showed the most significant reduction in HbA1c compared to the negative control and the G 100 ($p < 0.05$) (Figure 4.2B). These results indicate that the G 300 and G 500 were more effective in reducing MetS complications compared to the other tested doses. It can be concluded that the higher the concentration of kratom leaves, the greater the effect on reducing BGL and HbA1c. However, this study is still limited to in vivo testing with a relatively short observation period. Further studies are needed to evaluate the long-term effects, HbA1c reduction, and more specific molecular

mechanisms, such as the regulation of GLUT2 gene expression or the insulin signaling pathway.

5. Activity of Kratom Leaves on Rat Body Weight

This study measured the body weight (BW) of rats (Figure 3). This measurement was conducted to observe obesity in each rat. The diet used was HFD. In the negative control group, the mean BW of rats was 221.5 grams. After 12 weeks of HFD administration, the mean BW increased to 304.5 grams (37.41%). Subsequently, the rats were weighed again after 7 days of testing, showing a decrease in mean BW to 272.17 grams (10.61%), and were weighed again on day 14 of testing, showing a further decrease in mean BW to 244.33 grams (19.71%).

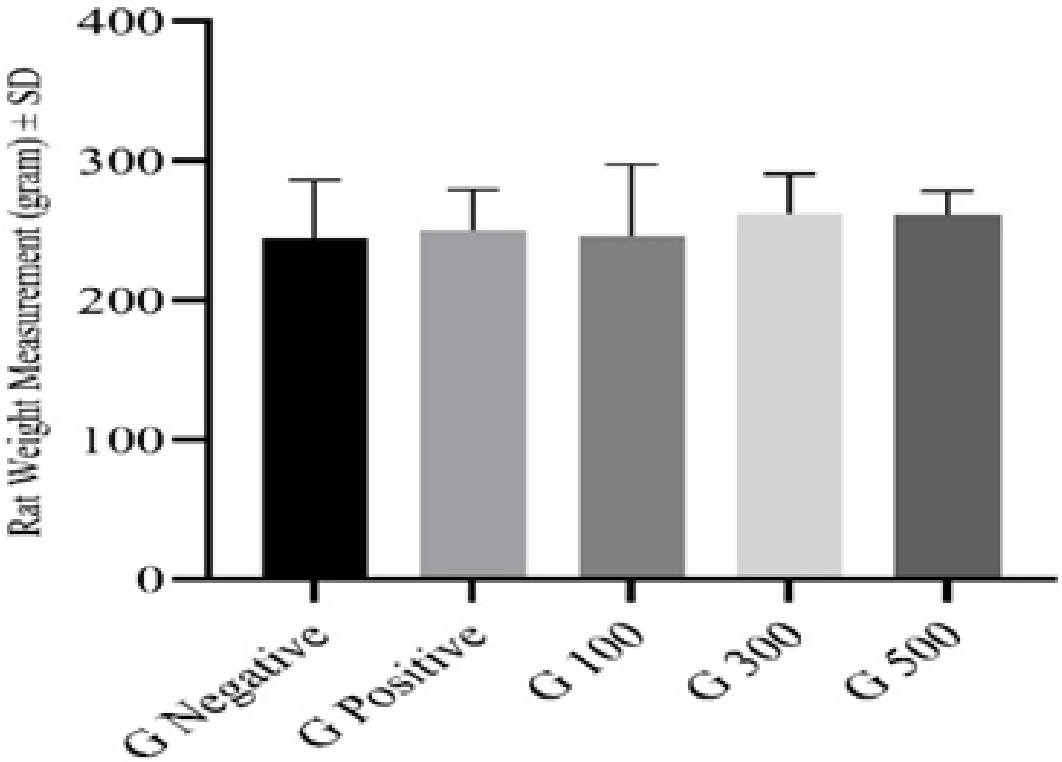

Figure 3. Rat Body Weight Profile

In the positive control group, the mean BW of rats was 230.17 grams initially, which increased to 295.17 grams (28.23%) after 12 weeks of HFD administration, then decreased to 266.5 grams (9.71%) after 7 days of testing, and further declined to 250.33 grams (15.19%) by day 14. In the G 100, the mean BW started at 212.83 grams, rose to 299.17 grams (28.85%) post-HFD, then decreased to 251.17 grams (16.04%) after 7 days, and further dropped to 246.25 grams (17.68%) by day 14. In the G 300, the mean BW was initially 218 grams, increased to 297.83 grams (26.80%) after HFD, then decreased to 271.83 grams (8.72%) after 7 days, and further declined to 261.60 grams (12.16%) by day 14. In the G 500, the mean BW started at 223.50 grams, rose to 297.17 grams (24.79%) post-HFD, then decreased to 272.83 grams (8.19%) after 7 days, and further dropped to 260.80 grams (12.23%) by day 14. However, there were no significant

differences in body weight reduction among all test groups ($p > 0.05$), indicating that the rats experienced similar increases in body weight across all groups.

