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Assessment of Possible Food-Drug Interactions of Pearl Millet Diet on Gliclazide in Diabetic Rats

Asha Nandabaram[1], Vinod Kumar Nelson[2] and Vinyas Mayasa[1*]
[1]*Department of Pharmacology, GITAM School of Pharmacy, GITAM Deemed to be University, Sanga Reddy, Telangana, India*
[2]*Centre for Global Health Research, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai 602105, Tamil Nadu, India*

Abstract

Pearl millet, with its low glycaemic index, helps stabilize blood sugar levels, making it a potential dietary intervention for diabetic patients. This study investigated the interaction between a 60% pearl millet diet (PEMD) and gliclazide in diabetic rats. Diabetes was induced using the streptozotocin (STZ)-nicotinamide model, with rats classified as diabetic if their fasting plasma glucose exceeded 250 mg/dL. The effects of gliclazide (1 mg/kg) were evaluated in combination with the optimized 60% pearl millet diet (PEMD60) in both single-dose (SD) and repeated-dose (MD) studies. The combination of gliclazide and PEMD60-MD resulted in a significant increase in blood glucose reduction compared to the single-dose treatment. Additionally, serum gliclazide levels, HbA1c, insulin levels, and pharmacokinetic parameters such as Cmax, t1/2, Tmax, and AUC were altered in the combination therapy, though some changes were not statistically significant. The interaction between gliclazide and pearl millet may be due to pharmacokinetic alterations, possibly involving metabolic interactions. These findings suggest that physicians should monitor patients on gliclazide who consume pearl millet to prevent potential hypoglycaemia and adjust gliclazide dosages as needed.

Keywords*: Blood Glucose, Diabetic Rats, Gliclazide, Pearl Millet, Pharmacodynamics, Pharmacokinetics.*

Introduction

Diabetes, particularly Type 2 Diabetes Mellitus (T2DM), has emerged as a major global health issue, with an estimated 51% increase in diabetic cases worldwide by 2045.[1] This rise poses significant challenges to healthcare systems, especially in low- and middle-income countries where dietary diversification is limited. Maintaining normal blood glucose levels with medication is a challenging task, and prolonged elevated blood glucose levels can lead to several complications, such as microvascular and macrovascular disorders. Current therapies for type II diabetes include sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, meglitinides, incretin mimetics, and DPP4 inhibitors [2]. Managing diabetes involves lifestyle changes, dietary modifications, and medication. Diet, in particular, can have a major impact on the quality of life of those with diabetes, as well as those at risk for diabetes.[3] However, the current management strategies often face challenges related to the long-term use of medications, such as potential side effects and issues with drug efficacy. For people with diabetes, including low GI foods in the diet helps manage blood sugar levels. Choosing low-GI foods can help prevent spikes in blood sugar levels and improve blood sugar control over time [4]. Dietary fibre is essential for

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****Corresponding Author: vmayasa@gitam.edu***

maintaining good health. It swells in the intestine, slowing food movement through the small intestine. This helps reduce the rate of glucose absorption, which is beneficial for managing certain types of diabetes, such as non-insulin-dependent diabetes mellitus [5]. The fibre's high viscosity, glycaemic index, and water-holding capacity also help lower blood glucose and insulin response [6]. In addition, dietary fibre components bind bile salts, thereby promoting cholesterol excretion from the body, which can lower blood cholesterol levels. They also bind food toxins in the intestines, reducing their toxicity and promoting overall gut health [7]. However, different foods can have different effects on blood sugar levels. Monitoring your blood glucose levels regularly is vital, especially when adding new foods to your diet. Changes in your diet can affect the effectiveness of antidiabetic drugs such as gliclazide [8]. Dietary interventions, particularly those focusing on whole grains and low-glycaemic-index foods, have shown promise in managing blood glucose levels [9]. The glycaemic index (GI) measures how much the carbohydrates in food affect the rate and extent of change in postprandial blood glucose concentration [10]. There is enough evidence that millets have several properties that make them a suitable food option for diabetic patients [11]. Experiments on diabetic mice showed that adding millet protein to their diet increases insulin sensitivity and lowers blood sugar and triglyceride levels [12]. Despite these benefits, there is a lack of comprehensive studies addressing the interactions between millet-based diets and diabetes medications like gliclazide, which are commonly prescribed for T2DM. While a millet-rich diet shows promise in improving glucose metabolism, the interaction between such diets and antidiabetic drugs has not been thoroughly explored. There is a need for research on how millet might influence the pharmacokinetics and pharmacodynamics of drugs like gliclazide, as these interactions could impact the effectiveness and safety of treatment. This study assesses the possible pharmacokinetic and pharmacodynamic interactions between pearl millet and gliclazide in diabetic rats. It seeks to explore whether millet co-administration affects gliclazide's bioavailability, efficacy, or safety, thereby providing insights into potential food-drug interactions in diabetes management.

The primary objective of this study is to assess the interactions between pearl millet diet and gliclazide in diabetic rats, focusing on pharmacokinetic and pharmacodynamic changes, as well as their implications for clinical practice.

This research is novel in its exploration of the potential interactions between a millet-based diet and an antidiabetic drug, gliclazide, addressing a gap in the current literature regarding food-drug interactions in diabetes management. By evaluating the combined effects of dietary millet and gliclazide, the study could lead to more personalized and effective approaches to managing diabetes through diet and pharmacotherapy.

Materials and Methods

Experimental Design

The study was conducted in a controlled laboratory environment where standardized animal housing conditions were maintained. Wistar albino rats of either sex weighing between 220 g – 270 g were used in the study, sourced from Mahaveer Enterprises, Hyderabad, India, and were housed at an ambient temperature of 25 ± 2 °C and relative humidity of 50 ± 15%, with a 12-hour light/12-hour dark cycle. Rats had ad libitum access to water and a commercial pellet diet provided by Rayan's Biotechnologies Pvt. Ltd, Hyderabad, India.

