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**ORIGINAL ARTICLE**

# Effects of Kratom (*Mitragyna speciosa*) Hydrogel Application on Pancreatic Histopathology in Type 2 Diabetic Mice

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## ARTICLE INFO

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## ABSTRACT

**Background:** Type 2 diabetes mellitus is a metabolic disorder characterized by elevated blood glucose caused by insulin resistance and impaired insulin production by pancreatic β-cells due to oxidative stress. Kratom (*Mitragyna speciosa*) has been widely investigated for its antidiabetic, anti-inflammatory, and antioxidant effects, attributed to its alkaloid, flavonoid, phenolic, and saponin contents. This study aimed to evaluate the potential of topical kratom hydrogel as an innovative approach to improving pancreatic histology in type 2 diabetic mice, which has not been previously reported.

**Methods:** Fifteen mice were divided into three groups: untreated diabetic group (DM), diabetic group treated with 5% kratom hydrogel (K5), and diabetic group treated with 15% kratom hydrogel (K15). Treatments were administered for two weeks. Parameters assessed included the percentage of healthy β-cells and acinar cells, as well as histological scoring of islet damage. Data were analyzed using parametric or non-parametric tests according to the normality distribution of each parameter.

**Results:** Administration of 5% kratom hydrogel significantly increased the percentage of healthy β-cells ($p<0.05$) compared with 15% kratom hydrogel, which unexpectedly showed a lower proportion of healthy cells than the untreated group. Interestingly, the higher dose appeared to exert more toxic effects, whereas the lower dose provided better protective effects. No significant differences were observed in acinar cell parameters or islet damage scores, possibly due to the limited sample size.

**Conclusion:** These findings provide preliminary evidence supporting the systemic therapeutic potential of topical kratom hydrogel, particularly in determining the effective dose and the need for larger sample sizes to obtain more consistent outcomes.

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## Introduction

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder worldwide, and its prevalence is expected to continue rising. The condition is primarily caused by two mechanisms: insufficient insulin secretion by pancreatic β-cells and insulin resistance, or a combination of both[1]. As a result, the body fails to maintain glucose homeostasis, leading to chronic hyperglycemia, which is the hallmark of diabetes mellitus[2].

Globally, type 2 diabetes mellitus accounts for more than 90% of all diabetes cases. According to the International Diabetes Federation[3], an estimated 589 million people aged 20–79 years worldwide have diabetes. In recent years, however, the incidence of diabetes has increased two- to threefold among younger individuals under 40 years of age[4]. This rise is driven by various factors, including social, economic, demographic, environmental, and genetic factors[3]. In Indonesia, the prevalence of diabetes is projected to increase from 9.19% in 2020 (18.69 million cases) to 16.09% in 2045 (40.7 million cases)[5].

This growing burden underscores the need for effective therapeutic approaches to prevent severe comorbidities such as cardiovascular disease, neuropathy, and diabetic foot. Hyperglycemia and chronic inflammation contribute to β-cell damage, reduced insulin secretion, and further deterioration of glycemic control[4]. Although numerous antidiabetic drugs are available, their long-term use is associated with side effects including insomnia, headache, hypoglycemia, renal damage, constipation, diarrhea, and gastrointestinal disturbances[6]. Therefore, phytochemical- or herbal-based agents with lower toxicity, affordability, better compliance, and a safer profile are considered promising alternatives[7].

One medicinal plant gaining increasing attention in diabetes management is kratom (*Mitragyna speciosa*), a tropical tree of the Rubiaceae family native to Southeast Asia, particularly Thailand, Malaysia, and Indonesia. Traditionally, kratom has been used to relieve fever, fatigue, pain, and diabetes. Phytochemical analyses have revealed a wide range of bioactive compounds, including indole alkaloids (e.g., mitragynine, paynantheine, speciociliatine-N-oxide, speciofoline, and corynoxine A), flavonoids, phenolics, triterpenoids, saponins, and glycosides. These constituents exhibit anti-inflammatory, antioxidant, antipsychotic, antidepressant, and antidiabetic properties[8].