A study by Kumarnsit et al., (2018) demonstrated that kratom leaf extract suppresses food intake in rats. Acute administration at doses of 45–50 mg/kg reduced food consumption to 45–48 g/kg/24 hours compared to controls (88 g/kg/24 hours). This effect was long-lasting, as daily administration of 40 mg/kg/day for 60 days consistently suppressed daily feed intake, resulting in a significantly lower total 60-day intake. Consequently, body weight gain in the rats was inhibited. This appetite-suppressing effect is thought to occur through the action of its main active compound, mitragynine, which affects the central nervous system regulating satiety. After STZ induction, there was an increase in blood glucose and HbA1c levels across all treatment groups. This increase indicates that STZ successfully damaged pancreatic beta cells, leading to insulin deficiency and hyperglycemia. The chronic hyperglycemic condition accompanied by insulin resistance resulting from simultaneous HFD administration represents a clinical picture of MetS in humans. Thus, the elevation of BGL and HbA1c levels after STZ induction confirms that the test animals had entered a metabolic phase equivalent to MetS conditions.

6. Activity of Kratom Leaves on Lipid Profile

Figure 4 shows the lipid profile results in rats. The parameters tested were body weight, cholesterol, and triglycerides (TG). In addition, LDL and HDL were also tested in this study. Levels are categorized as high if cholesterol ≥ 240 mg/dL, TG ≥ 200 mg/dL, and LDL ≥ 190 mg/dL, while levels are categorized as low if HDL ≤ 40 mg/dL (Prinita & Darmawi, 2023).

