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Antidiabetic and Hypolipidemic Efficacy of Glu-NK Decoction in a High-Fat Diet and Streptozotocin-Induced Mouse Model of Type 2 Diabetes

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a global metabolic disorder demanding effective and safe therapeutic strategies. Polyherbal formulations offer a promising multi-target approach. **Aim:** To evaluate the hypoglycemic efficacy and metabolic effects of Glu-NK in a High-Fat Diet (HFD) and streptozotocin (STZ)-induced T2DM mouse model. **Methods:** Swiss albino mice received HFD with fructose supplementation for 8 weeks, followed by low-dose STZ (100 mg/kg, i.p.) to induce T2DM. Diabetic mice were randomly assigned to receive distilled water (model control), glibenclamide (15 mg/kg/day), or Glu-NK at 96 or 48 mL/kg/day for 2 weeks. **Results:** Both Glu-NK doses significantly reduced fasting blood glucose levels after 2 weeks, with the higher dose (96 mL/kg/day) demonstrating effects comparable to glibenclamide ($p < 0.001$ vs. model control). Glu-NK treatment significantly decreased total cholesterol and LDL-cholesterol ($p < 0.05$ to $p < 0.01$) and increased hepatic glutathione levels ($p < 0.05$ to $p < 0.001$) compared to diabetic controls. A favourable trend toward improvements in HDL-cholesterol and pancreatic oxidative stress parameters was observed. However, hepatorenal function markers (AST, ALT, creatinine, urea) and histopathological features showed no significant improvement after 2 weeks of treatment.

Major Finding: These findings suggest that while Glu-NK holds potential as a complementary metabolic therapy, longer treatment durations are required to facilitate meaningful tissue recovery. Further studies are warranted to evaluate its long-term tissue-protective efficacy and mechanisms of action.

Keywords: Antidiabetic, Glu-NK, High-Fat Diet, Mouse Model, Oxidative Stress, Streptozotocin

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1. Introduction

Diabetes mellitus is a chronic metabolic disease characterised by persistent hyperglycemia resulting from impaired insulin secretion and/or action due to pancreatic β-cell dysfunction[1]. The global burden of diabetes continues to escalate dramatically. According to the International Diabetes Federation's Diabetes Atlas 11th edition, approximately 589 million adults worldwide were living with diabetes in 2024, with

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projections indicating a rise to 853 million by 2050, accompanied by substantial mortality and global health expenditure exceeding USD 1 trillion[2]. Type 2 Diabetes Mellitus (T2DM) accounts for over 90% of all diabetes cases and is the primary driver of diabetes-related morbidity, including cardiovascular disease, nephropathy, neuropathy, and retinopathy[1,3].

Current pharmacological management of T2DM encompasses multiple drug classes with complementary mechanisms of action. As outlined in the American Diabetes Association's Standards of Care in Diabetes-2025, first-line and adjunctive therapies include metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, sulfonylureas, and insulin[4]. While these agents effectively reduce hyperglycemia and provide cardiorenal protection, their chronic use is frequently associated with adverse effects, including weight gain, hypoglycemia, gastrointestinal disturbances, and cardiovascular risks[4]. These limitations underscore the need for safer, better-tolerated adjunctive therapeutic options.

In response to the growing global burden of T2DM and the limitations of existing therapies, intensive research efforts have focused on developing novel pharmacological agents targeting emerging pathways in T2DM pathogenesis[5]. Among these approaches, herbal medicines have gained considerable attention as promising complementary therapeutic options for long-term T2DM management. Systematic reviews and meta-analyses have demonstrated that herbal interventions can improve glycemic control, enhance insulin sensitivity, optimise lipid profiles, strengthen antioxidant defences, and reduce the risk of diabetic complications, often with superior tolerability compared to conventional synthetic agents[6–9]. Polyherbal formulations represent a particularly promising strategy, as they can provide enhanced therapeutic efficacy through synergistic multi-target mechanisms that address the complex, multifactorial pathophysiology of T2DM[10]. Several individual medicinal plants have demonstrated significant antidiabetic activity in both preclinical models and clinical trials. For example, *Biophytum sensitivum*, *Momordica charantia*, and *Gymnema sylvestre* have all shown hypoglycemic effects through various mechanisms[11–13]. However, despite these promising attributes, the clinical translation and widespread adoption of polyherbal formulations are often hindered by significant challenges. These include variability in phytochemical standardisation, unpredictable bioavailability, potential herb-drug interactions, and a general scarcity of rigorous, evidence-based preclinical and clinical studies validating their exact mechanisms of action and long-term safety.

Building on this evidence base, Glu-NK was developed as a specifically tailored polyherbal formulation. It is deeply rooted in the clinical experiences of renowned traditional Vietnamese physicians, Tue Tinh and Nguyen Kieu, and was formulated according to the classical compounding principle of 'Emperor, Minister, Assistant, and Courier'. Based on this criterion, *Biophytum sensitivum* (sour, cool) acts as the principal ‹Emperor› herb to clear heat. *Radix Fallopiae multiflorae* nourishes the blood and enhances liver-kidney functions. *Herba Ecliptae*, *Herba Centellae asiaticae*, and *Fructus Momordicae charantiae* act synergistically to cool the blood, promote diuresis, and further tonify the liver and kidneys. Meanwhile, *Rhizoma Smilacis glabrae*, *Semen Sennae torae*, and *Gymnema sylvestre* are integrated to enhance detoxification, regulate metabolic pathways, and provide potent hypoglycemic effects. Finally, *Gossampinus malabarica* serves as the ‹Courier› herb to guide the active constituents and stabilise the overall formulation. While the individual constituent herbs possess extensively documented pharmacological activities, their specific synergistic interaction within this exact combination has not been previously evaluated, making this study the first to provide modern scientific validation for this traditional remedy. This formulation was strategically designed to achieve synergistic, multi-target therapeutic effects by simultaneously modulating multiple pathways involved in T2DM pathophysiology, including glucose uptake, lipid metabolism, and oxidative stress. We hypothesised that the oral administration of the Glu-NK extract would synergistically mitigate hyperglycemia, ameliorate dyslipidemia, and reduce tissue oxidative stress in a combined HFD and streptozotocin (STZ)-induced T2DM mouse model. To test this hypothesis, the present study was conducted to comprehensively evaluate the hypoglycemic and metabolic effects of Glu-NK in this established *in vivo* model. The present study

was conducted to investigate the hypoglycemic and metabolic effects of Glu-NK in a combined HFD and streptozotocin (STZ)-induced T2DM mouse model. This model closely mimics the pathophysiological features of human T2DM, including obesity, insulin resistance, and progressive β-cell dysfunction. The findings will provide essential preclinical evidence to support the development of Glu-NK as a safe and effective adjunctive therapy for the management of T2DM and help address the escalating global burden of this disease.