Persistent hyperglycemia is known to induce lipotoxicity and glucotoxicity, leading to oxidative stress in the endoplasmic reticulum of β-cells. This condition increases reactive oxygen species (ROS) production, stimulates IL-1β release, macrophage infiltration, and inflammation, ultimately resulting in β-cell dysfunction and impaired insulin secretion[1]. Given its antioxidant, anti-inflammatory, and antidiabetic activities, kratom represents a potential therapeutic alternative. Topical delivery via kratom hydrogel may enhance bioavailability and exert therapeutic effects by improving pancreatic histology under hyperglycemic and inflammatory conditions[9]. However, studies on the topical application of kratom hydrogel remain limited, and this research aims to provide an innovative approach with promising potential in diabetes therapy.

## Methods

This study employed an in vivo experimental posttest-only control group design to evaluate pancreatic function via histology following kratom hydrogel administration in burn wounds of streptozotocin-induced type 2 diabetic mice (*Mus musculus*)[10,11].

### Materials

Ethanol extract of kratom leaves (*Mitragyna speciosa*), streptozotocin, citrate buffer, 0.9% NaCl, 10% neutral buffered formalin, hematoxylin-eosin, 0.5% Na CMC, glycerin, propylene glycol, methylparaben, distilled water, ketamine, and xylazine.

### Preparation of Kratom Hydrogel

The preparation began by extracting 500 g of kratom powder through maceration in 3500 mL of 96% ethanol (1:7 ratio). The mixture was kept in the dark for 5 days with occasional stirring and then filtered. The filtrate was evaporated at 50°C using a rotary evaporator to obtain a concentrated extract[8,12,13].

**Table 1.** Formulation of Kratom Hydrogel

| Ingredient | **Function / Role** | **Concentration (g)** | |
|---|---|---|---|
| | | **Kratom 5%** | **Kratom 15%** |
| kratom leaf ethanol extract | Active Compound | 1.5 | 4.5 |
| Na-CMC | Gelling Agent | 1.25 | 1.25 |
| glycerin | Humectant | 3.0 | 3.0 |
| methylparaben | Preservative | 0.075 | 0.075 |
| propylene glycol | Penetration Enhancer | 1.0 | 1.0 |
| ethanol 96% | Solvent/Penetration Enhancer | 5 | 5 |
| distilled water | Solvent | up to 30 g | up to 30 g |

*g = gram

The hydrogel was prepared by dissolving methylparaben in hot distilled water until homogeneous. Na-CMC, a hydrophilic polymer, was then dispersed in hot distilled water, mixed with the methylparaben solution, and homogenized (Formula 1). Formula 2 was prepared by mixing propylene glycol and glycerin, after which Formulas 1 and 2 were combined and homogenized. The previously obtained kratom leaf ethanol extract was dissolved in 5 g of 96% ethanol using a porcelain container. Propylene glycol and ethanol served as carriers, solvents, and penetration enhancers[14]. The kratom extract was gradually added to the mixture while stirring, and the remaining distilled water was incorporated until homogeneous. The mixture was left at room temperature for approximately 24 hours before use.

**Experimental Animals and Diabetes Mellitus Modeling**

The study used 15 male *Mus musculus* mice (6–8 weeks old, 25–30 g) divided into three groups: DM (positive control, STZ only), K5 (5% kratom hydrogel), and K15 (15% kratom hydrogel). Animals were obtained from Pusvetma Surabaya and acclimatized for 1 week. Baseline blood glucose was measured using a GCU (Gluco Dr), followed by diabetes induction with STZ at 50 mg/kg body weight via intraperitoneal injection for 3 consecutive days[15]. One week later, a burn wound was created on the dorsal area using a 1 × 1 cm metal plate heated with a Bunsen burner as a diabetic ulcer model[11,16]. Kratom hydrogel was applied topically once daily according to the treatment group for 2 weeks. In the fourth week, surgery was performed after fasting, blood glucose was re-measured, and anesthesia was administered via intraperitoneal injection of ketamine (70 mg/kg) and xylazine (10 mg/kg, 0.03 mL). The pancreas was excised, rinsed with physiological NaCl, and fixed in 10% formalin for histological preparation[8]. All procedures were conducted at the Laboratory of the Faculty of Medicine, Universitas Nahdlatul Ulama Surabaya, and approved by the UNUSA Health Research Ethics Committee (Approval No.: 0250/EC/KEPK/UNUSA/2025).

