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The Effect of Kratom Leaf Alkaloid Extract on Blood Glucose Levels Using an In Vivo Method

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ABSTRACT

Kratom contains alkaloids, flavonoids, saponins, and tannins, which have traditionally been used to boost energy and treat various health conditions, including diabetes. This study aims to analyze the effect of kratom leaf alkaloid extract on blood glucose levels in vivo using a quasi-experimental design. The subjects were 27 male Swiss Webster mice (Mus musculus), divided into three treatment groups receiving kratom leaf alkaloid extract at doses of 0.147 mg/20gBW, 0.294 mg/20gBW, and 0.588 mg/20gBW. The alkaloid extract was obtained through fractionation. Each treatment group was replicated nine times using purposive sampling. An oral glucose tolerance test was conducted to measure blood glucose levels. The Simple Linear Regression test results showed a p-value of 0.000 (p < 0.05), indicating a significant effect of kratom leaf alkaloid extract on blood glucose levels in vivo.

Keywords: *Kratom Leaf, Blood Glucose, In Vivo Method*

ABSTRAK

Kratom mengandung alkaloid, flavonoid, saponin, dan tanin yang secara tradisional digunakan untuk berbagai pengobatan, termasuk diabetes. Penelitian ini bertujuan menganalisis pengaruh ekstrak alkaloid daun kratom terhadap kadar glukosa darah secara in vivo menggunakan desain quasi-experiment. Subjek penelitian adalah 27 ekor mencit jantan Swiss Webster yang dibagi menjadi tiga kelompok perlakuan dengan dosis ekstrak alkaloid 0,147 mg/20gBB, 0,294 mg/20gBB, dan 0,588 mg/20gBB. Ekstrak diperoleh melalui fraksinasi, dan uji toleransi glukosa oral digunakan untuk mengukur kadar glukosa darah. Hasil uji regresi linear sederhana menunjukkan p-value = 0,000 (p < 0,05), sehingga terdapat pengaruh signifikan ekstrak alkaloid daun kratom terhadap penurunan kadar glukosa darah.

Kata kunci: Daun Kratom, Glukosa Darah, Metode *In Vivo*

INTRODUCTION

Kratom (Mitragyna speciosa Korth.) is a plant widely distributed across Southeast Asia, including Indonesia, particularly in the Kapuas Hulu Regency, West Kalimantan (1). The most commonly utilized part of the plant is its leaves, which contain approximately 57 active compounds, 40 of which are classified as alkaloids. The primary alkaloids found in kratom leaves are mitragynine and 7-hydroxymitragynine, with concentrations varying depending on environmental growing conditions. Kratom leaves from Kapuas Hulu have been reported to contain approximately 54% mitragynine relative to total alkaloid content. Alkaloid extraction typically involves solvents such as methanol, ethanol, isopropanol, or n-butanol, and is performed using techniques such as maceration, sonication, or Soxhlet extraction. This process is often followed by acid-base extraction to isolate a high-purity alkaloid fraction (2).

Traditionally, kratom leaves have been used in folk medicine to treat ailments such as cough, diarrhea, pain, opioid dependence, and gastrointestinal infections. Pharmacological studies have confirmed a wide range of biological activities associated with kratom, including analgesic, antipyretic, antidiarrheal, antidepressant, antibacterial, antidiabetic, antinociceptive, anti-inflammatory, and antioxidant properties.(3).

Antioxidants play a crucial role in protecting the body against oxidative stress caused by free radicals and may help prevent various degenerative diseases, including cancer, autoimmune disorders, cardiovascular diseases, and diabetes mellitus (4). Diabetes mellitus is a chronic metabolic condition characterized by impaired insulin secretion or action, resulting in elevated blood glucose levels (5). Both natural and synthetic antioxidants have been shown to improve insulin receptor sensitivity and enhance pancreatic β-cell function, thereby contributing to better regulation of blood glucose levels (6).

Previous research has shown that ethanol extracts of kratom leaves contain active compounds such as alkaloids, tannins, saponins, and flavonoids, which exhibit strong antioxidant activity, as indicated by a DPPH radical scavenging value of 91.86 ppm (7). Kratom alkaloids have also been reported to stimulate the secretion of growth hormone (GH), leading to increased production of insulin-like growth factor-1 (IGF-1), which helps lower blood glucose levels and inhibit gluconeogenesis, thus reducing insulin demand (8).