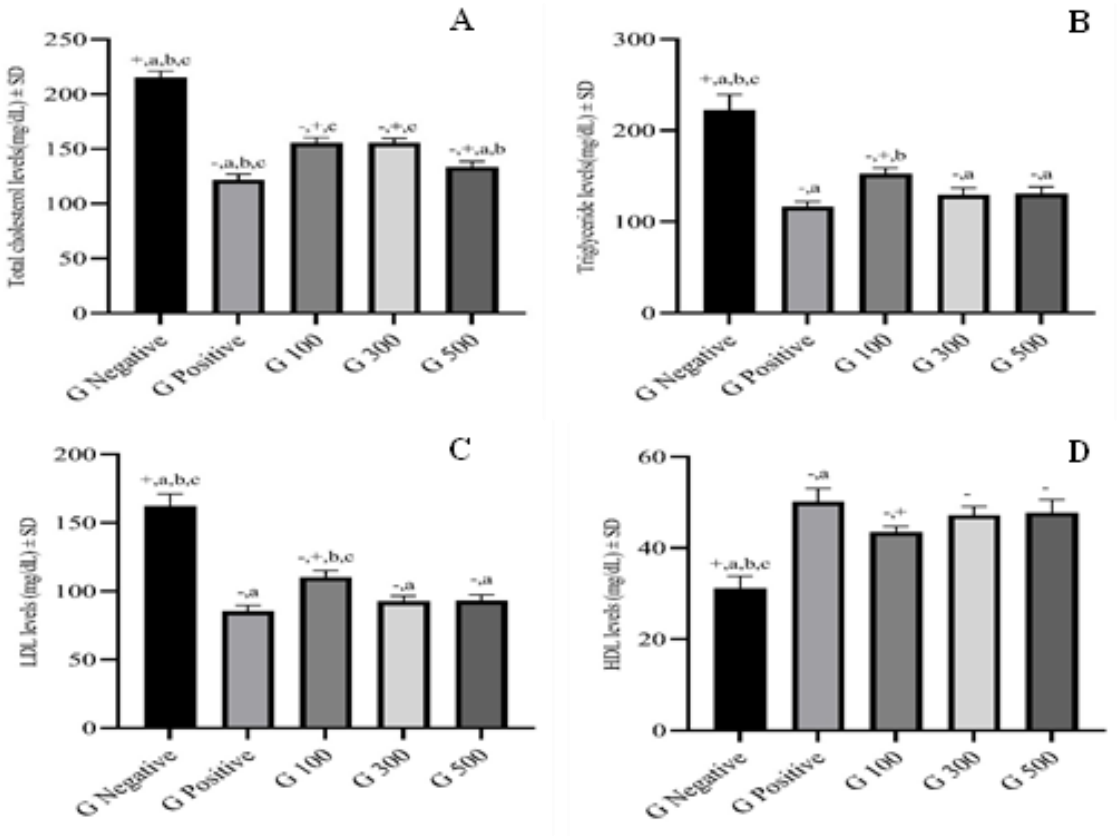

Figure 4. Lipid profile of rats. (A) Total cholesterol level; (B) Triglyceride level; (C) LDL level; (E) HDL level. (–) Significantly different from the negative control ($p < 0.05$); (+) significantly different from the positive control ($p < 0.05$); (a) significantly different from G 100 ($p < 0.05$); (b) significantly different from G 300 ($p < 0.05$); (c) significantly different from G 500 ($p < 0.05$).

In the negative control group, the mean baseline levels of cholesterol, triglycerides (TG), LDL, and HDL were 102 mg/dL, 91.66 mg/dL, 55 mg/dL, and 56 mg/dL, respectively, which shifted to 203 mg/dL (99.01%), 209.16 mg/dL (128.18%), 162 mg/dL (194.54%), and 31 mg/dL (45.61%) after induction, indicating hyperlipidemia; after 14 days, these values further worsened to 215.50 mg/dL (111.27%), 222.66 mg/dL (142.91%), and 170 mg/dL (209.09%) for cholesterol, TG, and LDL, while HDL decreased to 29 mg/dL (49.12%), confirming that this group remained hyperlipidemic. In the positive control group, baseline values of 109 mg/dL, 91.66 mg/dL, 49 mg/dL, and 53 mg/dL for cholesterol, TG, LDL, and HDL changed post-induction to 201.67 mg/dL (101.67%), 210.5 mg/dL (129.65%), 158 mg/dL (129.65%), and 34 mg/dL (35.84%), respectively, but after 14 days of simvastatin treatment, cholesterol, TG, and LDL decreased to 121.67 mg/dL (39.66%), 116.66 mg/dL (44.57%), and 170 mg/dL (49.36%), while HDL increased to 47 mg/dL (46.99%), bringing this group back to a normal lipid profile. In the G 100, baseline values of 102 mg/dL, 91.5 mg/dL, 56 mg/dL, and 56 mg/dL for cholesterol, TG, LDL, and HDL became 203 mg/dL (99.01%), 211.66 mg/dL (131.32%), 162 mg/dL (189.28%), and 31 mg/dL (44.64%) post-induction, but after 14 days of treatment, cholesterol, TG, and

LDL decreased to 155.75 mg/dL (23.27%), 152.5 mg/dL (27.95%), and 120 mg/dL (30.86%), while HDL increased to 43 mg/dL (27.90%), indicating normalization of the lipid profile. Similarly, in the G 300, post-induction values of 203 mg/dL (99.01%), 208.33 mg/dL (128.17%), 145 mg/dL (190%), and 30 mg/dL (43.39%) for cholesterol, TG, LDL, and HDL (from baseline values of 102, 91.16, 50, and 53 mg/dL, respectively) decreased after 14 days to 155.75 mg/dL (23.27%), 129.6 mg/dL (37.79%), and 88 mg/dL (39.31%) for cholesterol, TG, and LDL, while HDL increased to 46 mg/dL (34.78%), resulting in a normal lipid profile. Likewise, in the G 500, baseline values of 101, 93.16, 54.17, and 58.33 mg/dL for cholesterol, TG, LDL, and HDL changed post-induction to 203 mg/dL (99.01%), 211 mg/dL (126.49%), 156.33 mg/dL (65.35%), and 33.16 mg/dL (41.65%), respectively, but after 14 days of treatment, cholesterol, TG, and LDL decreased to 133.6 mg/dL (34.18%), 130.8 mg/dL (38%), and 93.2 mg/dL (40.38%), while HDL increased to 47.8 mg/dL (30.62%), also achieving a normal lipid profile. Overall, all treatment groups (positive control and all doses) successfully normalized the lipid profile after 14 days, in contrast to the negative control group, which remained hyperlipidemic.