2. Materials and Methods

2.1 Plant Material

Glu-NK is a polyherbal liquid extract developed as a traditional Vietnamese remedy for supportive management of type 2 diabetes mellitus. Each 200 mL of Glu-NK extract is prepared from 100 g of authenticated crude herbal material containing *Biophytum sensitivum* (20 g), *Radix Fallopiae multiflorae* (15 g), *Herba Ecliptae* (5 g), *Herba Centellae asiaticae* (5 g), *Fructus Momordicae charantiae* (15 g), *Rhizoma Smilacis glabrae* (10 g), *Semen Sennae torae* (10 g), *Caulis et folium Gymnemae sylvestris* (10 g), and *Gossampinus malabarica* (D.C.) (10 g). All raw materials were collected from certified medicinal plant cultivation areas in Vietnam. They were botanically authenticated and processed in accordance with the quality standards specified in the Vietnamese Pharmacopoeia V and institutional quality standards, yielding a liquid extract[14].

To characterise the phytochemical profile, the total phenolic and flavonoid contents of the Glu-NK decoction were quantified.

2.2 *In Vitro* Antioxidant Capacity

2.2.1 DPPH Radical Scavenging Assay

Free radical scavenging activity was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method[15]. A DPPH stock solution (0.1 mM in methanol) was mixed with the extract at various concentrations (1:1 v/v). The mixture was incubated in the dark at room temperature (25 ± 2°C) for 30 minutes, and the absorbance was measured at 517 nm. Ascorbic acid served as the positive control. The IC_{50} value was calculated from the percentage of inhibition, determined in triplicate.

2.2.2 Ferric Reducing Antioxidant Power (FRAP) Assay

Reducing capacity was determined using a modified FRAP assay[15]. Fresh FRAP reagent was prepared by mixing 10 mM TPTZ (in 40 mM HCl), 20 mM $FeCl_3 \cdot 6H_2O$, and 300 mM acetate buffer (pH 3.6) in a 1:1:10 ratio. The extract solution (300 µL) was mixed with FRAP reagent (2.7 mL) and incubated at 37°C for 20 minutes. Absorbance was measured at 593 nm. Results were expressed as µmol ferrous ion equivalents per millilitre (µmol Fe^{2+}-Eq/mL), with ascorbic acid as the reference standard.

2.3 Drugs and Chemicals

Streptozotocin (1 g/vial) was purchased from Sigma-Aldrich (Singapore). Glibenclamide tablets (5 mg; Domesco Medical Import-Export Joint Stock Corporation, Vietnam) were used as the positive control. Serum triglyceride, HDL-cholesterol, and total cholesterol levels were determined using commercial diagnostic kits (Erba Diagnostics, Germany). Blood glucose was measured using On Call Plus and On Call EZII glucose test strips and meters (ACON Laboratories, Inc., USA). Haematological parameters were analysed using ABX Minidil LMG diluent (Horiba ABX Diagnostics, France) on a Vet abc™ Animal Blood Counter (Horiba ABX, France). Citrate buffer (pH 4.5) and distilled water were also employed.

2.4 Animals

Healthy *Swiss* albino mice of both sexes (weight: 30 ± 2 g) were supplied by the National Institute of Hygiene and Epidemiology (Hanoi, Vietnam). Animals were housed in individual polypropylene cages (10 mice per cage) under standard laboratory conditions (temperature: 25 ± 2°C; relative humidity: 50 ± 5%; 12-h light/dark cycle). Before the study, all mice were acclimatised for 7 days with free access to a standard pellet diet and water *ad libitum*.

2.5 Study Design

The study was conducted in two phases: (1) induction of type 2 diabetes mellitus (T2DM) in *Swiss* albino mice using a combination of high-fat diet and streptozotocin, and (2) evaluation of the therapeutic effects of Glu-NK and glibenclamide (positive control) in the established T2DM model[16–18].

2.5.1 Phase 1: Induction of the T2DM Model

Mice were randomly divided into two groups. Baseline fasting blood glucose was measured from the tail vein blood after overnight fasting. Group 1 received a Normal-Fat Diet (NFD), while Group 2 received a HFD containing 42.89% saturated fat combined with 55% fructose syrup (Daesang Corporation, Korea) for eight consecutive weeks[17,18]. After 8 weeks, fasting blood glucose was measured again. Mice in Group 2 then received a single intraperitoneal injection of streptozotocin (STZ, 100 mg/kg body weight) dissolved in citrate buffer (pH 4.5),[8,9] while Group 1 received citrate buffer alone. Seventy-two hours post-injection, fasting blood glucose was measured a third time in double. STZ-treated animals with an average fasting blood glucose level of>8 mmol/L were considered diabetic and proceeded to Phase 2.

2.5.2 Phase 2: Treatment and Evaluation

Non-diabetic mice from Group 1 served as the normal control (Group 1) and received distilled water orally. Diabetic mice from Group 2 were randomly divided into four groups (n=10/group): Group 2 (diabetic model control) received distilled water; Group 3 (positive control) received glibenclamide (15 mg/kg/day); Group 4 received low-dose Glu-NK (48 mL/kg/day); Group 5 received high-dose Glu-NK (96 mL/kg/day). The selected doses were derived from the recommended therapeutic dosages for each constituent herb as prescribed by the Vietnamese Pharmacopoeia[14], and the safety profile confirmed by preliminary acute and repeated-dose subchronic toxicity studies. The oral treatments were initiated immediately following the subsequent group randomisation. All treatments were administered orally once daily for 2 weeks. Fasting blood glucose levels were measured at baseline (t_0, before treatment), after 1 week (t_1), and after 2 weeks (t_2) of treatment.

At the end of the treatment period, mice were euthanised. Blood was collected for biochemical analysis. The liver and pancreas were excised, weighed, and processed (60% of animals per group) for assessment of organ weights, antioxidant status, gross pathology, and histopathology.

To ensure experimental rigour and minimise bias, the investigators responsible for daily treatment administration, animal handling, biochemical assays, and histopathological examinations were blinded to the group allocations until the final data analysis was completed.

