Antihyperlipidemic Activity of Kratom Leaves (*Mitragyna speciosa*) In Vivo and In Silico

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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-MS/MS. 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, as well as molecular docking using PyRx. 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 ($p<0.05$). The docking results confirmed strong binding affinities between kratom leaf alkaloids and the therapeutic target HMG-CoA. Thus, kratom leaf alkaloids have the potential to be developed as antihyperlipidemic agents through inhibition of the HMG-CoA reductase enzyme.

Keywords: *Hyperlipidemia, In silico, In vivo, Kratom Leaf.*

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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* (Myosa) leaves have been traditionally utilized by communities in Thailand and Malaysia for treating diabetes and inflammation (La-up et al., 2021). In Indonesia, Myosa 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 Myosa use may influence serum lipid profiles. In study involving 58 Myosa users and 19 healthy controls, Myosa 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 Myosa users and 100 healthy controls, Myosa 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 Myosa may play a role in regulating lipid profiles.

To further explore the molecular mechanism underlying the potential antihyperlipidemic activity of Myosa, 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 Myosa leaf extract possesses antihyperlipidemic activity by improving the lipid profile and reducing body weight in an in vivo animal model, and that its bioactive compounds may act as inhibitors of HMG-CoA reductase through competitive binding at the enzyme's active site, as predicted by in silico molecular docking. Therefore, this study aims to identify the effect of Myosa leaf extract on body weight, LDL, HDL, TG, and

total cholesterol levels in experimental rats, as well as to evaluate the in silico molecular docking interaction between bioactive compounds of Myosa and the HMG-CoA reductase enzyme as a protein target in cholesterol biosynthesis.

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 Myosa 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 Myosa 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 Myosa Leaves

Fresh Myosa 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 Myosa Simplicia

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).

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).

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).

LC-MS/MS Analysis of Myosa Leaves

LC-MS/MS was used to identify bioactive compounds in Myosa 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 Myosa leaves.

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.

1. HFD + no treatment (0.5% Na CMC, orally) – G Negative

2. HFD + Myosa extract 100 mg/kg, orally – G 100
3. HFD + Myosa extract 300 mg/kg, orally – G 300
4. HFD + Myosa extract 500 mg/kg, orally – G 500
5. HFD + simvastatin 50 mg/kg, orally – G Positive

All treatments were administered for 14 days.

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.

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.

Protein Target and Molecular Docking Analysis

This study used target proteins associated with hyperlipidemia (HMG-CoA reductase, PDB ID: IHW9) (Khotimah, 2025). The target protein structures were obtained from the RCSB Protein Data Bank. Protein structures were prepared using Discovery Studio by removing water and heteroatoms and adding hydrogens. Using PyRx v0.8, docking simulations were performed by centering the grid box on the active site and setting the exhaustiveness to 100. For each ligand, binding affinities (kcal/mol) and conformations were recorded. Subsequently, the highest-ranked poses were visually inspected to identify hydrogen bonds and other crucial interactions with surrounding residues (Chaudhary Kurmi & Karati, 2025). Ligand can be downloaded in PubChem.

C. RESULT AND DISCUSSION

1. Extraction Yield of Myosa Leaves

Ethanol extraction (96%) of Myosa leaves using maceration produced 29.7 g of extract, whereas Aristyawan et al., (2023) obtained 53.12 g using methanol. Solvent polarity, temperature, light, and humidity influence extraction yield (Zebua et al., 2024). Ethanol extracts polar, semi-polar, and non-polar compounds due to its OH and ethyl groups, making it a universal solvent (Agustini et al., 2023). Ethanol also has antibacterial effects that prolong sample shelf life (Dyrda et al., 2019). Maceration is suitable for thermolabile compounds and is performed in sealed containers to prevent evaporation (Bitwell et al., 2023). Appropriate selection of solvents and conditions is crucial for maintaining sample quality.

2. LC-MS/MS Analysis Results of Myosa Leaves

LC-MS/MS analysis of Myosa leaves identified several alkaloids: 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 1).** Mitragynine constitutes approximately 66% of the total alkaloid content (Fields et al., 2026). Permatasari et al., (2025) reported a composition of mitragynine (60%), 7-hydroxymitragynine (2%), speciogynine (15%), paynantheine (15%), and speciociliatine (15%), indicating that alkaloids dominate the phytochemical profile of Myosa leaves.