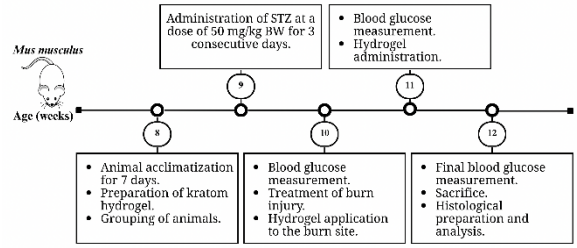


**Figure 1.** Experimental workflow showing acclimatization, diabetes induction, hydrogel treatment, and histological preparation and analysis.

**Mitragynine Bioinformatics Analysis**

In silico analysis was conducted to assess the pharmacological potential of mitragynine. Its chemical structure was obtained from PubChem, biological activity predictions from Way2Drug (PASS Online), and protein target predictions from SwissTargetPrediction. Protein-protein interactions of the identified targets were analyzed using STRING DB. All data were obtained from publicly accessible databases in 2025.

**Histopathological Examination**

Histopathological examination was performed using a light microscope (Nikon Eclipse Ei) with Optilab Sigma MTN020 connected to a computer. Each slide was observed in five fields at 400× magnification. Assessment was conducted qualitatively and quantitatively. The qualitative method evaluated Langerhans islets using a 0–4 scoring system (Score 0: 0–20% damage, normal boundaries, no edema; Score 1: 21–40% damage, clear boundaries, mild edema; Score 2: 41–60% damage, partially unclear boundaries, moderate edema; Score 3: 61–80% damage, unclear boundaries, severe edema; Score 4: 81–100% damage, very unclear boundaries, total destruction)[12,13,17-19]. The quantitative method measured the percentage of healthy beta cells (polygonal, pale cytoplasm, round nuclei) and healthy acinar cells (cuboid/ pyramidal, round basal nuclei), while damaged cells were identified based on morphological changes indicative of inflammation or necrosis[20-23]. Analysis was performed using ImageJ.

**Data Analysis**

Data were analyzed using GraphPad Prism 10 and presented as mean ± SD and graphs[8,10]. Comparisons between groups were performed using one-way ANOVA followed by Tukey's HSD post hoc test for beta cell and acinar cell parameters, and using the Kruskal–Wallis test followed by Dunn's post hoc test for scoring parameters.

## Results

**Prediction of Mitragynine Protein-Protein Interactions**

Based on the Way2Drug analysis, no biologically relevant or significant activity related to type 2 diabetes mellitus was detected (Pa<0.3). However, protein–protein interaction (PPI) analysis identified nine proteins involved in metabolic processes associated with type 2 diabetes, insulin resistance, insulin secretion, and the AGE-RAGE signaling pathway in diabetic complications (Table 2). These findings suggest a potential role of mitragynine in modulating

biological pathways associated with type 2 diabetes mellitus.

**Table 2**. Protein Targets in Type 2 Diabetes KEGG Pathways (STRING DB)

| KEGG Pathway | ID | Protein Target |
|---|---|---|
| Type 2 Diabetes Mellitus | hsa04930 | CACNA1C, MTOR, MAPK8 |
| Insulin Resistance | hsa04931 | SLC27A1, AGT, MTOR, MAPK8 |
| Insulin Secretion | hsa04911 | GNAQ, GNA11, CACNA1C |
| AGE-RAGE Signaling Pathway in Diabetic Complications | hasa04933 | NOX4, JAK2, AGT, MAPK8 |

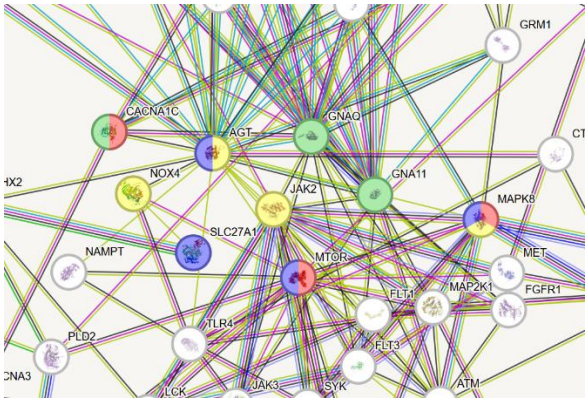


**Figure 2.** Protein–protein interaction (PPI) network of mitragynine target proteins predicted using STRING DB. Red nodes: type 2 diabetes mellitus; purple: insulin resistance; green: insulin secretion; yellow: AGE–RAGE signaling pathway in diabetic complications. The pattern indicates the potential of mitragynine to modulate target proteins involved in insulin regulation and inflammatory processes relevant to the pathogenesis of type 2 diabetes mellitus.