2.6 Serum Biochemical Markers

Serum levels of Total Cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C) were measured to evaluate lipid profiles. Hepatocellular injury was assessed by serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Renal function was evaluated by measuring serum creatinine and urea concentrations.

2.7 Oxidative Stress Markers

For oxidative stress parameters, liver and pancreas tissue homogenates (10% w/v) were prepared in ice-cold phosphate-buffered saline (PBS, pH 7.4) and centrifuged at 10,000 rpm for 15 minutes at 4°C. The supernatant was used for assays.

2.7.1 Malondialdehyde (MDA)

Lipid peroxidation was measured using high-performance liquid chromatography (HPLC; Shimadzu, Japan) with visible detection at 532 nm[19]. Supernatants were deproteinized with trichloroacetic acid (TCA, 10%) and reacted with thiobarbituric acid (0.8%). Results were expressed as nmol MDA/50 mg tissue.

2.7.2 Reduced Glutathione (GSH)

GSH levels were quantified via HPLC using Ellman's reagent (DTNB) with detection at 330 nm[20]. Supernatants were deproteinized with TCA (10%) and reacted with DTNB in phosphate buffer (pH 8.0). Results were expressed as μg GSH/50 mg tissue.

2.8 Histopathological Examination

A total of 30 liver and pancreas samples (6 per group) were examined. Organs were weighed using a digital precision balance, fixed in 10% neutral buffered formalin, paraffin-embedded, sectioned, and stained with hematoxylin and eosin (HandE). Sections were evaluated for morphological changes by an independent pathologist who was blinded to the experimental treatment groups. Sections were examined under a light microscope (Olympus BX43, Japan), and photomicrographs were captured using an attached digital camera (Olympus SC180, Japan) at 200× magnification.

2.9 Statistical Analysis

All data were analysed using SPSS software version 26.0 (IBM Corporation, Armonk, NY, USA). Results are presented as mean ± Standard Deviation (SD). Statistical comparisons between groups were performed using Student's t-test for two-group comparisons and one-way analysis of variance (ANOVA) followed by Bonferroni's post-hoc tests for multiple group comparisons. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Phytochemical Standardisation

Total phenolic content was determined using the Folin-Ciocalteu method[21], yielding 1.37 ± 0.08 mg Gallic Acid Equivalents (GAE)/mL for the water extract and 0.62 ± 0.01 mg GAE/mL for the methanol extract. Total flavonoid content was quantified via the Dowd method[22], yielding 3.37 ± 0.19 mg Quercetin Equivalents (QE)/mL for the water extract and 2.41 ± 0.01 mg QE/mL for the methanol extract. Values represent the mean ± SD of three independent determinations.

3.2 *In Vitro* Antioxidant Capacity of Glu-NK Decoction

The antioxidant potential of the Glu-NK decoction was evaluated using two complementary assays across multiple dose concentrations. All experiments were performed in independent triplicates, and the results are expressed as mean ± Standard Deviation (SD). In the DPPH radical scavenging assay, the aqueous extract demonstrated stronger activity (IC_{50} = 0.576 ± 0.05 mg/mL) compared to the methanolic extract (IC_{50} = 1.10 ± 0.10 mg/mL). Both extracts were significantly less potent than the ascorbic acid control (IC_{50} = 4.47 µg/mL). Conversely, the FRAP assay indicated that the methanolic extract possessed a superior reducing capacity (32.65 ± 2.1 µmol Fe^{2+}-Eq/mL) compared to the aqueous extract (22.56 ± 5.7 µmol Fe^{2+}-Eq/mL). Strong linear correlations between concentration and absorbance were observed for both standards and extracts (R^2 = 0.99).

3.3 Effects of Glu-NK on Body Weight and Blood Glucose Levels

Diabetic induction period: (a) Body weight progression of mice fed a NFD (n=10) or HFD (n=40) over 8 weeks; (b) Fasting blood glucose levels in NFD and HFD groups at baseline (T0), after 8 weeks of diet (T8w), and 72 hours post-STZ injection (T+72h); Treatment period: (c) Body weight changes during the 2-week treatment period across experimental groups (n=10 per group); (d) Fasting blood glucose levels at baseline (t_0), after one week (t_1), and after two weeks (t_2) of treatment with glibenclamide or Glu-NK. **,*** p<0.01, p<0.001 compared to baseline (induction); $^{\Delta}$, $^{\Delta\Delta\Delta}$ p<0.05, p<0.001 compared to the NFD group (induction) or the model group (treatment); $^{\$}$,$^{\$\$}$p<0.05, p<0.01 compared to baseline (induction).

Body weight increased progressively in both diet groups. Mice on the HFD showed pronounced weight gain from week 4 onward ($p < 0.001$), with significantly greater increases compared to the NFD group at weeks 4, 6, and 8 ($p < 0.05$) (Figure 1a). Fasting blood glucose remained stable in the NFD group throughout the induction period. After 8 weeks of HFD feeding, glucose levels in the HFD group rose significantly versus baseline ($p < 0.001$). At 72 hours post-STZ injection, glucose levels increased markedly by 207.4% compared to pre-STZ values ($p < 0.001$) and were significantly higher than in the NFD group ($p < 0.001$), confirming successful establishment of the diabetic model (Figure 1b).

The hypoglycemic effect of Glu-NK demonstrated a delayed, time-dependent pattern. After the first week of treatment, fasting blood glucose levels remained elevated; neither the Glu-NK doses (48 or 96 mL/kg/day) nor the glibenclamide positive control (15 mg/kg/day) produced a statistically significant improvement ($p > 0.05$). However, after two weeks of treatment, the high-dose Glu-NK (96 mL/kg/day) yielded a highly significant reduction in fasting blood glucose compared to the diabetic control ($p < 0.001$), achieving an efficacy comparable to that of glibenclamide. The low-dose Glu-NK (48 mL/kg/day) demonstrated a moderate but non-significant trend toward reduction at the end of the 2 weeks (Figure 1c and 1d).