Experimental Methodology

This study involved the assessment of pharmacodynamic responses, focusing on

blood glucose and insulin levels in STZ-induced diabetic rats who are fed a 60% pearl millet diet and treated with gliclazide. Ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC) of Sarojini Naidu Vanitha Pharmacy Maha Vidyalaya, located in Tarnaka, Secunderabad, Telangana, India (registered under CCSEA no.: 287/R/S/2000/CPCSEA, IAEC No: SNV/08/2022/PC/1) approved every experimental procedure carried out in compliance with guidelines. Throughout the investigations, the protocols for handling and providing care for laboratory animals were adhered to. Before experimentation, the rats were fasted for 18 hours with access to water. The experimental design involved inducing diabetes through intraperitoneal injection of nicotinamide (100 mg/kg) followed by STZ (60 mg/kg) dissolved in citrate buffer. Diabetes was confirmed by fasting blood glucose levels above 250 mg/dL. Diabetic rats were divided into five groups, each with six rats, and underwent treatment across three stages, separated by a seven-day washout period:

1. **Stage I:** Vehicle control (water) and gliclazide (1 mg/kg) were administered, and blood samples were collected at different time intervals for glucose analysis.
2. **Stage II:** Pearl millet diet (60%) was administered to diabetic rats.
3. **Stage III:** Pearl millet diet (60%) was administered with gliclazide for single-dose (1 day) and multiple-dose (28 days) interaction studies.

Description of the Laboratory Methods

Preparation of Drug Solutions

Millet Preparation: Pearl millet was dried, finely ground, and sieved to achieve a consistent powder, which was mixed with the basal diet in a 60% ratio.

Gliclazide Solution: A 10 mg/mL gliclazide stock solution was prepared using 0.1N NaOH for solubilization, with distilled water added for volume adjustments and dilutions as required.

Collection of Blood Samples

Blood samples were collected from the retro-orbital plexus using a capillary tube at designated time intervals (0, 1, 2, 3, 4, 6, 8,10, and 12 hours post-administration). Samples (0.2 mL) were centrifuged to obtain serum and blood glucose levels were analyzed using the GOD/POD method. HbA1c and insulin levels were measured at peak intervals using the Ion Exchange Resin Method and an Invitrogen ELISA kit, respectively.

Bioanalytical Method

Plasma gliclazide concentrations were measured using HPLC with a Waters 2487 unit. The mobile phase (acetonitrile, methanol, and water in a 40:35:25 ratio) was delivered at a flow rate of 1.00 mL/min. Each sample was prepared with an internal standard (ibuprofen, 50 µg/mL), mixed with methanol, vortexed, and centrifuged. The supernatant was evaporated and reconstituted before injection into the HPLC system.

Description of Statistical Methods Used

Statistical analysis involved two-way ANOVA with Bonferroni post-tests to determine significance levels (***$P < 0.001$; **$P < 0.01$; *$P < 0.05$ compared to control). Pharmacokinetic parameters were calculated using Pk Solver software.

Results

The effect of gliclazide and a 60% Pearl Millet Diet (PEMD) on blood glucose levels in diabetic rats was evaluated across various treatment conditions. Blood glucose levels were measured at time intervals from 0 to 12 hours (Figure 1). The study included diabetic rats treated with gliclazide alone (1 mg/kg body weight), PEMD alone, and the combination of PEMD with gliclazide.

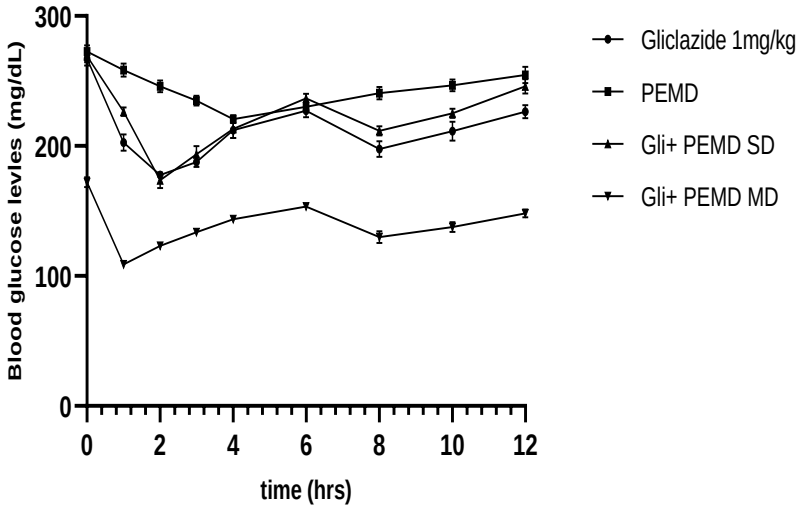

Figure 1. Effect of Gliclazide and Pearl Millet Diet (PEMD) on Blood Glucose Levels in Diabetic Rats

The findings indicated that gliclazide alone resulted in a 33.46% reduction in blood glucose levels at 2 hours and a 25.94% reduction at 8 hours post-administration. When administered alone, PEMD achieved a maximum reduction of 19.04% at 4 hours. For the combined single-dose treatment of gliclazide and PEMD (Gli+PEMD-SD), blood glucose reduction reached 35.47% at 2 hours and 21.35% at 8 hours. The combined multiple-dose administration (Gli+PEMD-MD) showed an enhanced glucose-lowering effect, with reductions of 36.89% at 1 hour and 24.45% at 8 hours. These results, illustrated in Figure 2, suggest that the combination of gliclazide with PEMD yields a synergistic effect, enhancing blood glucose reduction in diabetic rats.

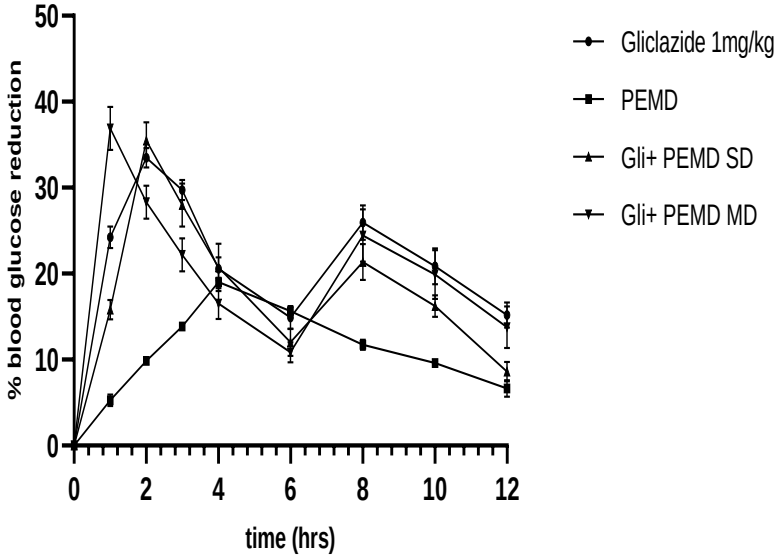

Figure 2. Effect of Gliclazide and PEARL Millet Diet (PEMD) on % Blood Glucose Reduction in Normal Rats

This study aimed to assess whether the hypoglycaemic effect of gliclazide could be enhanced through synergistic action or pharmacokinetic interactions when combined with pearl millet. Optimized doses of millet and gliclazide were administered, and serum

gliclazide levels were measured in single-dose (SD) and multiple-dose (MD) supplementation. So, the effect of gliclazide and a combination of Pearl millet diet (PEMD 60) on blood glucose levels was observed in single- and multiple-dose studies on diabetic rats.