Differences in findings compared to previous studies may result from different sampling locations, as altitude, rainfall, and geographical location affect plant bioactive compounds (Wang et al., 2024). Structural membrane modifications represent a natural mechanism for modulating plant defense, while photosynthetic activity influences plant growth and metabolism (Reshi et al., 2023). Thus, sampling location significantly affects the types and quantities of compounds in the sample

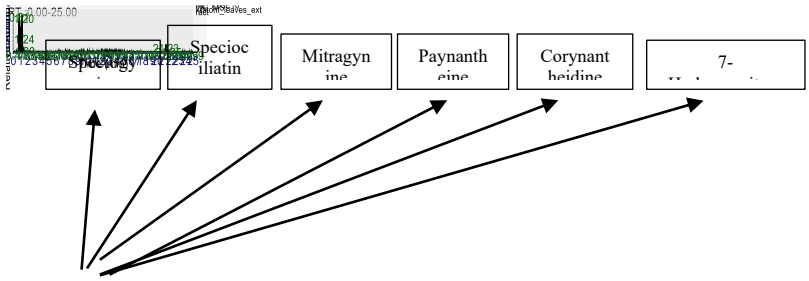

Figure 1. Identification Myosa Leaves with LC-MS/MS

Results of Simplicia Characterization of Myosa Leaves

This study evaluated the characteristics of Myosa leaf simplicia to ensure the quality of the Myosa leaves used as the research sample. The results of the simplicia characterization tests are presented in Table 1.

Tabel 1. Results of Simplicia Characterization of Myosa Leaves

No.	Parameter	Result ± SD (%)	Requirements (%)
1	Water Content	14,480 ± 0,049 %	≤ 10
2	Total Ash Content	0,027 ± 0,003 %	≤ 16,6
3	Acid-Insoluble Ash Content	0,004 ± 0,000 %	≤ 0,70

Note: SD= Standart Deviasion

The water content of Myosa leaf simplicia was 14.480 ± 0.049%, which did not meet the required standard of ≤ 10% (Handayani et al., 2019). This may be attributed to suboptimal drying processes, such as insufficient drying time or inadequate temperature. Another possible cause of high-water content is poor storage conditions, allowing the simplicia to reabsorb moisture from the environment due to relatively high humidity. Additionally, excessively thick leaf cuts may hinder complete water

evaporation from the inner part of the leaves. Samples with high water content tend to become an ideal medium for the growth of fungi, yeast, and bacteria (Maryam et al., 2020).

The total ash content of Myosa leaf simplicia was 0.027 ± 0.003%, which met the required standard of ≤ 16.6% (Fatimawali et al., 2020). This indicates that the simplicia was nearly free from inorganic contaminants such as sand, dust, and metal particles that might have been introduced during leaf collection and drying. Furthermore, a low total ash content minimizes the risk of spectral interference when analyzing the compounds present in Myosa leaves using instrumentation (Noureen et al., 2019).
The acid-insoluble ash content of Myosa leaf simplicia was 0.004 ± 0.000%, which met the required standard of ≤ 0.70% (Fatimawali et al., 2020). This result demonstrates that the Myosa leaf simplicia was free from contamination by sand, soil, and dust that are typically introduced during harvesting or drying. This is important because contaminants such as sand or soil can interfere with the extraction and analytical processes (Nurlela et al., 2023).

Activity of Myosa Leaves on Lipid Profile

The effect of Myosa leaves on the lipid profile is shown in **Figure 2.** The evaluated parameters included body weight, total cholesterol, and triglycerides (TG). Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were also assessed in this study. The rats exhibited a reduction in body weight after treatment **(Figure 2A).** This weight loss was directly correlated with decreased levels of cholesterol, LDL, and triglycerides **(Figures 2B, 2C, and 2D)**, as well as an increase in HDL levels **(Figure 2E)**. G 500 demonstrated the most significant potential in reducing LDL, cholesterol, and triglycerides, as well as increasing HDL, compared to the negative control ($p < 0.05$). This indicates that the higher the concentration of Myosa leaves, the greater the effect on reducing LDL, cholesterol, and triglycerides, as well as increasing HDL.