3.4 Effects of Glu-NK on Serum Biochemical Parameters

HFD/STZ-induced diabetic mice exhibited a significantly dysregulated lipid profile, with elevated serum Total Cholesterol (TC), triglycerides (TG), and LDL-Cholesterol (LDL-C), and reduced HDL-Cholesterol

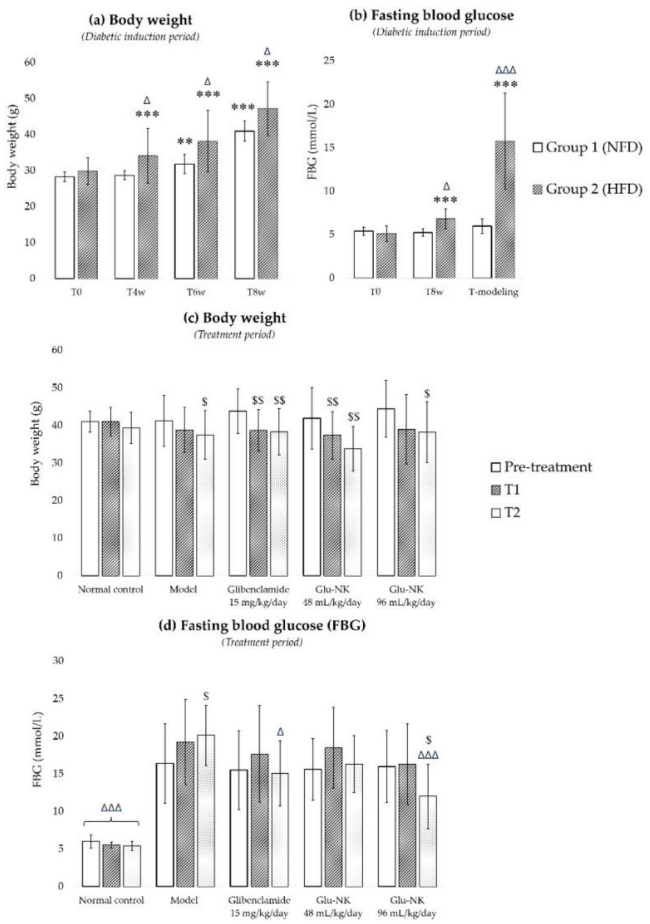


Figure 1. Changes in body weight and fasting blood glucose during the induction and treatment of T2DM.

(HDL-C) compared to normal controls ($p < 0.001$ or $p < 0.05$). Glibenclamide treatment did not significantly improve TC or LDL-C levels ($p > 0.05$). In contrast, both doses of Glu-NK significantly reduced TC and LDL-C ($p < 0.05$ or $p < 0.01$) and showed a positive trend toward increasing HDL-C ($p > 0.05$) after two weeks of treatment (Figure 2).

Serum ALT levels were elevated in all diabetic groups (diabetic control, glibenclamide, and both Glu-NK groups) compared to the normal control ($p < 0.05$ or $p < 0.01$), with no significant differences between the diabetic treatment groups ($p > 0.05$). No significant differences were observed across groups for serum AST, creatinine, or urea levels ($p > 0.05$) (Figure 2).

3.5 Effects of Glu-NK on Oxidative Stress and Organ Weights

Diabetic mice developed significant hepatomegaly, evidenced by increased relative liver weight compared to normal controls ($p < 0.01$). Neither glibenclamide nor Glu-NK treatment for two weeks altered this parameter (Figure 3a). Pancreatic weight showed a decreasing trend in diabetic groups, consistent with partial β-cell loss, but this did not reach statistical significance (Figure 3b).

In the liver, Glu-NK treatment significantly increased GSH levels compared to the diabetic model group ($p < 0.05$ and $p < 0.001$, respectively), and showed a trend toward reducing MDA ($p > 0.05$) (Figure 3a). In contrast, in the pancreas, neither GSH nor MDA levels were significantly altered by any treatment compared to the diabetic control ($p > 0.05$) (Figure 3b).

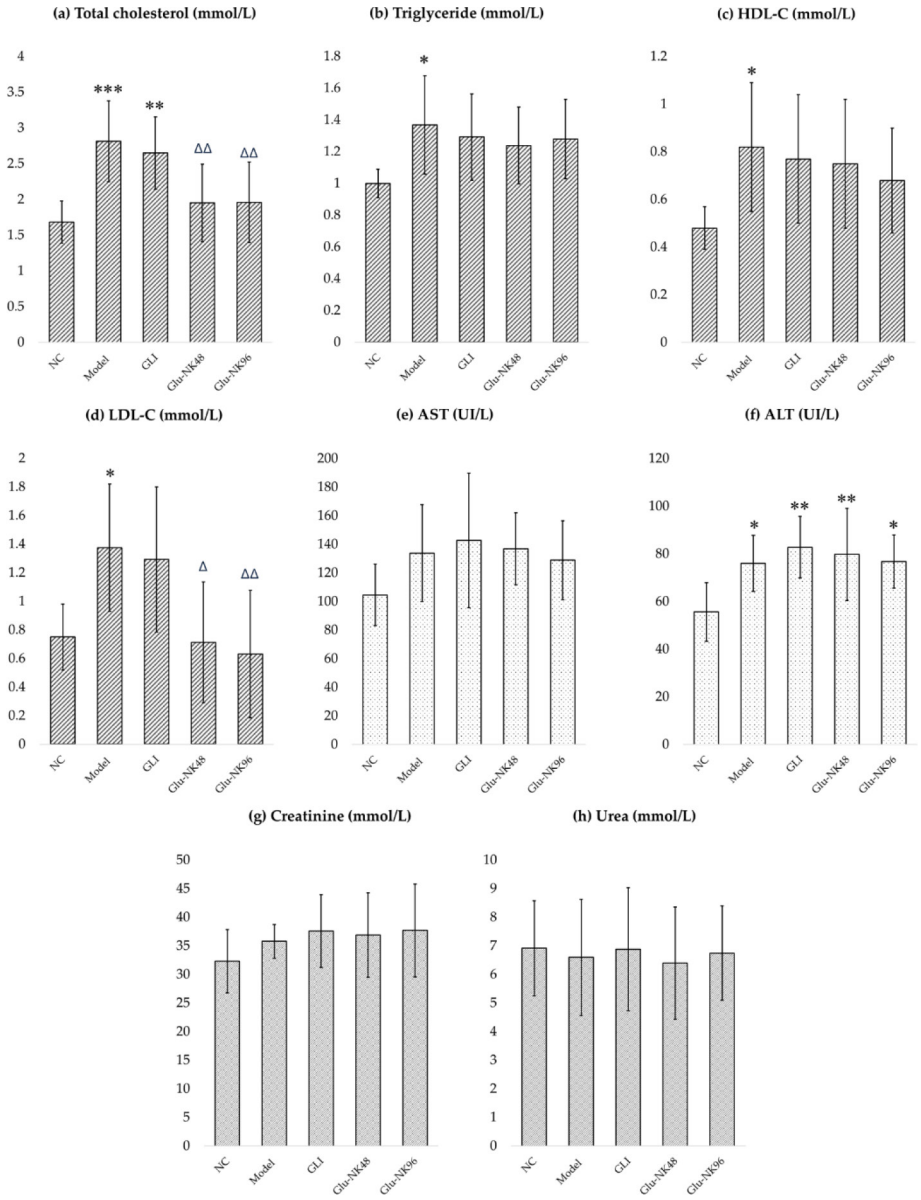
3.6 Effects of Glu-NK on Gross and Histopathological Features of Liver and Pancreas

Gross Pathology: Livers in all diabetic groups appeared paler and less uniform with a looser texture compared to normal controls, although Glu-NK-treated livers appeared slightly firmer than the model group. No gross morphological differences were noted in the pancreas across groups.