A study by Purintrapiban et al. demonstrated that mitragynine mimics insulin by enhancing glucose transport into muscle cells (9). Another study found that ethanol extract of kratom leaves administered at a dose of 0.294 mg/20g body weight effectively reduced blood glucose levels, showing comparable results to glibenclamide at a dose of 0.13 mg/20g body weight (10).

Based on the aforementioned scientific evidence, this study aims to analyze the effect of kratom leaf alkaloid extract on blood glucose levels using an in vivo experimental model.

METHODS

This study employed a quasi-experimental design, which includes a control group but does not entirely control for external variables that may influence the experimental process (11). This study utilized mice as experimental subjects and received ethical approval from the Health Research Ethics Committee (KEPK) of the Health Polytechnic of the Ministry of Health in Pontianak, under approval number 130/KEPK-PK.PKP/VI/2021.

The study population consisted of mice (Mus musculus). The sample comprised male Swiss Webster mice aged 2–3 months and weighing between 20–30 grams. The sample size was determined using the Federer formula, yielding 9 mice per group across three treatment groups, for a total of 27 mice (12). Sampling was conducted using purposive sampling based on inclusion and exclusion criteria. Inclusion criteria: Swiss Webster strain, male, body weight of 20–30 grams, age 2–3 months, no anatomical abnormalities, and active movement. Exclusion criteria:

inactive mice, presence of abnormal exudate, weight loss exceeding 10%, or death during the adaptation period (13).

An oral glucose tolerance test (OGTT) was used to assess blood glucose levels. The procedure involved fasting the mice for 12 hours, measuring their fasting blood glucose levels, administering oral glucose, and remeasuring glucose levels after 60 minutes. In cases of hyperglycemia, the mice were given the alkaloid extract, and final blood glucose levels were measured 60 minutes later.

Simplicia preparation: Fresh kratom leaves were washed, dried, blended, and stored. Moisture content was determined using the gravimetric method. Alkaloid extraction was carried out using maceration with methanol, purification with n-hexane, and separation with ethyl acetate to obtain the alkaloid fraction.

Phytochemical tests were conducted to detect the presence of secondary metabolites: Alkaloids were tested using Dragendorff's reagent, Flavonoids were identified using the Shinoda and $FeCl_3$ tests, Tannins were tested using 1% gelatin solution and Saponins were examined using the foam test. (14).

RESULTS AND DISCUSSION

This study began with the collection of kratom (Mitragyna speciosa (Korth.) Havil.) leaves from Selimbau Subdistrict, Kapuas Hulu Regency. Plant specimen identification was conducted at the Biology Laboratory of the Faculty of Mathematics and Natural Sciences, Tanjungpura University. The preparation of simplicia was carried out at the Chemistry-Biology Laboratory, Pontianak State Polytechnic. A total of 2.6 kg of fresh kratom leaves were washed and dried using a cabinet dryer for one day, yielding 590 grams of dried simplicia. Moisture content was determined using the gravimetric method, resulting in a water content of 4.13%.

A total of 590 grams of simplicia were macerated using methanol, yielding 3 liters of macerate. After evaporation, 105.5 grams of thick extract were obtained, with a drying loss of 2.98%. Fractionation was conducted to isolate the alkaloid compound, resulting in 7.1 grams of alkaloid extract.

Phytochemical screening of the alkaloid extract confirmed the presence of alkaloids, while flavonoids, saponins, and tannins were not detected.

Based on the analysis, the alkaloid extract of kratom leaves significantly reduced blood glucose levels, particularly at the dose of 0.147 mg/20g body weight (BW).

Table 1. Percentage Reduction in Blood Glucose Levels

Treatment Dose	Initial Glucose (mg/dL)	Post-Induction (mg/dL)	Post-Treatment (mg/dL)	% Reduction
0,147 mg/20gBB	78,78	240,89	86,89	64%
0,294 mg/20gBB	79	184,67	99,67	46%
0,588 mg/20gBB	78,78	245,67	99,33	60%

The data were found to be normally distributed and homogeneous. Therefore, a parametric statistical analysis was performed using a simple linear regression test. The test results indicated a significant effect of kratom leaf alkaloid extract on blood glucose reduction.