Based on the calculation of the Atherogenic Index of Plasma (AIP) using the formula log10(TG/HDL) Anggraini et al., (2025), it was observed that before induction, all groups had AIP values ranging from 0.206 to 0.238. However, after induction, there was an increase in all groups, with AIP values ranging from 0.792 to 0.842, indicating the formation of an atherogenic condition due to the treatment. On day 14 of observation, the negative control group showed the highest AIP (0.871) because it received no intervention, while the positive control group showed an AIP of 0.395. Furthermore, the administration of extract kratom leaves at various doses demonstrated a dose-responsive improvement effect, where G 100 resulted in an AIP of 0.550, while G 300 and G 500 reduced AIP to 0.450 and 0.437, respectively, indicating that the higher the dose of extract kratom leaves administered, the greater the reduction in AIP. This suggests the potential of extract kratom leaves in improving the lipid profile and reducing the risk of atherosclerosis in test animals.

In monitoring total cholesterol, the G 500 showed a significant reduction potential compared to the negative control, G 100, and G 300 ($p < 0.05$) (Figure 4.4A). Meanwhile, the reduction potential for TG and LDL in the G 300 and G 500 was significant compared to the negative control and G 100 ($p < 0.05$) (Figures 4.4B and 4.4C). Furthermore, the increase in HDL in the G 100, G 300, and G 500 was significant compared to the negative control group ($p < 0.05$) (Figure 4.4D). This indicates that the higher the concentration of kratom leaves, the greater the effect on reducing LDL, cholesterol, and TG, as well as increasing HDL.

This effect may be attributed to the alkaloid content found in kratom leaves. Kratom leaves contain approximately 40 alkaloids, some of which belong to the oxindole class and are known to influence lipid metabolism. In addition, their relatively high antioxidant activity also contributes to the reduction of triglyceride levels trigliserida (La-up et al., 2021). However, there was no significant body weight reduction effect observed in all control groups (Figure 4.3A). Simvastatin, as a positive

control, works by inhibiting the HMG-CoA reductase enzyme, thereby reducing cholesterol synthesis in the liver. However, simvastatin does not directly reduce body weight. Weight loss causes fat stored in adipose tissue to be mobilized and oxidized into energy (Sethi et al., 2025). Consequently, the availability of substrates for very low-density lipoprotein (VLDL) synthesis in the liver is reduced, leading to decreased levels of LDL and triglycerides in the blood (Burks et al., 2024). Furthermore, the reduction of visceral fat also increases adiponectin levels, a hormone that plays a role in increasing HDL levels through various protective mechanisms, including the activation of the adenosine monophosphate-activated protein kinase-endothelial nitric oxide synthase (AMPK-eNOS) pathway (Yan et al., 2024).

A previous study involving 581 kratom users aged 18 years and older reported a prevalence of 49.1%. The study showed that kratom use was associated with increased HDL levels ≥ 60 mg/dL with an odds ratio (OR) of 1.82 (95% CI: 1.17–2.82) and decreased triglyceride levels < 90 mg/dL with an OR of 2.01 (95% CI: 1.26–3.21). Additionally, the duration of kratom use was positively correlated with HDL levels ($r = 0.139$, $p = 0.019$) (La-up et al., 2021). These epidemiological findings support the preclinical evidence that kratom leaf extract is associated with increased HDL and decreased triglycerides. Although the correlation between duration of use and HDL levels was relatively weak ($r = 0.139$), its statistical significance ($p = 0.019$) indicates a consistent positive contribution. Furthermore, a study by Kaewchompoo et al., (2025) highlighted the role of Mitragynine in modulating adipogenesis and its potential influence on transcription factors such as C/EBPβ and PPARγ, which play crucial roles in adipocyte differentiation, thereby contributing to weight reduction in rats.

D. CONCLUSION

This study highlights the potential of Kratom leaves (*Mitragyna speciosa*) as an alternative therapeutic agent for managing antihyperglycemic. The antihyperlipidemic effects were indicated by decreased levels of triglycerides, cholesterol, and LDL, along with increased HDL levels. These findings support the hypothesis that Kratom leaves have the potential to be developed as an alternative treatment for hyperlipidemia. This potential is likely attributed to the compounds 7-Hydroxymitragynine, Corynantheidine, Mitragynine, Paynantheine, Speciociliatine, and Speciogynine, which are the compounds identified from the LC-HRMS results. However, this study did not isolate specific compounds from Kratom leaves. Therefore, further studies are required to validate the effectiveness of individual Kratom-derived compounds against the active sites of the therapeutic target proteins in order to confirm the docking simulation results.

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