Histopathology: The biochemical and metabolic improvements observed with Glu-NK treatment were not accompanied by a significant reversal of structural tissue damage within the brief 2-week intervention period. The diabetic model group displayed mild inflammation and granular hepatocyte degeneration (ballooning). Two weeks of Glu-NK administration failed to induce any marked histological recovery or structural restoration in the hepatic architecture (Figure 4). Similarly, in the pancreas, sections from all diabetic mice (both treated and untreated) exhibited significant islet atrophy, reduction in β-cell mass, and inflammatory cell infiltration compared to normal controls. Glu-NK treatment did not significantly reverse, halt, or attenuate these profound structural changes in the pancreatic islets within the 2-week study timeframe (Figure 5).

4. Discussion

Type 2 Diabetes Mellitus (T2DM) remains one of the most pressing non-communicable diseases globally, driven by a complex interplay of genetic predisposition, obesity, and lifestyle factors[13]. Obesity plays a pivotal

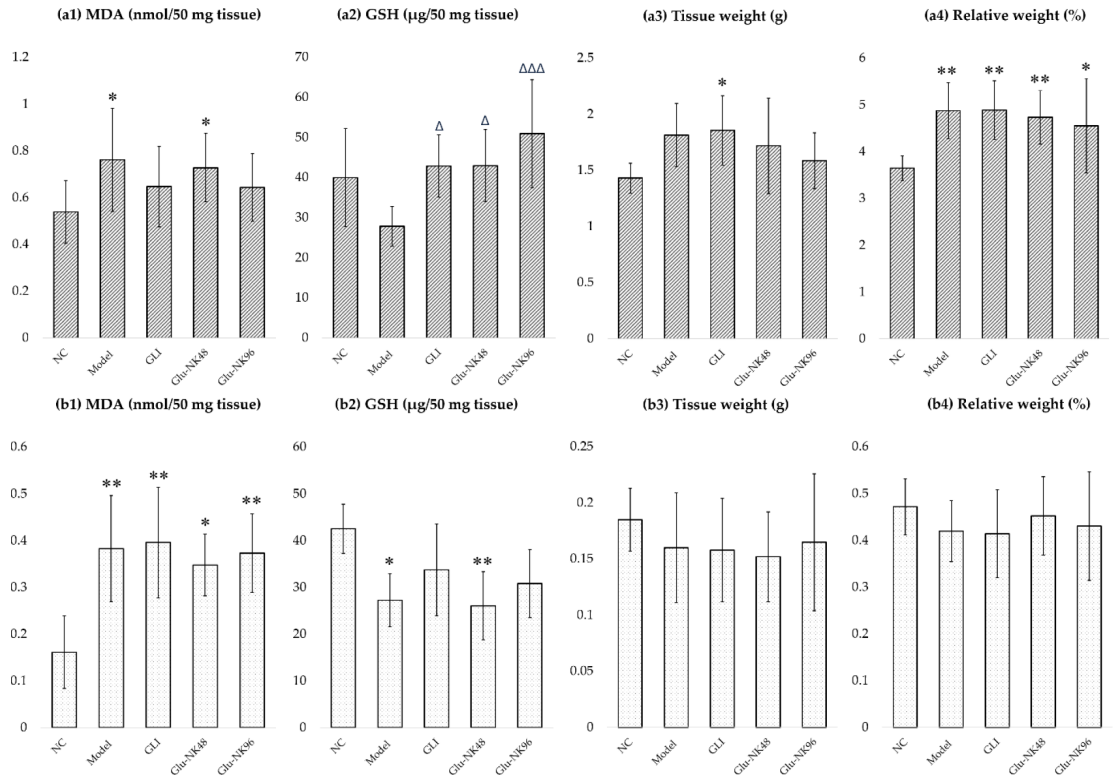


Bar graphs showing serum levels of (a) total cholesterol, (b) triglycerides, (c) HDL-cholesterol, (d) LDL-cholesterol, (e) AST, (f) ALT, (g) creatinine, and (h) urea. Data are presented as mean ± SD (n=10 per group). NC: normal control; Model: diabetic control group; GLI: glibenclamide 15 mg/kg/day; Glu-NK48: Glu-NK 48 mL/kg/day; Glu-NK96: Glu-NK 96 mL/kg/day. *,**,***p<0.05, p< 0.01, p< 0.001 compared to the normal control group; $^{\Delta,\Delta\Delta}$p<0.05, p<0.01 compared to the model group.

Figure 2. Effects of Glu-NK on serum biochemical parameters after 2 weeks of treatment.

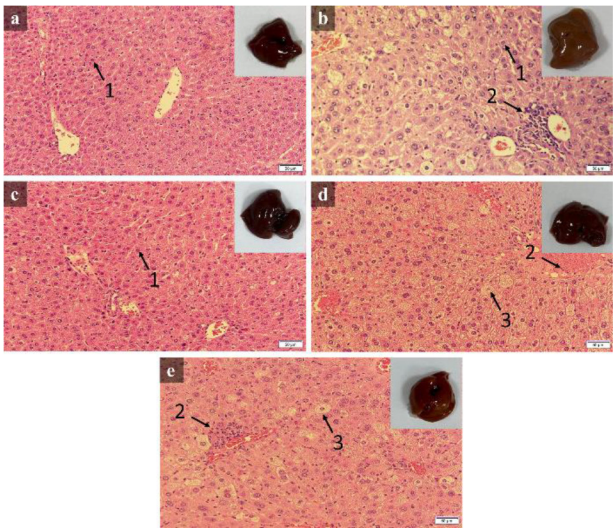
role in T2DM pathogenesis, with epidemiological data indicating that 80–90% of individuals with T2DM are overweight or obese[23]. Obesity exacerbates insulin resistance through multiple mechanisms, including adipokine dysregulation (e.g., reduced adiponectin), ectopic fat deposition in liver and muscle, and chronic low-grade inflammation mediated by pro-inflammatory cytokines such as TNF-α and IL-6, which are secreted by hypertrophied adipocytes and by infiltrating macrophages[24,25].