The findings revealed no significant changes in serum gliclazide levels with the single dose (SD) of pearl millet alone. However, administration of gliclazide produced elevated serum levels corresponding to peak blood glucose reduction times, reaching 13.09 µg/mL at 2 hours and 10.47 µg/mL at 8 hours. When combined with the single-dose PEMD (Gli+PEMD-SD), serum gliclazide levels increased to 14.98 µg/mL at 2 hours and 7.20 µg/mL at 8 hours. Multiple-dose administration (Gli+PEMD-MD) showed levels of 15.23 µg/mL at the 1-hour mark and 8.98 µg/mL at 8 hours (Figure 3).

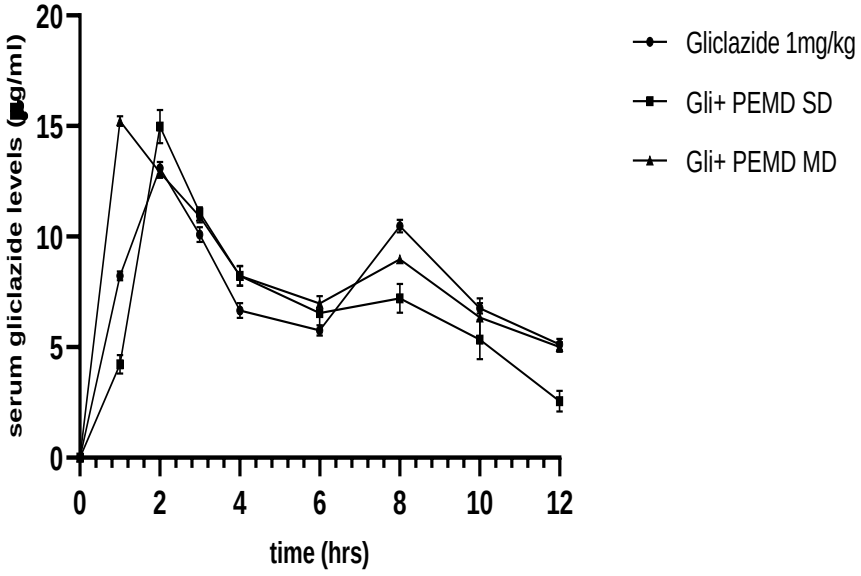

Figure 3. Serum Gliclazide Levels of Rats Treated with Gliclazide and a Combination of Pearl Millet Diet (PEMD 60) in Single and Multiple Dose Studies in Diabetic Rats

Pharmacokinetic analysis indicated an increase in Cmax with a decrease in AUC and MRT. Figure 4 compares HbA1c and insulin levels to changes in blood glucose. No significant correlation was observed between the altered blood glucose levels and the combined administration of PEMD with gliclazide, suggesting limited pharmacodynamic interaction. Serum gliclazide levels showed an increase at the respective peak times. Treatment with gliclazide alone yielded serum levels of 13.09 µg/mL at 2 hours and 10.47 µg/mL at 8 hours. Combined with PEMD single-dose (Gliclazide + PEMD-SD), peak serum gliclazide levels rose to 14.98 µg/mL at 2 hours and 7.20 µg/mL at 8 hours. For the multiple-dose combination (Gliclazide + PEMD-MD), levels reached 15.23 µg/mL at 1 hour and 8.98 µg/mL at 8 hours. Despite these changes, there were no significant pharmacokinetic alterations in the diabetic rats with the combined administration, except for an increase in Cmax of 15.23 µg/ml. The effects of the millet diet in combination with gliclazide on insulin levels and HbA1c at specific time points in diabetic rats are shown in Figure 4. In gliclazide-treated rats, serum insulin levels were observed at 2hr as 18.98 µU/mL. The combination of Gliclazide + PEMD (single-dose) showed serum insulin levels of 17.76 µU/mL at 2 hours, while Gliclazide + PEMD (multiple-dose) resulted in serum insulin levels of 14.56 µU/mL at 1 hour. HbA1c levels were also measured to evaluate

their association with blood glucose reduction. In gliclazide-treated rats, HbA1c was 8.98 mg/dL at 2 hours. For the Gliclazide + PEMD (SD) group, HbA1c was 10.98 mg/dL at 2 hours, and in the Gliclazide + PEMD (MD) group, HbA1c reached 6.09 mg/dL at 1 hour.

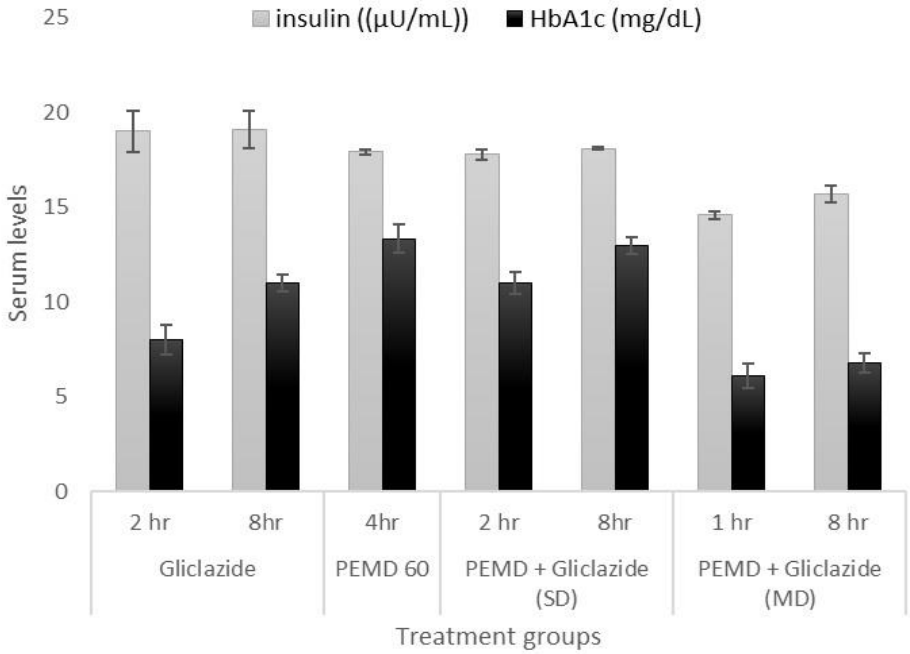

Figure 4. Mean Serum Insulin (µIU/mL) and HbA1C (mg/dL) in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of PEMD at Peak Hours of Blood Glucose Reduction

