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The Potential Hypoglycemic Activity of *Gnetum latifolium* Ethanolic Leaf Extract

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Abstract: The study aimed to evaluate the potential hypoglycemic activity of *Gnetum latifolium* ethanolic leaf extract. This investigation was initiated due to the limited research on the hypoglycemic properties of *G. latifolium*, utilizing ethanolic extraction methodology applied to the leaves. The extract was administered at three distinct concentrations corresponding to 25%, 50%, and 75% of the LD_{50}, with metformin serving as the positive control and distilled water as the negative control group. A high-sugar diet protocol was employed to induce hyperglycemia in Swiss male albino mice. The main results demonstrated a significant dose-dependent decrease in blood glucose levels among treated mice, as measured through in vivo tail-tip blood sampling assays. Statistical analysis using one-way ANOVA was used to reveal significant differences which have a p-value of 0.74 between treatment groups. By establishing *G. latifolium* as a promising natural hypoglycemic agent, this study aims to open the door for further research into its clinical applications and therapeutic mechanisms.

Keywords: *Gnetum latifolium, Hypoglycemic Activity, Ethanolic Leaf Extract, High-Glucose Induced Diet, Tail Tip Blood Sampling.*

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I. INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases of the century and was characterized by hyperglycemia, an increase in blood glucose levels above normal limits (>125 mg/dL while fasting) (Goyel 2023). People with diabetes often experienced elevated blood sugar levels. Postprandial hyperglycemia is a condition that causes high blood sugar within a four-hour window after meals. Eating food raises blood sugar levels, and although people with hyperglycemia produce insulin, it doesn't work properly after they eat. This insufficient insulin leads to a spike in their blood sugar levels (Mouri 2023).

Various species of Gnetum genus have demonstrated significant anti-diabetic activity. For instance, G. ula, G. genum L., G. genom var tenerum have shown potential in lowering the blood glucose levels (Suksanga et al., 2022). Despite the promising anti-diabetic properties demonstrated by the Gnetum species, there is still a lack of scientific research specifically investigating *Gnetum latifolium* on its hypoglycemic activity. Considering its traditional use and phytochemical present from other gnetum species, this study aims to evaluate the hypoglycemic potential of *Gnetum latifolium.*

II. METHODS AND PREPARATION

- *Extraction of the Ethanolic Leaf Extract of Gnetum latifolium*

The powdered plant components were extracted with 90% ethanol using maceration. The dried and pulverized leaves of *G. latifolium* were soaked in 90% ethanol at a ratio of 1:5 (100 grams of pulverized leaves soaked in 500 mL of 90% ethanol). The mixture was kept at a room temperature of 20–22°C for two weeks with periodic shaking for three days using an orbital shaker at a speed of 120 rpm (Juthy et al., 2024). After three days of maceration, the mixture was filtered using Filter paper in a glass funnel. The mixture was then macerated with similar solvents to fully extract the plant material.

The filtrate was collected and evaporated using a water bath at 45 °C until a thick extract or semi-solid paste was obtained (Ermi and Fatmawati 2021). The semi-solid paste was kept at 4°C in the refrigerator until used. The average percentage yield of the ethanolic leaf extract was determined through triplicate analysis of samples and computed using the formula given below (Abbas, 2024).

$$\%\text{w/w}\ \frac{\text{weight of crude extract (g)}}{\text{weight of G.latifolium dried leaf sample (g)}} X100$$

- *Acute Oral Toxicity Test*

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OECD Test Guideline No. 425 Acute Oral Toxicity: Up and Down Procedure was used. The test substance was administered in a single dose by gavage. Animals were fasted prior to dosing; food was withheld for 3-4 hours but not water. Following the fasting period, the animals were weighed, and the test substance, ethanolic leaf extract of *G. latifolium*, was administered via oral gavage in a single dose to Swiss albino mice. The fasted body weight of each animal was determined, and the dose was calculated according to body weight. The starting dose was selected from one to four levels of the dosing procedure with fixed doses of 5, 50, 300, and 2000 mg/kg in the sighting study. If the ethanolic leaf extract of *Gnetum latifolium* induced mortality, further testing at a lower dose level was conducted to evaluate safety and establish a more accurate toxicity threshold. After the substance was administered, animals were observed at least once during the first 30 minutes after dosing, periodically during the first 24 hours (with special attention given during the first 4 hours), and daily thereafter for a total of 14 days.

➢ *High Glucose-Induced Diet*

During the induction period, the Swiss male albino mice consumed standard laboratory pellets and received an oral glucose solution administered via gavage, consisting of 20 grams of 50% D-glucose per kilogram of body weight. D-glucose was in suspension form using a ratio of 1:1 (20 g of D-glucose was diluted in 20 ml of distilled water). This intervention was conducted once daily over a two-week timeline, with hyperglycemic development expected to occur within approximately one week. The measurement of blood glucose levels was conducted at the end of each week over a two-week period (Zhan et al. 2019).