Given the strong link between obesity and T2DM, our study employed an HFD to induce obesity in Swiss albino mice as a foundational step in disease modelling, followed by a low-dose streptozotocin injection. This combined approach produces metabolic conditions that closely mimic the pathophysiological features of human T2DM[26]. Fructose, a monosaccharide primarily metabolised in the liver, plays a central role in energy metabolism. However, excessive fructose intake disrupts metabolic homeostasis and contributes to



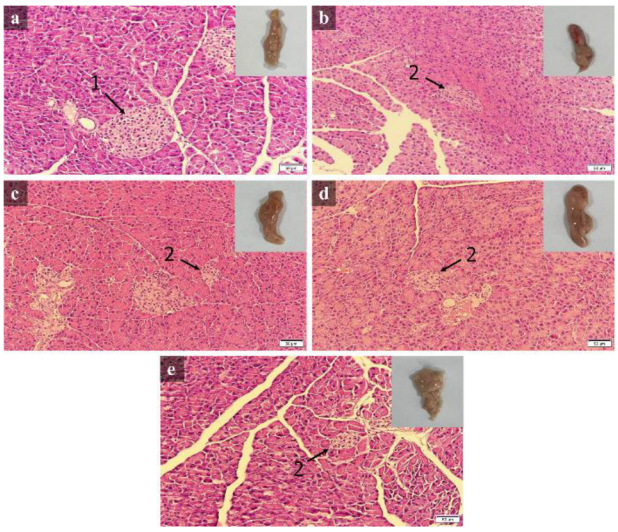
(a) Liver tissue and (b) Pancreas tissue: tissue weight, relative organ weight, MDA level, and GSH level. Data are presented as mean ± SD (n=10 per group). NC: normal control; Model: diabetic control group; GLI: glibenclamide 15 mg/kg/day; Glu-NK48: Glu-NK 48 mL/kg/day; Glu-NK96: Glu-NK 96 mL/kg/day. *,**p<0.05, p<0.01 compared to the normal control group; $^{\Delta}$,$^{\Delta\Delta\Delta}$p<0.05, p<0.001 compared to the model group.

Figure 3. Effects of Glu-NK on organ weight and oxidative stress markers in liver and pancreas.



(1) Normal hepatocytes with preserved architecture and minimal lipid accumulation; (2) Inflammatory cell infiltration in portal and periportal areas; (3) Ballooning degeneration of hepatocytes characterised by cellular swelling and cytoplasmic rarefaction. (a) Normal control; (b) Diabetic control (Model); (c) Glibenclamide 15 mg/kg/day; (d) Glu-NK 48 mL/kg/day; (e) Glu-NK 96 mL/kg/day.

Figure 4. Gross morphology and representative histopathological images of liver tissue from experimental groups (HandE staining, 200× magnification).



(1) Normal pancreatic islets with preserved size, architecture, and β-cell population; (2) Atrophied pancreatic islets with diminished β-cell mass, vacuolar degeneration, and inflammatory cell infiltration. (a) Normal control; (b) Diabetic control (Model); (c) Glibenclamide 15 mg/kg/day; (d) Glu-NK 48 mL/kg/day; (e) Glu-NK 96 mL/kg/day.

Figure 5. Gross morphology and representative histopathological images of pancreatic tissue from experimental groups (HandE staining, 200× magnification).

metabolic dysfunction[27]. Fructose acts as a metabolic amplifier by intensifying hepatic insulin resistance through dual mechanisms: direct inhibition of the insulin signalling pathway and indirect effects through lipogenesis and impaired fatty acid oxidation, which trigger endoplasmic reticulum stress and hepatic inflammation[28].

Consistent with these mechanisms, our 8-week HFD regimen elicited progressive weight gain, evident from week 4 onward, with body weights at weeks 6 and 8 significantly exceeding those of both baseline and normal-fat diet controls. These results demonstrate the successful establishment of diet-induced obesity, a critical prerequisite for modelling insulin resistance. Although post-HFD fasting glucose rose modestly compared to baseline and normal controls—reflecting compensated hyperinsulinemia typical of prediabetes—low-dose STZ precipitated a dramatic surge in glucose within 72 hours, confirming partial β-cell destruction via GLUT2-mediated uptake, nitrosourea-induced DNA alkylation, and subsequent apoptosis and necrosis[29].

The administration of a sub-diabetogenic dose of STZ serves as a strategic model for mimicking the early stages of T2DM. Unlike high doses that cause total β-cell death, this threshold-level dose induces only partial ablation and functional dysregulation of pancreatic β-cells, sufficient to compromise insulin secretory capacity and lead to impaired glucose tolerance without triggering full-scale type 1 diabetes. This model effectively replicates the progressive decline in β-cell mass and metabolic instability characteristic of early-stage T2DM pathogenesis[26,30]. The combination of HFD and low-dose STZ accurately reflects the pathological progression of T2DM in humans, including weight gain, insulin resistance, hyperglycemia, and pancreatic β-cell dysfunction (Figure 1)[31,32]. During the subsequent 2-week treatment phase, a general trend of mild weight reduction was observed across all STZ-injected diabetic groups, including the untreated model control (Figure 1c). This weight loss is a well-documented physiological consequence of STZ-induced insulin deficiency, which drives systemic catabolism, muscle wasting, and fluid loss (polyuria).

Because the untreated model control also exhibited this weight decrease, the reductions observed in the Glu-NK and glibenclamide-treated groups cannot be attributed to a specific anti-obesity or fat-reducing therapeutic effect of the interventions. Rather, it reflects the ongoing diabetic catabolic state, which was not fully reversed by any treatment within the short 2-week timeframe. Another limitation of our model is the absence of insulin quantification, which hinders direct assessment of insulin resistance.