The following figures represent the Mean lipid profile values in Gliclazide, Millet diet, and single and multiple dose Combinations of millet diet at peak hours of blood glucose reduction. No significant decrease in lipid levels was observed with gliclazide alone, PEMD alone, or the single-dose combination (Gli+PEMD-SD). However, in the multi-dose regimen of the combined diet and gliclazide, triglyceride levels were significantly decreased ($p>0.05$) compared to the STZ control group. Total cholesterol levels showed a significant reduction to 89.23 mg/dL with the multi-dose Gli+PEMD (MD) treatment, achieving a highly significant difference (***$p<0.001$) compared to the diabetic control. Triglyceride levels significantly decreased to 143.45±2.07 mg/dL with the multi-dose (MD) combination of PEMD and gliclazide (***$p<0.001$) compared to the diabetic control. HDL levels, reduced in the diabetic control group (37.09±1.23 mg/dL), increased significantly with MD administration of PEMD and gliclazide, reaching 53.98±2.45 mg/dL. LDL and VLDL levels also showed significant reductions with the millet diet and gliclazide combination at multi-dose levels (***$p<0.001$) after 28 days. LDL levels dropped to 65.09±3.31 mg/dL with Gli+PEMD-MD compared to the diabetic control (180.87±3.09 mg/dL), while VLDL levels decreased from 26.87±0.87 mg/dL in the STZ control to 17.09±3.05 mg/dL with PEMD, though this reduction was not statistically significant (*$p>0.05$).

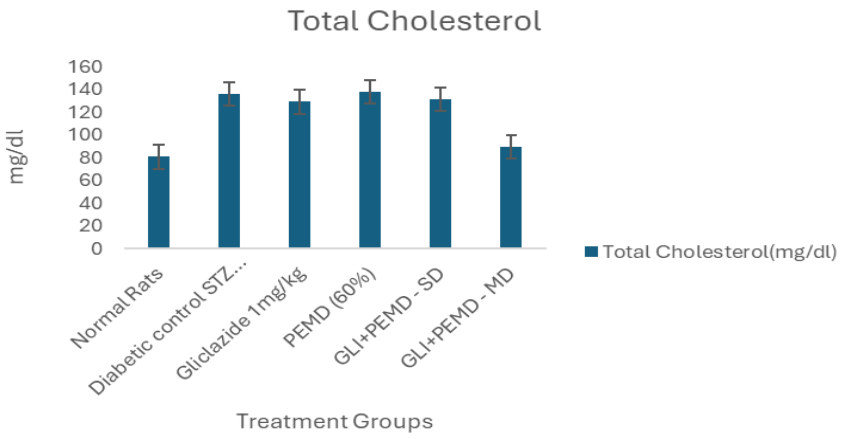

Figure 5. Total Cholesterol values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction

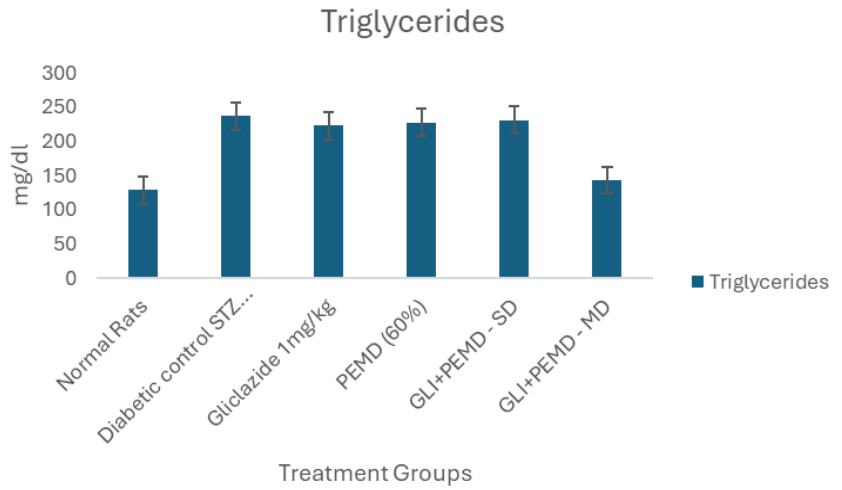

Figure 6. Triglyceride values in Gliclazide, Millet diet, and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction

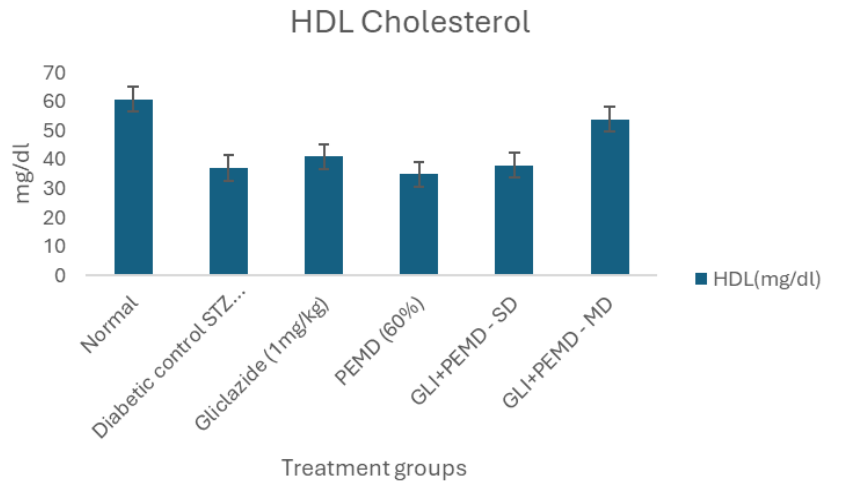

Figure 7. HDL Cholesterol values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction

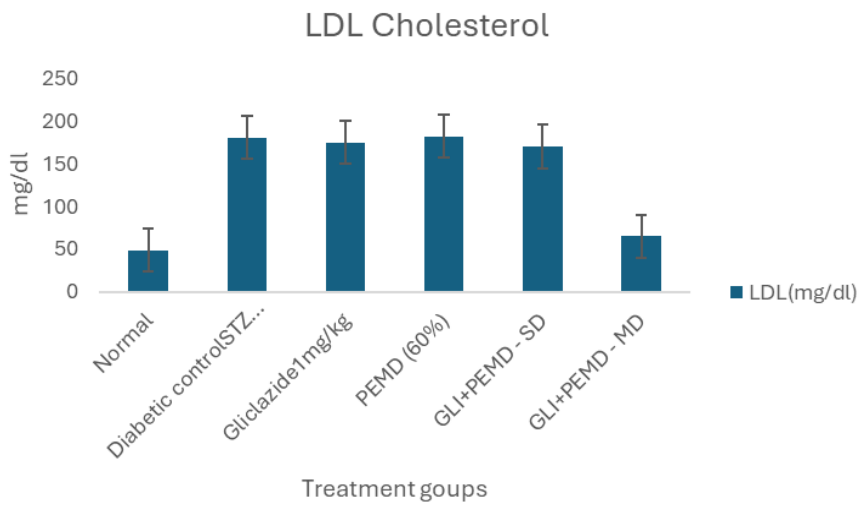

Figure 8. LDL Cholesterol values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction

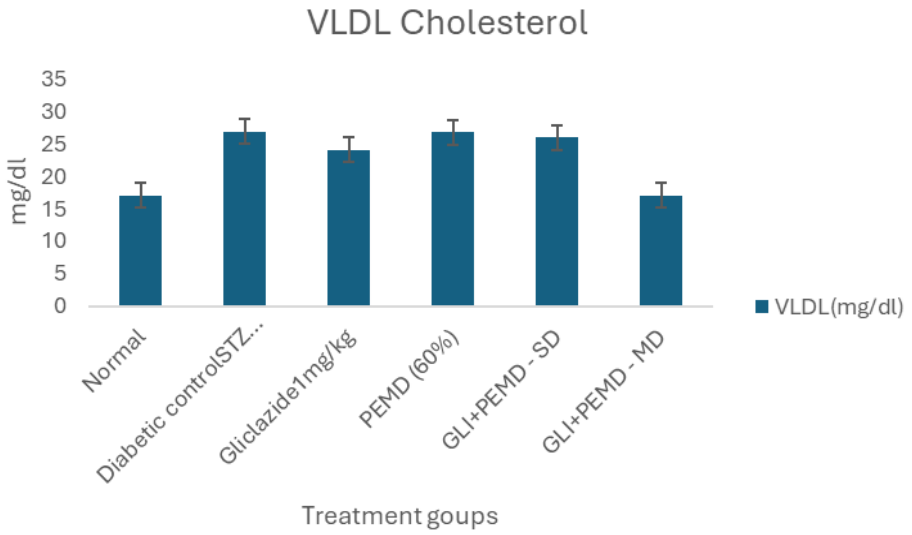

Figure 9. VLDL Cholesterol values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction

The following Figures represent Mean Liver profile values in Gliclazide, Millet diet, and single and multiple dose Combinations of millet diet at peak hours of blood glucose reduction in diabetic rats. The figures present the impact of treatment on liver function in STZ-induced diabetic rats. The Millet diet alone did not significantly change liver function parameters. However, the multi-dose treatment significantly normalized these parameters. The SGOT levels in the diabetic control group were 135.67±1.98 mg/dl, which decreased to 84.27±2.14 mg/dl in the Gli+PEMD-MD group in Figure 10. Similarly, in Figure 11, SGPT levels reduced from 80.50±2.89 mg/dl in the diabetic control to 84.27±2.14 mg/dl in the Gli+PEMD-MD group. ALP levels in the diabetic control group were 272.67±2.54 mg/dl, but these declined to 189.09±4.23 mg/dl in the Gli+PEMD-MD group (***p<0.001) in figure 12. Bilirubin levels decreased from 1.45±0.003 mg/dl in the diabetic control group to 0.82±0.005 mg/dl in the Gli+PEMD-MD group (***p<0.001) in Figure 13. Albumin levels also reduced from 6.94±0.87 mg/dl in the diabetic control group to 4.21±0.67 mg/dl in the Gli+PEMD-MD group (***p<0.001) in Figure 14.

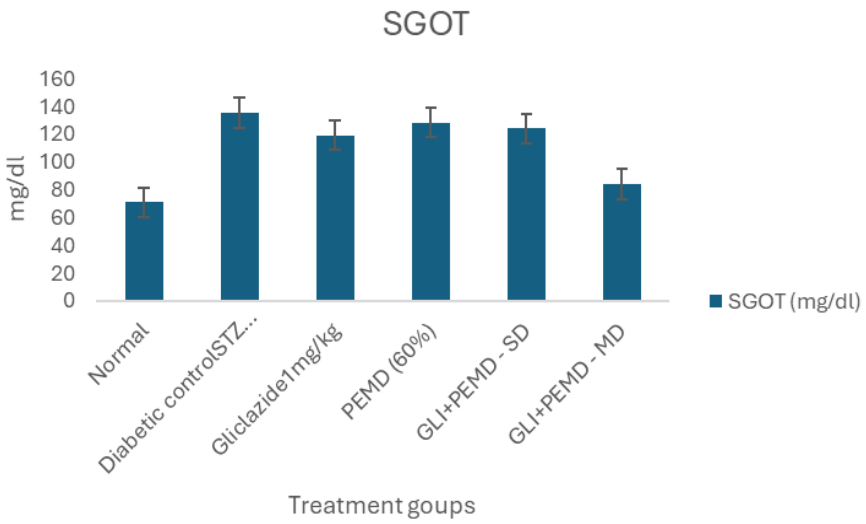

Figure 10. Mean SGOT values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Pearl Millet Diet (60%) at Peak Hours of Blood Glucose Reduction in Diabetic Rats