➢ *Tail Tip Sample Procedure*

Blood samples were collected from the tails of mice. The tail was pricked with a lancet pen containing a lancet, and a drop of blood was squeezed into a Glucometer. After blood collection, the pricked side of the tail was rubbed with a cotton soaked in alcohol. Blood glucose was measured on the 7th, 14th, and days. The collected blood was placed on test strips and analyzed using a Glucometer (One Touch Select) (Lopez-Pacheco 2020).

➢ *Experimental Set-Up*

Thirty Swiss male albino mice were taken and kept in the animal house of the Adventist Medical Center College Department of Pharmacy. The mice were divided into six groups, with five Swiss male albino mice in each group, to evaluate the potential hypoglycemic activity of *Gnetum latifolium* ethanolic leaf extract. Group A was kept as a healthy group with body weights ranging from 25–35 grams, while Groups B, C, D, E, and F were given 50% D-glucose. Group A served as the normal control without any treatment. Group B was given distilled water as the negative control for 21 days via oral gavage. Group C was given 50 mg/kg daily of Metformin via oral gavage. Metformin was prepared in suspension form. Groups D, E, and F received ethanolic extracts of *Gnetum latifolium* leaves at low, medium, and high doses, respectively. The *Gnetum latifolium* extracts were also administered via oral gavage (Athraa, 2022). After these treatments, the blood glucose levels of each animal were tested using the tail-tip method.

III. RESULTS

➢ *Preparation of the Plant Extract*

The crude ethanolic leaf extract of *Gnetum latifolium* is dark green, solid in mass and has a pungent odor. The figure below shows the extract of the crude of *Gnetum latifolium.* The percentage yield based on three replicants of 20 grams of dried powdered leaves of *Gnetum latifolium* soaked in 500 mL of 90% ethanol is 5.41%. Table 5 shows the individual yield obtained from each replicant.

Table 5 Percentage Yield of Ethanolic Leaf Extract of Gnetum Latifolium

Samples	Weight of powdered leaves	Weight of the Crude Extract	Percentage yield
1	20g	1.35g	6.75%
2	20g	0.6g	3%
3	20g	1.3g	6.5%
		Mean value	5.41%

➢ *Phytochemical Screening of Gnetum Latifolium*

This table presents the results of a phytochemical screening of *Gnetum latifolium* which was conducted at MSU IIT (College of Science and Mathematics, Department of chemistry). The table categorizes different phytochemical tests and their implications are represented by symbols:

- +++ (high presence)
- ++ (moderate presence)
- + (low presence)

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Table 6 Phytochemical Screening of Gnetum Latifolium

Tests	Implication
Test for Alkaloids	+++
Test for Flavonoids	++
Test for Phenols	+++
Test for Saponins	++
Test for Tannins	+
Test for Steroids	+
Test for Terpenoids	+

The results indicated that alkaloids and phenols were highly present, as denoted by the symbol (+++). Flavonoids and saponins showed moderate presence (++), while tannins, steroids, and terpenoids were detected in low quantities (+). These findings suggest that *Gnetum latifolium* is particularly rich in alkaloids and phenols.

➢ *Acute Toxicity Test*

The doses of the acute toxicity test were 5, 50, 300, 2000 mg/kg body weight. No deaths were recorded after 24 hours of administration of the various doses of the ethanolic leaf extract of Gnetum latifolium. The low dose was 50 mg/kg, middle dose was 300 mg/kg and the high dose was 2000 mg/kg. The liver, kidney, intestines and spleen of the mice were also in a good condition.

➢ *Statistical Analysis*

The researcher applied a one-way Analysis of Variance (ANOVA). The ANOVA test yielded an f-value of 0.4939 and a p-value of 0.74. Since the p-value is substantially higher than the 0.05 level of significance, the results indicate that there is no statistically significant difference in blood glucose-lowering effects among the treatment groups (low, middle, and high doses of *Gnetum latifolium*) and the control groups (Metformin and distilled water). This suggests that, within the scope of this study, the ethanolic leaf extract did not demonstrate a statistically comparable hypoglycemic effect to Metformin. As a result, no post-hoc test was necessary, as the absence of significant differences indicates that further comparisons would not provide meaningful insights.