**Effects of Kratom Hydrogel on Pancreatic Beta Cells**

As shown in Figure 2A, there were significant differences in the proportion of pancreatic beta cells among all groups following hydrogel treatment. The K5 group exhibited a higher proportion of healthy cells compared to the DM group, whereas the K15 group showed a decreased proportion of healthy cells relative to the DM group. The effects of kratom on Langerhans islet histology and beta cells are illustrated in Figure 3.

**Effects of Kratom Hydrogel on Langerhans Islet Damage Scoring**

As shown in Figure 3, the K5 group exhibited lower damage compared to the DM and K15 groups, with the highest damage observed in the K15 group. Assessment was based on the percentage of damage, degree of edema, and islet boundaries. Although the differences were not statistically significant, descriptive differences among groups were still evident in the graph (Figure 2B).

**Effects of Kratom Hydrogel on Langerhans Islet Damage Scoring**

As shown in Figure 2C, no significant differences were observed among all groups. Descriptively, 5% kratom treatment exhibited a trend toward a higher proportion of healthy cells compared to the untreated group, whereas 15% kratom decreased the proportion of healthy cells. These findings are supported by histological observations shown in Figure 4.

**Table 3.** Descriptive Statistics (mean ± SD) of the Analyzed Parameters

| Parameters | DM (n=4) | K5 (n=4) | K15 (n=4) |
|---|---|---|---|
| Average Healthy Beta Cell | 0.45 ± 0.02 | 0.53 ± 0.03 | 0.35 ± 0.04 |
| Damage Scoring | 2.12 ± 0.61 | 1.77 ± 0.54 | 2.27 ± 0.23 |
| Average Healthy Acinous Cell | 0.46 ± 0.03 | 0.53 ± 0.04 | 0.45 ± 0.07 |

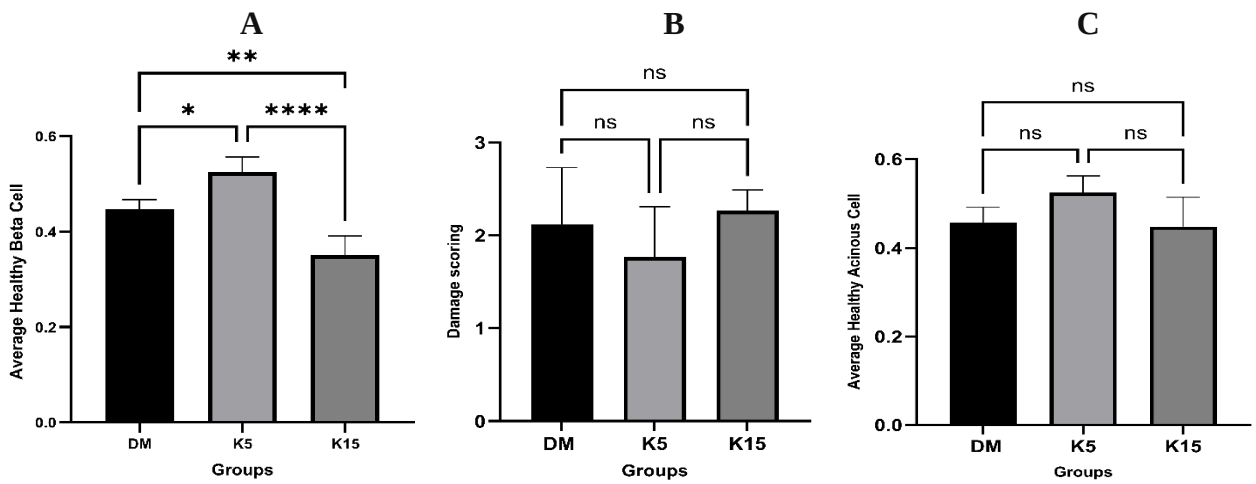

**Figure 3.** Effects of Kratom administration on the percentage of healthy beta cells **(A)**, histological scoring of Langerhans islet damage **(B)**, and the percentage of healthy acinar cells **(C)**. Three experimental groups were evaluated: DM (untreated diabetes), K5 (diabetes + 5% Kratom), and K15 (diabetes + 15% Kratom). Data are presented as mean ± SD (n = 4). *p < 0.05 (K5 vs. DM); **p < 0.01 (DM vs. K15); ****p < 0.0001 (K5 vs. K15) indicate the levels of statistical significance between groups.