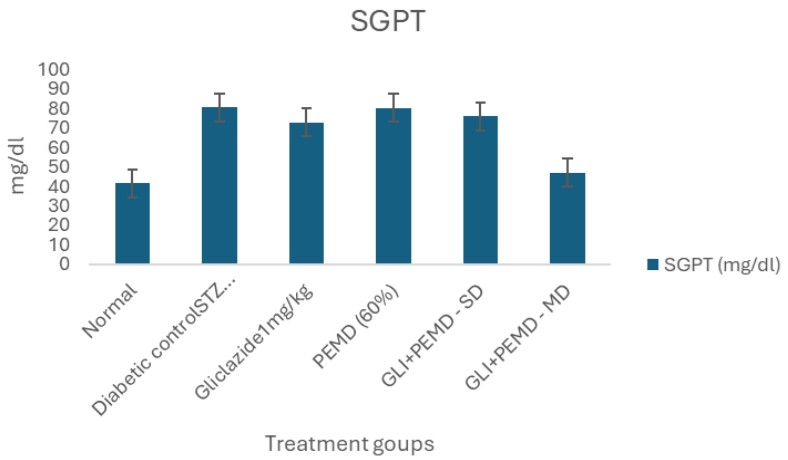

Figure 11. Mean SGPT values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Pearl Millet Diet (60%) at Peak Hours of Blood Glucose Reduction in Diabetic Rats

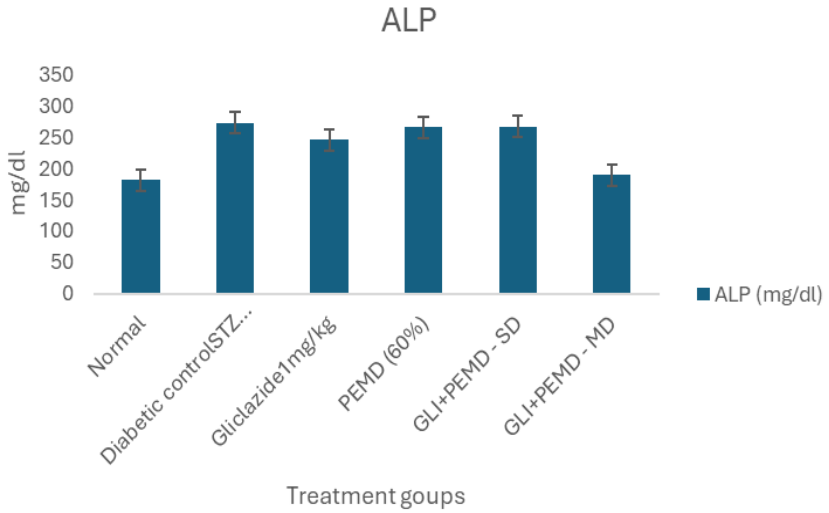

Figure 12. Mean ALP values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Pearl Millet Diet (60%) at Peak Hours of Blood Glucose Reduction in Diabetic Rats

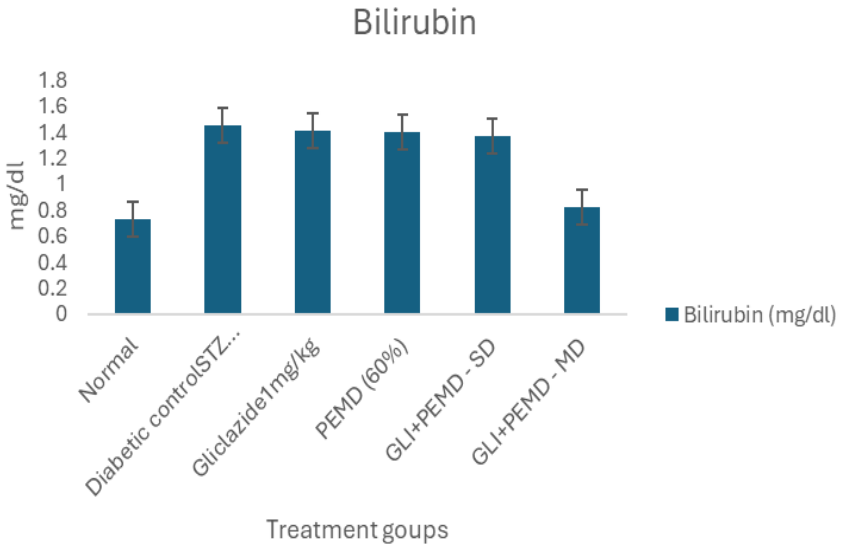

Figure 13. Mean Bilirubin Values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Pearl Millet Diet (60%) at Peak Hours of Blood Glucose Reduction in Diabetic Rats

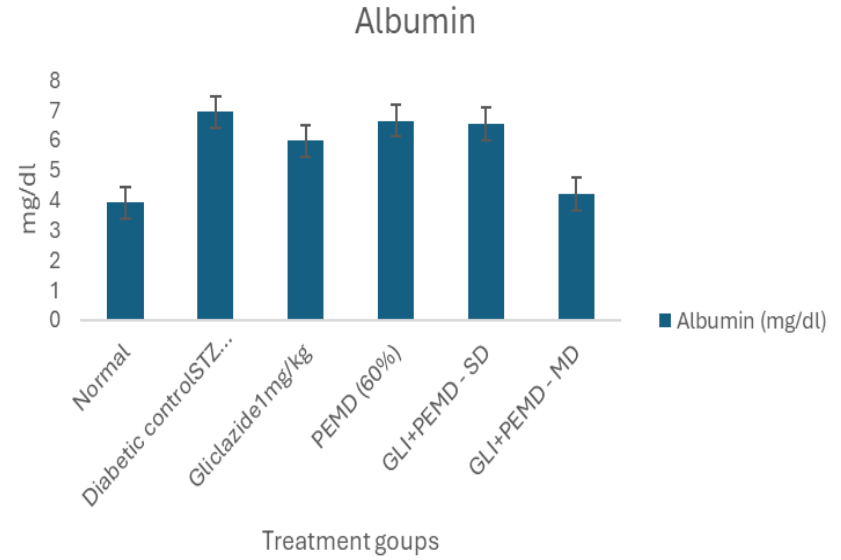

Figure 14. Mean Albumin values in Gliclazide, Millet Diet, and Single and Multiple Dose Combinations of Pearl Millet Diet (60%) at Peak Hours of Blood Glucose Reduction in Diabetic Rats