The hypoglycemic effect of Glu-NK became evident at week 2, as both tested doses significantly reduced fasting blood glucose levels compared with the diabetic control group, with the higher dose (96 mL/kg/day) achieving effects comparable to those of glibenclamide (Figure 1). The absence of significant effects at week 1 is consistent with the delayed onset commonly observed with herbal interventions. This delay can be attributed to the complex pharmacokinetic characteristics of herbal medicines, in which multiple bioactive constituents undergo variable absorption, distribution, hepatic metabolism—primarily via cytochrome P450-mediated pathways—and elimination. Such processes may require sufficient time to reach effective systemic exposure and therapeutic activity[33,34]. Interestingly, glibenclamide did not exhibit significant glucose-lowering effects until the second week of treatment. This delayed onset may be explained by the profound glucotoxicity inherent in the HFD/STZ model, which temporarily blunts the secretagogue responsiveness of the remaining β-cells[35]. Furthermore, the high degree of peripheral insulin resistance induced by the 8-week HFD regimen required sustained elevation of endogenous insulin to overcome receptor desensitisation and achieve statistically significant reductions in blood glucose levels.

The comparable efficacy of Glu-NK to glibenclamide suggests a broader, multi-pronged pharmacological profile that may result from synergistic interactions among its diverse bioactive components. While the exact molecular mechanisms of the Glu-NK formulation were not experimentally investigated in the present study, existing literature on its individual constituent herbs provides plausible hypothetical pathways. For instance, the antidiabetic efficacy of *Fructus Momordicae charantiae* has been previously reported to involve constituents like charantin, polypeptide-p, and vicine. In isolated studies, these compounds have been shown to engage multiple pharmacological targets, including the mitigation of insulin resistance via SOCS-3/JNK

pathways and the systemic modulation of glucose metabolism through the inhibition of key enzymes such as PTP1B, α-amylase, and 11β-HSD1[12]. Similarly, previous research on *Gymnema sylvestre* suggests it may support glycemic control and structural integrity, with some studies indicating an ability to foster the regeneration and functional restoration of pancreatic β-cells[36]. Furthermore, *Biophytum sensitivum* has demonstrated potent α-glucosidase inhibitory activity in prior models[11]. Beyond these primary hypoglycemic drivers, the remaining components play critical supportive roles. As outlined in our traditional compounding rationale, these botanicals act synergistically as 'Ministers, Assistants, and Couriers' to enhance hepatorenal function, promote systemic detoxification, cool the blood, and optimise the bioavailability of the active constituents. It is crucial to emphasise, however, that attributing the observed *in vivo* effects of Glu-NK directly to these specific mechanisms—such as PTP1B inhibition, SOCS-3/JNK modulation, or β-cell regeneration—remains highly speculative at this stage. Further targeted molecular and biochemical investigations are required to definitively confirm which of these pathways are actively engaged by the combined polyherbal extract in this specific T2DM model.

While the precise aetiology of Metabolic Syndrome (MetS) remains incompletely understood, insulin resistance is widely recognised as the fundamental driver of its pathogenesis. Dyslipidemia is a critical link in the progression of insulin resistance and was clearly manifested in our diabetic model group, with significantly elevated plasma triglycerides, total cholesterol, and LDL cholesterol levels[37,38]. These metabolic abnormalities confirm successful transition to a MetS-like state.

In this context, Glu-NK demonstrated superior therapeutic potential by effectively ameliorating HFD-induced dyslipidemia. Specifically, Glu-NK treatment resulted in marked reductions in total and LDL cholesterol, with a positive trend in HDL cholesterol. Notably, these lipid-modulating effects far surpassed those of glibenclamide, which showed negligible impact on the lipid profile (Figure 2). This distinction underscores that, whereas glibenclamide primarily targets insulin secretion, Glu-NK provides a more comprehensive metabolic intervention by addressing both glucose and lipid derangements.

The lipid-modulating effects of Glu-NK are likely anchored by *Momordica charantia*. Zhang *et al.* demonstrated that *M. charantia* fruit powder effectively mitigates hyperglycemia and dyslipidemia induced by a high-fat diet, with its aqueous extract significantly reducing serum cholesterol and triglyceride levels in diabetic subjects[12]. According to Karale *et al.*, these anti-obesity and hypolipidemic effects are mediated by a complex regulatory network involving nuclear receptors and transcription factors, including PPARs, LXRs, SREBPs, and Sirtuins[39]. This coordinated molecular action effectively prevents adipocyte hypertrophy and limits visceral fat accumulation, thereby addressing the core metabolic disruptions of the HFD/STZ model.

Despite the significant reductions in total cholesterol and LDL-C, serum TG levels remained less responsive, showing no statistically significant improvement after two weeks of Glu-NK treatment. This differential lipid response may be attributed to the severe, persistent insulin resistance and partial β-cell loss inherent to the HFD/STZ model. The clearance of circulating TGs is highly dependent on the activity of endothelial lipoprotein lipase (LPL), an enzyme that requires adequate insulin signalling for activation[40]. Given the short two-week intervention window, it is likely that endogenous insulin sensitivity was not sufficiently restored to fully activate LPL and facilitate rapid TG clearance from the bloodstream. Furthermore, while the bioactive compounds in Glu-NK appear to rapidly modulate cholesterol synthesis and excretion pathways, reversing the profound hepatic TG overproduction and adipose tissue lipolysis established by 8 weeks of HFD feeding likely requires a more prolonged therapeutic duration.

Extensive research has established that individuals with metabolic syndrome exhibit diminished plasma antioxidant enzyme activities alongside elevated biomarkers of oxidative damage compared to healthy controls, fundamentally driving systemic oxidative stress[41]. In this context, the evaluation of total polyphenols and flavonoids in Glu-NK is essential, as these compounds represent the primary antioxidant constituents that scavenge free radicals through hydrogen atom transfer or electron donation mechanisms. Our phytochemical analysis revealed that the aqueous extract demonstrated superior total

polyphenol and flavonoid content, correlating closely with enhanced DPPH radical scavenging activity. However, the methanolic extract exhibited higher ferric reducing power (FRAP), suggesting that the antioxidant compounds in Glu-NK operate through multiple mechanisms depending on solvent polarity. Although the methanolic extract contained lower polyphenol content, its superior FRAP values suggest the presence of aglycone flavonoids with potent electron-donating capacity,[42] while the aqueous extract concentrates polar glycosides that preferentially scavenge radicals via hydrogen atom transfer[43].