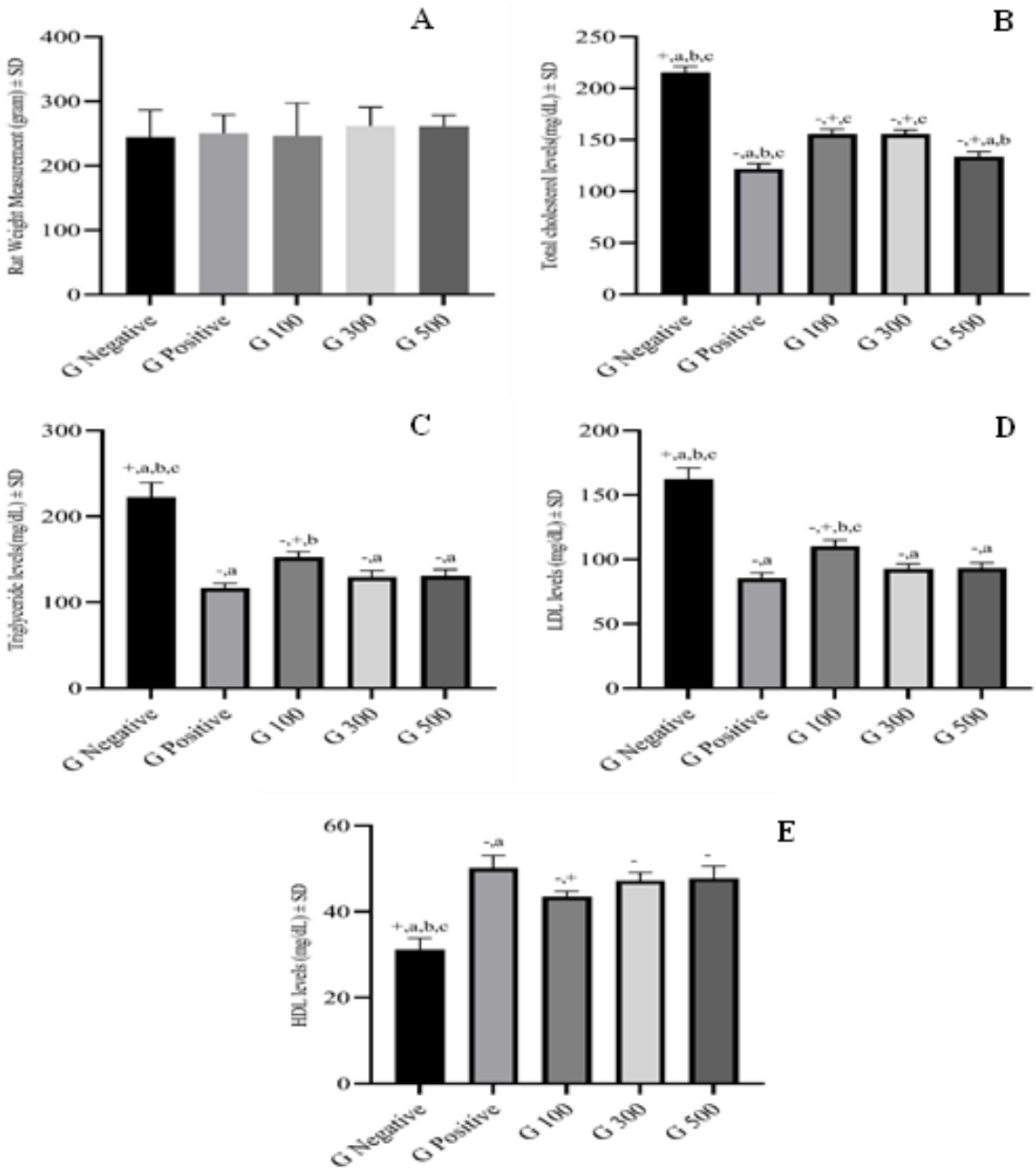

Figure 2. Lipid Profile of Rats. (A) Body weight of rats; (B) Total cholesterol level; (C) Triglyceride level; (D) LDL level; (E) HDL level. (–) Significantly different from the negative control ($p < 0.05$); (+) significantly different from the positive control ($p < 0.05$); (a) significantly different from G 100 ($p < 0.05$); (b) significantly different from G 300 ($p < 0.05$); (c) significantly different from G 500 ($p < 0.05$).

This effect may be attributed to the alkaloid content found in Myosa leaves. Myosa leaves contain approximately 40 alkaloids, some of which belong to the oxindole class and are known to influence lipid metabolism. Furthermore, their relatively high antioxidant activity also contributes to the reduction of triglyceride levels (La-up et al., 2021).

However, no significant reduction in rat body weight was observed across all control groups (Figure 4.3A). Simvastatin, used as a positive control, works by

inhibiting the HMG-CoA reductase enzyme, thereby reducing cholesterol synthesis in the liver. Nevertheless, simvastatin does not directly reduce body weight. Weight loss leads to the mobilization and oxidation of fat stored in adipose tissue into energy (Sethi et al., 2025). Consequently, the availability of substrates for very low-density lipoprotein (VLDL) synthesis in the liver decreases, resulting in reduced blood levels of LDL and triglycerides ((Burks et al., 2024). Additionally, the reduction in visceral fat also increases adiponectin levels, a hormone that plays a role in raising HDL levels through various protective mechanisms, including the activation of the AMPK-eNOS pathway (Yan et al., 2024).