Tabel 2. Summary of Simple Linear Regression Analysis of Alkaloid Extract on Blood Glucose Reduction

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.875[a]	.766	.761	36.18032	.766	170.145	1	52	.000

a. Predictors: (Constant), Treatment Group

b. Dependent Variable: Blood Glucose Levels

Regression equation: y = 352,185 – 128,444x.

This equation indicates that each increase in the treatment dose results in a significant decrease in blood glucose levels.

Tabel 3. *Coefficients* Ekstrak Alkaloid Daun Kratom Terhadap Kadar Glukosa Darah Metode *In Vivo*.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Correlations		
		B	Std. Error	Beta			Zero-order	Partial	Part
1	(Constant)	352.185	15.570		22.620	.000			
	Treatment Group	-128.444	9.847	-.875	-13.044	.000	-.875	-.875	-.875

a. Dependent Variable: Blood Glucose Levels

Bivariate analysis using simple linear regression showed a strong correlation (R = 0.875) and a coefficient of determination (R^2) of 76.6%, indicating that the alkaloid extract contributed 76.6% to the reduction in blood glucose levels in mice, with the remaining 23.4% attributed to other factors. ANOVA also showed significant results ($p = 0.000 < 0.05$), further confirming the extract's effect.

After a 12-hour fasting period, mice exhibited hyperglycemia following glucose induction. Positive controls were treated with glibenclamide, while negative controls received distilled water. These comparisons confirmed that the reduction in blood glucose levels was attributable to the alkaloid extract.

The mechanism by which alkaloids reduce blood glucose levels is believed to involve several pathways, including: Regeneration of pancreatic β-cells, Increased insulin secretion, Inhibition of glucose absorption in the intestines and enhancement of glucose transport, Inhibition of glucose-6-phosphatase and fructose-1,6-bisphosphatase, reducing hepatic glucose production, Stimulation of Growth Hormone-Releasing Hormone (GHRH), leading to increased Insulin-like Growth Factor-1 (IGF-1), which aids in lowering blood glucose levels.

These findings align with previous research by Annisa Nur Pratiwi (2018), which demonstrated that ethanol extract of kratom leaves at a dose of 0.294 mg/20g BW had a glucose-lowering effect comparable to glibenclamide (10).

Overall, this study confirms that kratom leaf alkaloid extract has a significant glucose-lowering effect in mice, with the 0.147 mg/20g BW dose producing the highest reduction rate of 64%.

However, several limitations should be acknowledged. The study was conducted exclusively on male Swiss Webster mice, and the results may not be directly translatable to humans without further investigation. The extract used was a crude alkaloid fraction, and the specific active compounds responsible for the hypoglycemic effect were not isolated or quantified. Moreover, the study did not assess potential toxicological effects or long-term safety of the extract, which are critical considerations for future clinical applications.

CONCLUSION

Based on the results of this study, it can be concluded that the alkaloid extract of kratom leaves (Mitragyna speciosa (Korth.) Havil.) has potential as a hypoglycemic agent. Phytochemical screening confirmed the presence of alkaloid compounds as the primary active constituents. The in vivo test in mice demonstrated that administration of the alkaloid extract at specific doses significantly reduced blood glucose levels, with the 0.147 mg/20g body weight dose yielding the highest reduction rate of 64%.

Statistical analysis indicated that the data were normally distributed and homogeneous, and there was a strong and significant correlation between extract administration and blood glucose reduction, as evidenced by the values of $R = 0.875$ and $R^2 = 0.766$. The derived regression equation, $y = 352.185 – 128.444x$, illustrates that increasing the dosage of the extract has a substantial impact on decreasing blood glucose levels.

This study provides scientific evidence that kratom leaf alkaloids have promising potential for development as phytopharmaceutical agents in blood glucose regulation. However, further research is needed—particularly toxicological studies, mechanistic investigations, and clinical trials in humans—to support its safe and effective use.

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