Mean enzymatic and non-enzymatic antioxidant values in the Gliclazide, Pearl Millet diet (60%) and single and multiple dose Combinations of millet diet at peak hours of blood glucose reduction in diabetic rats are shown in the figures. They represent the effect of selected diets and gliclazide on oxidative stress parameters, focusing on both enzymatic and non-enzymatic antioxidants. The findings indicate a significant reduction in lipid levels with gliclazide alone, PEMD treatment, and the single-dose administration of the combined regimen (Gli+PEMD-SD). In comparison to STZ-induced diabetic rats, which showed 1.68±0.03 IU/mg of SOD, the highest significant increase was observed with Gli+PEMD-MD, achieving 2.67±0.05 IU/mg (**p<0.001) in Figure 15. Catalase levels, which were reduced in the diabetic control, were significantly improved with Gli+PEMD-MD treatment, reaching 1.41±0.04 IU/min/mg in STZ-induced diabetic rats in Figure 16. The non-enzymatic parameter MDA, a marker of lipid peroxidation, was elevated in diabetic control rats (5.40±0.04 nmoles of MDA/mg). However, MDA levels were significantly

reduced with Gli+PEMD-MD treatment to 1.69±0.04 nmoles of MDA/mg at ***p<0.001 in Figure 17.GSH levels, which were lower in diabetic rats (14.44±0.16), were significantly increased in the treatment groups, particularly with multiple-dose administration. GSH levels reached 19.76±0.41 nmol/mg of protein for Gli+PEMD-MD as shown in Figure 18.

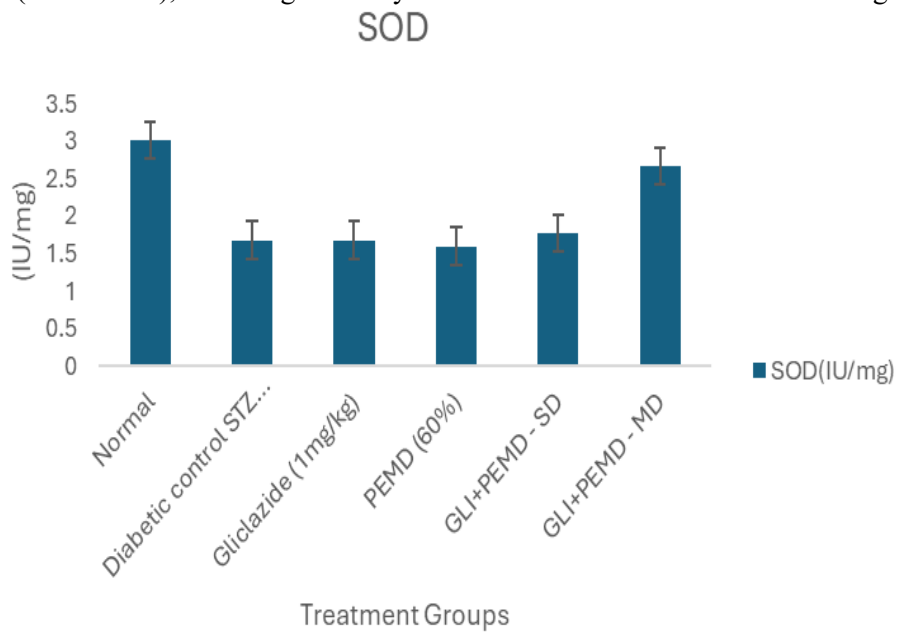

Figure 15. Mean SOD values in Gliclazide, Pearl Millet Diet (60%), and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction in Diabetic Rats

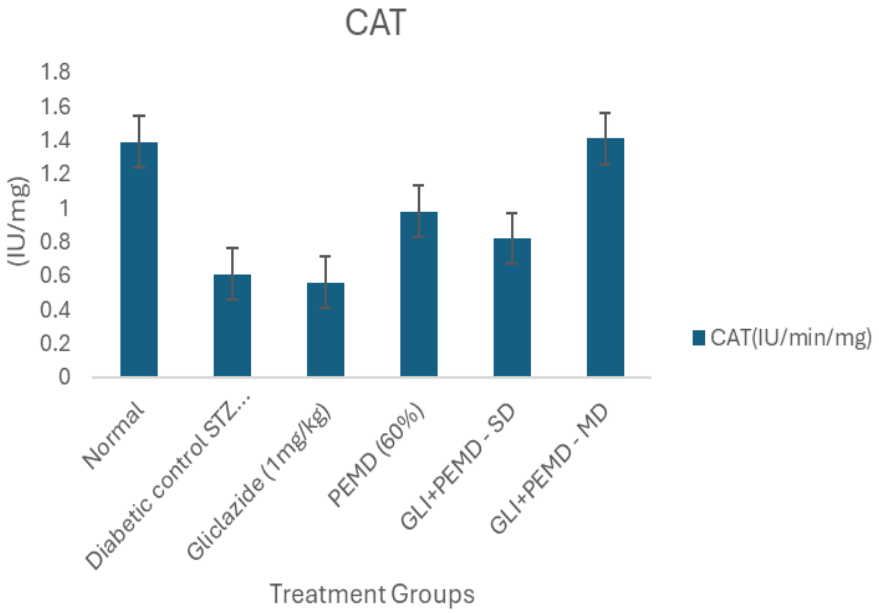

Figure 16. Mean CAT values in Gliclazide, Pearl Millet Diet (60%), and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction in Diabetic rats

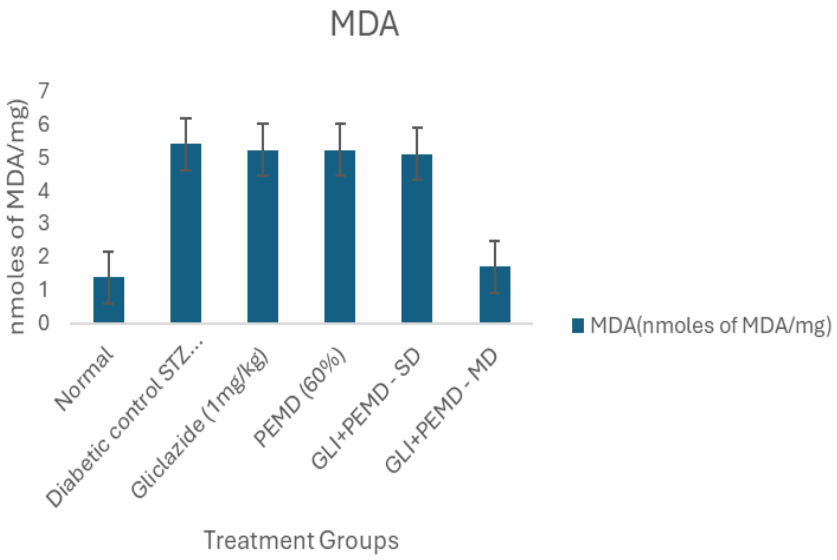

Figure 17. Mean MDA values in Gliclazide, Pearl Millet Diet (60%), and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction in Diabetic Rats