A previous study involving 581 Myosa users aged 18 years and older reported a prevalence of 49.1%. The study showed that Myosa 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). Furthermore, the duration of Myosa 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 Myosa 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. Additionally, 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 body weight reduction in rats.

Result of Molecular Docking Analysis

This study used six specific compounds from Myosa leaves for docking simulation. These compounds are 7-hydroxymitragynine (CID: 44301524), corynantheidine (CID: 6540753), mitragynine (CID: 3034396), paynantheine (CID: 3037629), speciociliatin (CID: 15560576), and speciogynine (CID: 15560577). Compounds with the lowest binding affinities indicate greater binding stability with the target protein (Table 2).

Table 2. Docking Simulation Results of Active Compounds from Myosa

Compounds	Target Protein	Binding affinity (kcal/mol)	Amino Acid Residues
Paynantheine	HMG-CoA reduktase	-6,6	ARG 590, GLU 559, ASN 658, LEU 857, LEU 853, ALA 856
Speciociliatin		-6,6	ASN 658, SER 661, ARG 590, LEU 853, ALA 856, HIS 752, LEU 562, GLU 559, MET 657
Corynantheidine		-6	GLU 559, ARG 590, ALA 856
Mitragynine		-6	GLU 559, MET 657, ASN 658

7-Hydroxymitragynine		-5,8	GLY 560, GLU 559, ARG 590
Speciociliatin		-3,9	ASN 658, SER 661, ARG 590, LEU 853, ALA 856, HIS 752, LEU 562, GLU 559, MET 657
Simvastatin		-6,2	ARG 590, ALA 856, LEU 853

Description: The complete docking results are provided in the supplementary material.

HMG-CoA reductase is an enzyme involved in cholesterol biosynthesis. Inhibition of this enzyme effectively reduces cholesterol levels (Dagar et al., 2025). Paynantheine (−6.6 kcal/mol) and speciociliatin (−6.6 kcal/mol) share similar amino acid residues with simvastatin, namely ARG 590, ALA 856, and LEU 853. In addition, paynantheine interacts with LEU 857 in HMG-CoA. According to (Fajriaty et al., 2024), LEU 857 is one of the important amino acids in the HMG-CoA target protein. The potential cholesterol-lowering effects (triglycerides, total cholesterol, and LDL) may be attributed to paynantheine and speciociliatin, which are predicted to have a mechanism of action similar to that of simvastatin.

Docking analysis can provide valuable insights into the binding modes of many active compounds (Jwaid & Adnan, 2024). A lower binding affinity value indicates stronger binding strength, and vice versa (Zothantluanga & Chetia, 2022). However, binding affinity values obtained from docking simulations are not definitive. Therefore, it is strongly recommended to examine further the interactions between the active compounds isolated from Myosa leaves and the target proteins. In vitro or in vivo testing is a commonly used approach to evaluate the interactions between active compounds and target proteins (Hawash et al., 2023). Hydrogen bonding is an important component in ligand binding, and its properties should be considered during drug development due to its significant impact on drug selectivity, metabolism, and absorption (Monisha et al., 2024).

In vivo results of Myosa leaves demonstrated real potential as a metabolic syndrome therapy because they affected blood glucose reduction, improved lipid profile, reduced oxidative stress, and suppressed inflammation. The docking simulation results of active compounds 7-hydroxymitragynine, corynantheidine, mitragynine, paynantheine, speciociliatin, and speciogynine against target proteins showed strong binding affinity (-6.6 kcal/mol). Therefore, Myosa leaves-based drugs have the potential as a future Antihyperlipidemic therapeutic. However, toxicity studies are still needed to ensure long-term safety.

D. CONCLUSION

This study highlights the potential of Myosa 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. Molecular docking analysis revealed that the active compounds of Myosa leaves (7-hydroxymitragynine, corynantheidine, mitragynine, paynantheine, speciociliatin, and speciogynine)

exhibited strong binding affinities toward the active sites of the therapeutic target proteins. These findings support the hypothesis that Myosa leaves have the potential to be developed as an alternative treatment for hyperlipidemia. However, this study did not isolate specific compounds from Myosa leaves. Therefore, further studies are required to validate the effectiveness of individual Myosa-derived compounds against the active sites of the therapeutic target proteins in order to confirm the docking simulation results.

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