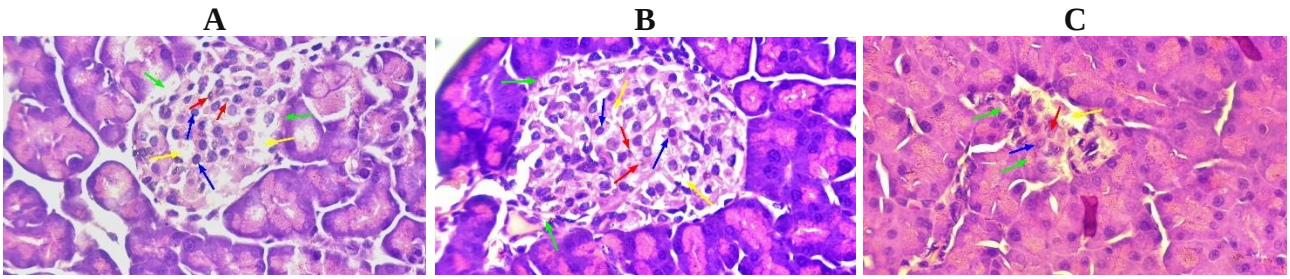


**Figure 4.** Histopathological features of pancreatic islets in mice stained with hematoxylin and eosin (HE) at 400× magnification. Healthy cells are indicated by number 2 in blue, while abnormal cells are indicated by number 8 in yellow. Four arrows highlight distinct structures: blue (healthy cells), red (abnormal cells), yellow (edema), and green (islet boundary). **(A)** DM group (untreated diabetes), showing moderate edema and partially indistinct boundaries; **(B)** K5 group (diabetes + 5% Kratom), showing moderate edema with clearly defined boundaries; **(C)** K15 group (diabetes + 15% Kratom), showing moderate edema with indistinct boundaries.

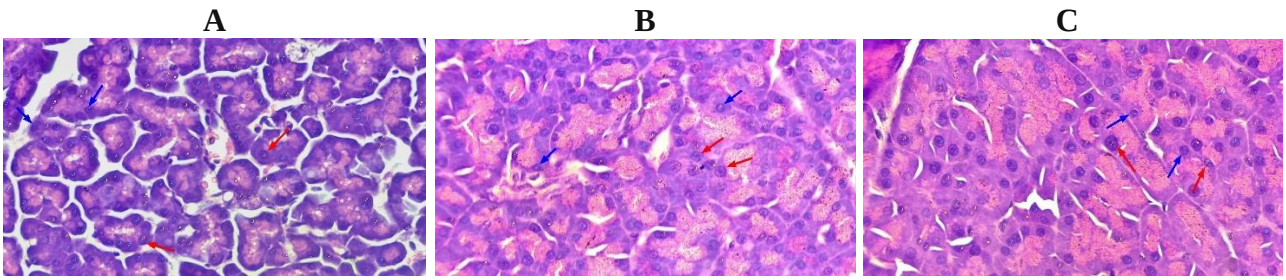


**Figure 5.** Histopathological features of pancreatic acinar cells in mice stained with hematoxylin and eosin (HE) at 400× magnification. Healthy cells are indicated by number 2 in blue, while abnormal cells are indicated by number 8 in yellow. Two arrows indicate different structures: blue (healthy cells) and red (abnormal cells). **(A)** DM group (untreated diabetes); **(B)** K5 group (diabetes + 5% Kratom); **(C)** K15 group (diabetes + 15% Kratom).

## Discussion

The results of this study indicate that topical application of 5% kratom hydrogel (K5) increased the proportion of healthy pancreatic beta cells compared to the diabetic control group (DM). However, at a higher concentration (15%, K15), the effect was reversed, with a lower proportion of healthy cells compared to the DM group. These findings suggest that low-dose kratom may exert a protective effect, whereas high doses tend to induce toxic effects.