Chronic hyperglycemia drives mitochondrial overproduction of Reactive Oxygen Species (ROS) via electron transport chain leakage and activates pro-oxidant pathways such as protein kinase C and the polyol pathway, all of which enhance oxidative stress in diabetic tissues[44]. Malondialdehyde (MDA), a major end-product of lipid peroxidation, serves as a robust biomarker for oxidative damage in T2DM. Glutathione (GSH) is a key intracellular antioxidant that directly scavenges ROS and supports enzymatic antioxidant systems; in T2DM, GSH levels are frequently depleted[45].

Glu-NK significantly boosted hepatic GSH and demonstrated trends toward MDA reduction (Figure 3) likely through the antioxidant properties of *Biophytum sensitivum*. This plant has been shown to scavenge superoxide and hydroxyl radicals—generated via riboflavin photoreduction and Fenton reactions, respectively—while inhibiting lipid peroxidation *in vitro*. Furthermore, its administration markedly elevates hepatic glutathione levels *in vivo*, effectively bolstering the endogenous antioxidant defence system[46]. Although Glu-NK treatment markedly improved oxidative stress parameters in the liver, no significant improvement was observed in the pancreas. This differential, organ-specific response can likely be attributed to distinct factors. First, pancreatic β-cells inherently possess extremely low baseline expressions of intrinsic antioxidant enzymes compared to hepatocytes[47,48]. This fundamental biological difference makes the pancreas exceptionally vulnerable to oxidative damage and markedly slower to regenerate its antioxidant defences. Second, streptozotocin specifically targets β-cells via GLUT2 transporter uptake, causing massive localised ROS generation, DNA alkylation, and subsequent irreversible cellular necrosis. Because the β-cell population is severely depleted and structurally compromised by STZ, the remaining tissue simply lacks the functional cellular machinery and synthetic capacity required to mount a robust GSH replenishment within a short 2-week window[49]. Finally, from a pharmacokinetic perspective, orally administered herbal bioactive compounds undergo extensive first-pass hepatic uptake. As the primary site of metabolism, the liver is exposed to significantly higher concentrations of these free radical-scavenging phytochemicals than peripheral organs like the pancreas, facilitating a much more rapid and pronounced local antioxidant response in hepatic tissues.

Hepatorenal assessments revealed elevated serum AST and ALT levels in diabetic groups, attributable to increased oxidative stress–induced mitochondrial membrane permeability. This process promotes the release of cytochrome C and activates calcium-dependent enzymes, including endonucleases, proteases, and lipases, ultimately leading to hepatocyte death through both apoptotic and necrotic pathways[50]. The absence of treatment-related differences suggests that Glu-NK's hepatoprotective effects require extended durations to normalise enzyme levels. Importantly, unaltered creatinine and urea levels support the safety profile of Glu-NK, consistent with the lack of nephrotoxicity observed in herbal formulations (Figure 2).

Organ weight measurements highlighted diabetic hepatomegaly resulting from hepatic steatosis, which remained unaltered by 2-week therapy. Pancreatic weight showed a non-significant trend toward reduction, consistent with partial β-cell loss due to STZ[30]. Gross morphological examination showed apparent improvement in liver texture; however, histopathological examination still revealed persistent hepatic degeneration and pancreatic islet atrophy with inflammatory changes, indicating incomplete tissue remodelling likely due to insufficient treatment duration (Figures 4 and 5).

Several limitations warrant consideration. First, the short 2-week treatment duration may have been insufficient for full herbal bioaccumulation and the manifestation of chronic therapeutic effects, particularly regarding tissue recovery and triglyceride clearance. Second, the absence of serum insulin

measurement limits our ability to directly quantify insulin resistance and assess the mechanistic depth of β-cell functional recovery. Third, the lack of an oral glucose tolerance test or insulin tolerance test restricts our comprehensive evaluation of systemic glucose dynamics and insulin sensitivity beyond fasting states. Fourth, the modest sample size may have reduced the statistical power to detect subtle treatment effects. Fifth, rodent metabolic physiology differs from that of humans, necessitating translational studies. Sixth, the phytochemical characterisation in this study was limited to the quantification of total phenolic and flavonoid contents. Advanced analytical methods were not performed to establish a definitive chromatographic fingerprint. Seventh, our histopathological evaluations were strictly qualitative without a standardised scoring system. Eighth, because this was designed as an initial proof-of-concept study, blood glucose was only monitored at three predefined time points. Future research directions should encompass chronic dosing studies to assess long-term efficacy; specific hormonal assays; multi-omics approaches to elucidate pathways; advanced phytochemical profiling to establish robust quality control fingerprints; the incorporation of quantitative histological scoring; high-frequency glycemic monitoring; clinical pharmacokinetic studies; and randomised controlled trials to validate therapeutic efficacy and safety in patients with T2DM.

5. Conclusion

The results of this preclinical study demonstrate that the polyherbal formulation Glu-NK exhibits promising antihyperglycemic, hypolipidemic, and hepatic antioxidant effects in an HFD/STZ-induced mouse model of T2DM. Over a two-week treatment period, the higher dose (96 mL/kg/day) effectively lowered fasting blood glucose and improved the atherogenic lipid profile without adversely affecting renal function markers. However, this short-term intervention was insufficient to reverse histopathological damage, normalise elevated liver enzymes, or alleviate pancreatic oxidative stress. It is important to emphasise that these findings represent early-stage preclinical evidence. Further rigorous studies are strictly necessary to confirm its long-term efficacy and safety profile before clinical application.

6. Ethical Committee Approval

: All experimental procedures complied with animal welfare guidelines and were approved by the Vietnam University of Traditional Medicine's Ethical Review Board (Approval No. 4724/QD-HVYDCT, dated December 11, 2024).

7. References

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Author Contribution

Ngai Hong Thi Tran: Conceptualization, supervision, resources; Giap Van Pham: Formal analysis, data curation; Huy Quoc Nguyen: Validation, visualization; Phuong Thi Le: Visualization, investigation; Si Dung Chu: Investigation, writing—original draft preparation; Hoang Minh Le: Investigation, visualization; Ha Thanh Thi Nguyen: Conceptualization, methodology; Trang Quynh Tran: Methodology, software; Quang Vinh Trinh: Software, data curation, writing—review and editing, formal analysis; Hang Thuy Thi Nguyen: Software, writing—original draft preparation; Lan Chi Ngoc Nguyen: Data curation, resources; Yen Hoang Kieu: Investigation, writing—original draft preparation; Van Anh Thi Pham: Validation, writing—review and editing, supervision. All authors have read and agreed to the published version of the manuscript.