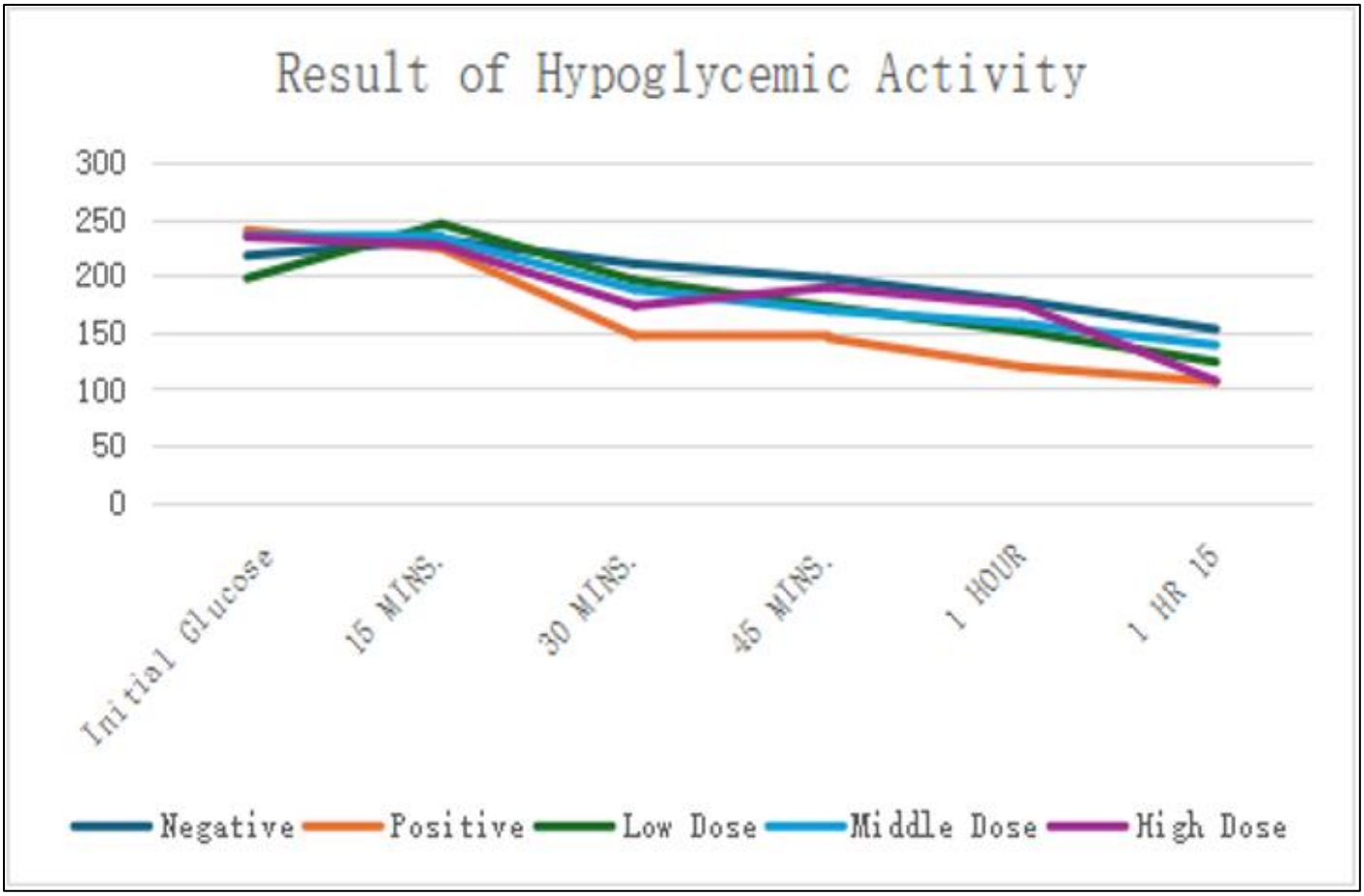

Fig 8 Line Chart Result of Ethanolic Extracts of Gnetum Latifolium (Low 50mg/Kg, Mid 300mg/Kg, High 2000mg/Kg) and the Control Groups (Positive and Negative) as time Increase.

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It presents a line chart illustrating the hypoglycemic activity of the ethanolic leaf extract of *Gnetum latifolium* at low, middle, and high doses compared to the control groups (positive and negative) over a series of time intervals. The x-axis represents the time points (initial glucose level, 15, 30, and 45 minutes, 1 hour, and 1 hour and 15 minutes), while the y-axis indicates the corresponding blood glucose levels in mg/dL. Across all groups, a general downward trend in blood glucose levels is observed, indicating a reduction over time. The positive control group, which received metformin, shows a consistent and significant decline in glucose levels, confirming its known efficacy. Notably, the high-dose *Gnetum latifolium* group closely mirrors the metformin group's performance, especially after one hour, suggesting a comparable hypoglycemic effect. Meanwhile, the low and middle-dose groups also exhibit reductions, though to a lesser extent. The negative control group shows the smallest change, implying minimal glucose regulation without treatment.

IV. CONCLUSION

Based on the study's findings, the ethanolic leaf extract of *Gnetum latifolium* demonstrated potential hypoglycemic activity, particularly at the high dose (2000 mg/kg), which achieved blood glucose reduction comparable to metformin after 75 minutes. The extract's rich phytochemical profile, particularly the high presence of alkaloids and phenols, likely contributes to its glucose-lowering effects. However, the ANOVA analysis revealed no statistically significant differences between treatment groups ($p=0.74$), indicating that the hypoglycemic effects were not significantly different from controls within the scope of this study. The delayed onset of hypoglycemic action compared to metformin suggests a different mechanism of action or slower absorption rate. The safety profile was established through acute toxicity testing, with no mortality observed at doses up to 2000 mg/kg. Based on the ANOVA results ($F = 0.4939$, $p = 0.74 > 0.05$), we accept the null hypothesis (H_{01}). The ethanolic leaf extract of *Gnetum latifolium* did not demonstrate statistically significant hypoglycemic activity comparable to metformin when analyzed across all treatment groups. In contrast to metformin's immediate action, the extract does have hypoglycemic effects at specific time points, but these effects are delayed, according to the paired t-test results.

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