The diabetes model used in this study was induced by streptozotocin (STZ). Streptozotocin is a compound that damages pancreatic beta cells through alkylation, leading to DNA fragmentation and depletion of NAD+ and ATP in mitochondria[24]. Consequently, increased free radicals trigger oxidative stress and activate apoptosis and necrosis pathways in beta cells, resulting in reduced insulin production and subsequent hyperglycemia[25].

The protective effect observed in the K5 group is consistent with previous studies reporting that alkaloids, particularly mitragynine, as well as other bioactive compounds such as flavonoids, phenolics, saponins, tannins, and glycosides, possess antioxidant, anti-inflammatory, and antidiabetic activities[8,9,26,27]. These protective mechanisms are mediated through the inhibition of prostaglandins via COX-2 suppression, reduction of iNOS activity, and decreased production of reactive oxygen species (ROS)[28,29]. This aligns with the pathogenesis of diabetes mellitus, where hyperglycemia and hyperlipidemia induce an imbalance that leads to excessive ROS generation[1]. In addition, kratom has been shown to inhibit α-glucosidase, thereby reducing glucose absorption[9,30]. Furthermore, in silico analysis

supports these findings by indicating kratom's involvement in modulating and inhibiting key inflammatory regulatory proteins such as MAPK, as well as regulating abnormal MTOR activation [31,32].

Topical application of kratom in hydrogel form is also a key aspect of this study. This route offers several advantages, including biocompatibility, biodegradability, non-toxicity, non-allergenicity, ease of use, and high water content, which enhances drug penetration through the skin[33,34]. Moreover, this administration route bypasses first-pass hepatic metabolism and prevents degradation of compounds in the gastrointestinal tract by acids or enzymes[9]. Consequently, it may improve the bioavailability of active compounds, allowing systemic effects to be achieved even at relatively low doses. Therefore, hydrogel formulations provide an alternative approach compared to the oral route, which is often associated with low bioavailability due to gastric degradation and hepatic metabolism.

Conversely, in the K15 group, the higher kratom dose resulted in indications of toxicity. This finding is consistent with previous reports showing that high-dose kratom administration in experimental animals increases levels of albumin, triglycerides, cholesterol, ALT, and AST[35,36]. This effect may be attributed to kratom's opioid agonist activity, which exerts addictive properties at high doses, or its inhibitory effect on several cytochrome P450 isoenzymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4[37]. However, it remains unclear whether these mechanisms are strictly dose-dependent or also occur at lower doses. Such toxicity may aggravate metabolic disturbances in diabetes by inducing hepatic injury, thereby impairing gluconeogenesis, increasing triglyceride levels, and ultimately contributing to both glucotoxicity and lipotoxicity[1].

Histopathological changes support these findings. In the K15 group, Langerhans islet damage was greater than in the DM group, characterized by unclear islet boundaries and interstitial edema, indicating an inflammatory process[38,39]. In contrast, the K5 group exhibited the mildest damage. Similar patterns were observed in pancreatic acinar cells, with the highest proportion of healthy cells in the K5 group and the lowest in the K15 group. These findings are consistent with the concept that diabetes can induce exocrine pancreatic damage through inflammatory cell infiltration and fat accumulation[1,40].

Although the differences were not statistically significant, these findings provide a descriptive indication that low-dose kratom may be more protective than high-dose kratom. However, the interpretation of these results is limited by the small sample size and the determination of the effective dose; therefore, further studies with larger sample sizes and varied dosing are required to confirm the validity of the findings and their implications. In addition, in silico analysis through protein target prediction suggested a potential involvement of active kratom compounds in pathways related to diabetes mellitus, which may correlate with the observed changes in pancreatic histopathology in mice. Nevertheless, the roles of these proteins require further investigation to obtain more conclusive results.

## Conclusion

This study demonstrates that topical administration of kratom hydrogel has the potential to exert systemic therapeutic effects on the pancreas, although the response is dose-dependent. Nevertheless, this study has several limitations, including the small sample size and the absence of a defined safe and effective dose, which necessitate cautious interpretation of the findings. These results provide a preliminary basis for the development of kratom hydrogel as a topical therapy. Further studies are required to evaluate and determine the optimal dose and an adequate sample size to achieve more consistent outcomes. In addition, in silico analysis indicates the involvement of molecular pathways relevant to the pathophysiology of diabetes, thereby opening opportunities for further exploration of the underlying molecular mechanisms.

## Conflict of Interest

No conflict of interest in this study

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