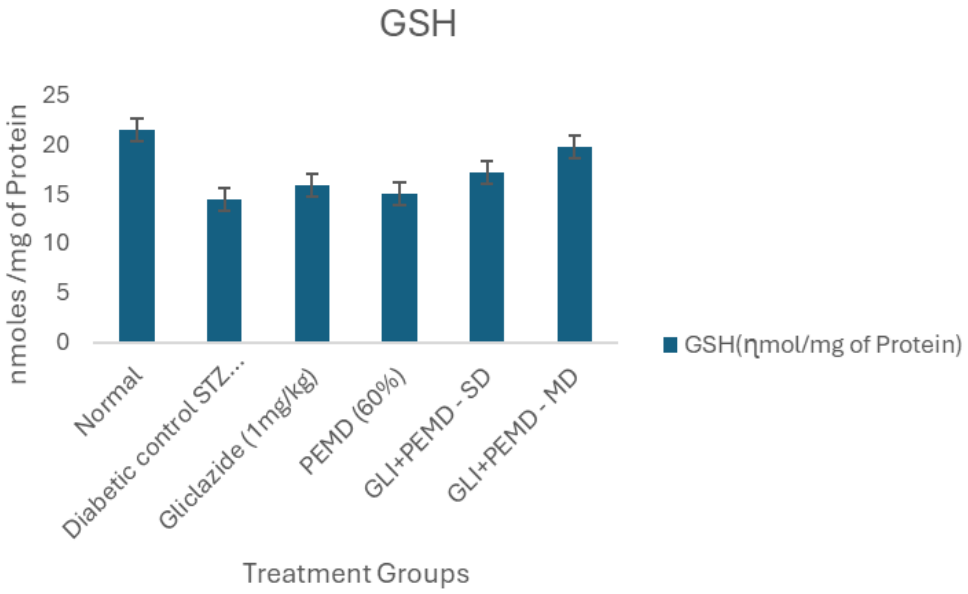

Figure 18. Mean GSH values in Gliclazide, Pearl Millet Diet (60%), and Single and Multiple Dose Combinations of Millet Diet at Peak Hours of Blood Glucose Reduction in Diabetic Rats

Discussion

The present study aimed to evaluate the impact of a millet-based diet (PEMD) on the effectiveness of gliclazide in STZ-induced diabetic rats, focusing on pharmacokinetic and pharmacodynamic interactions. The results support the hypothesis that millet consumption, particularly PEMD, may enhance gliclazide's glucose-lowering effect, potentially through mechanisms related to its bioactive compounds and effects on drug metabolism. The findings of this study align with the objectives outlined in the introduction, which highlighted the potential benefits of millets in managing type 2 diabetes (T2DM). Millets are known for their low glycaemic index, high fibre content, and presence of polyphenolic compounds, such as flavonoids, which can contribute to improved blood glucose control [13, 14]. The present results are consistent with earlier studies suggesting that millets, may play a significant role in modulating glucose metabolism and

improving insulin sensitivity [15, 16]. Specifically, the combination of the Pearl millet diet with gliclazide resulted in enhanced glucose reduction, particularly during the multiple-dose regimen, which underscores the potential synergistic effects between millet and the medication. Further, the study found that millet supplementation altered the pharmacokinetics of gliclazide, likely by inhibiting the CYP3A4 enzyme, a major metabolic pathway for gliclazide [17]. This interaction led to higher gliclazide concentrations in the bloodstream, which could enhance its therapeutic effects. These results are in agreement with previous research that has shown food-drug interactions influencing the absorption and metabolism of various medications [18]. The inhibition of CYP3A4 by millet, particularly its polyphenolic compounds, may explain the increased bioavailability and efficacy of gliclazide observed in this study. However, the results also suggest that the extent of the interaction between millet and gliclazide may depend on the dietary regimen. The multiple-dose regimen (MD) showed more pronounced effects compared to the single-dose regimen (SD), highlighting the importance of long-term dietary changes in managing diabetes and optimizing drug efficacy. This finding is consistent with earlier studies where the prolonged consumption of millet led to more significant improvements in glucose metabolism. The study also measured various biochemical parameters such as lipid profiles, liver enzymes, and antioxidant activity, which further confirmed the positive effects of millet on diabetes-related complications. The reductions in total cholesterol, triglycerides, and LDL-cholesterol levels observed with millet supplementation align with previous studies that reported similar effects of millet on lipid metabolism [12, 19]. Additionally, the millet diet enhanced antioxidant defence by increasing levels of superoxide dismutase (SOD) and catalase (CAT), which may help mitigate oxidative stress and prevent complications related to diabetes [20]. While the study provides promising results regarding the potential of millet-based diets in enhancing the therapeutic effects of gliclazide, it also raises important questions for future research. For instance, it would be beneficial to explore the specific molecular mechanisms underlying the pharmacokinetic interaction between millet and gliclazide, especially the role of flavonoids in modulating enzyme activity. Additionally, clinical studies are needed to confirm the findings in humans, as the current study was conducted in a rodent model. Further research could also investigate the long-term effects of millet consumption in combination with gliclazide on other metabolic pathways and potential adverse effects, such as liver toxicity or nutrient deficiencies due to anti-nutrients in millets.

Conclusion

In conclusion, this study provides valuable insights into the potential therapeutic effects of Pearl millet in combination with gliclazide for managing type 2 diabetes. The synergistic pharmacodynamic interaction and the positive modulation of lipid and antioxidant profiles suggest that Pearl millet could be a beneficial dietary adjunct to diabetes management. However, further research is needed to understand these interactions' scope fully and translate these findings into clinical practice.

Conflict of Interest

The authors of this study confirm that there are no competing interests.

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