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Exploring the Possible Food-Drug Interactions of Foxtail Millet Diet on Gliclazide in Healthy Rats

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KEYWORDS

Foxtail millet, Gliclazide, Pharmacodynamics, Pharmacokinetics, Blood Glucose

ABSTRACT:

Foxtail millet has a relatively low glycemic index, which means it helps keep blood sugar levels stable for a longer duration in patients with diabetes. A study was conducted to determine the potential interactions between a 30% and 60% foxtail millet diet (FOMD) and gliclazide in normal rats. The study evaluated the reduction of blood glucose by gliclazide (1 mg/kg) and FOMD 30 and 60. Further study was continued with an optimized diet of FOMD for single (SD) and repeated dose (MD) studies, and the GLI+FOMD60-MD study showed a significant increase in % blood glucose reduction compared to the single-dose study. The study also observed serum gliclazide levels in correlation to blood glucose levels. However, there was no reduction in HbA1c and no increase in insulin with GLI+FOMD60-MD. The pharmacokinetic parameters of gliclazide were estimated using the PK solver program. The analysis explained the changes in t1/2, Tmax, Cmax, AUC, and MRT corresponding to the serum levels of gliclazide in GLI+FOMD60-MD. The interactions observed may be due to the possible pharmacokinetic interactions probably by metabolic interactions. Physicians should be aware of these interactions to avoid potential hypoglycemia and adjust the dosage of gliclazide accordingly.

1. Introduction

Diabetes has become a highly problematic and increasingly widespread disease worldwide. It is estimated that over a 51% increase in diabetics worldwide by 2045, from 463 million in 2019 to 700 million in 2045, with type 2 diabetes accounting for about 90% of the total 87% of diabetes-related deaths occurring in low- and middle-income countries (Khan MAB., 2020). Management techniques for the prevention of diabetes in both high-risk and affected individuals consist primarily of lifestyle changes and dietary regulations in addition to medications. In particular, diet can have a major impact on the diabetic's regular life (Petersen KS., 2021). It is noteworthy that there are different prescribed diets in different countries. In T2DM, a balanced diet is a risk factor, proven in numerous studies that have proven the exact relationship between grains and the metabolism of glucose (Ren X., 2018). A lower carbohydrate and Mediterranean diet lowers HbA1c (HbA1c is a test of blood glucose levels over some time). In some cases, vegetarian and low glycemic index (GI) diets have been recommended to help reduce the use of diabetes medications. Many studies have shown the effectiveness of millet in improving glycemic control, reducing fasting and postprandial blood glucose concentrations reducing the insulin index and insulin resistance, and reducing the level of glycosylated hemoglobin (HbA1c). The glycemic index (GI) is a measure of how much the carbohydrates present in food affect the rate and extent of change in postprandial blood glucose concentration (Anitha S., 2021). Millet seed coat, commonly known as bran, contains a significant concentration of essential nutrients, fiber, and bioactive compounds such as tannins (Agrawal P., 2023). The high fiber and phenolic content of the diet make millet, especially foxtail millet, very fertile for DM. Foxtail millet is particularly rich in

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resistant starch, which can slow gastric emptying and lower blood glucose levels after consumption (Singh V., 2022). Additionally, animal experiments also showed that feeding foxtail millet improved insulin sensitivity and cholesterol metabolism in genetically diabetic type 2 mice. Human clinical trials are necessary to verify the results obtained from in vitro studies and animal experiments. Hence, the possibility of co-administration is there between the foxtail millet and antidiabetic drugs. However, Numerous studies have documented the effect of plant foods and herbal preparations on the bioavailability of drugs. Significant food components and phytochemicals have been hypothesized to affect drug transporters and metabolizing enzymes, potentially leading to significant nutrient-drug interactions. Drug–food interactions can have two primary therapeutic effects: either the bioavailability of the drug is reduced, leading to treatment failure, or it is increased, increasing the risk of adverse effects and may even induce toxicity. Drug transporters and drug-metabolizing enzymes are critical in altering the way drugs are absorbed, distributed, metabolized, and eliminated (ADME).

Therefore, the present study focused on establishing the possible pharmacokinetic and pharmacodynamic interactions between the foxtail millet and the popularly prescribed antidiabetic drug gliclazide in normal rats.

2. Materials and Methods:

Followed standard experimental protocols, which included different ratios of the millet diet as well as the reference drug, gliclazide. As subjects, we used Wistar albino rats of both sexes, which were obtained from Mahaveer Enterprises, Hyderabad, India. Rats were housed under standard laboratory conditions with an ambient temperature of 25 ± 2 °C, relative humidity of 50 ± 15%, and a 12 h light/12 h dark cycle. They received a commercial pellet diet from Rayan's Biotechnologies Pvt. Ltd, Hyderabad, India, and had access to water ad libitum. Ethical aspects were strictly adhered to and the experimental protocol underwent strict review and approval by both the Institutional Animal Ethics Committee and the regulatory body of the government (Regd No.SNV/08/2022/PC/1). To ensure uniformity and adherence to ethical standards, rats were subjected to an 18-hour fasting period during which they had access to water. This particular segment of the study focused exclusively on the assessment of pharmacodynamic response We paid special attention to blood glucose and insulin levels, and we chose gliclazide as the standard reference drug.

2.1 Preparation of drug solutions:

Millet preparation: Dried forms of millet were collected from the local market and fine powders of the obtained foxtail millet and sieved to fine powder. The millets are mixed with the basal diet at a ratio of 30% and 60% with foxtail millet.

Gliclazide: Gliclazide Stock Solution (10 mg/mL): The stock solution is prepared by adding a few drops of 0.1N NaOH to solubilize Gliclazide and adjusting the volume with distilled water. Appropriate dilutions were made with distilled water as and when needed.

2.2 Experimental design

Normal albino rats of either sex weighing between 220 g – 270 g were used in the study. The animals were fasted overnight for 18 hr before experimentation but allowed free access to water. Water was withdrawn during the experiment. Fasted rats were divided into four groups with six animals in each group and treated orally in the following manner. The experimental design in normal rats was conducted into 4 stages and each stage is separated by a washout period of 7 days:

Stage-I: Rats were administered with vehicle control (water) and standard (Gliclazide 1.0 mg/Kg bd. wt) and blood samples were collected at different time intervals and were analyzed for blood glucose

Stage II: Different groups of rats were fed with interacting foxtail millet, and blood samples were collected at different time intervals and were analyzed for blood glucose.

Stage III: Rats were fed with foxtail millet along with the gliclazide 1mg/kg bd. wt was administered and blood samples were collected at different time intervals and were analyzed for blood glucose.

Stage IV: Rats were fed with multiple doses of foxtail millet for 7 days and on a steady-state day with a 30-minute time difference Gliclazide was administered and blood samples were collected at different time intervals and were analyzed for blood glucose.

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2.3 Collection of blood samples:

Blood samples were carefully and systematically collected from rats via the retroorbital plexus using a standardized procedure. A fine glass capillary was gently inserted into the inner corner of the eye at a 45° angle to rupture the fragile venous capillary in the ocular venous plexus, and blood samples were collected at set time intervals (0, 1, 2, 3, 4 6, 8, 10 and 12 hours) after feeding. At each time point, approximately 0.2 ml of blood was collected and transferred to Eppendorf centrifuge tubes (1.5 ml, Tarson). The serum was then separated by centrifugation and transferred using an automatic pipette. The glucose oxidase/peroxidase (GOD/POD) method was used for immediate blood glucose analysis. Serum gliclazide levels are estimated using a Pk solver. At each peak hour, HbA1c levels (ion exchange resin method) and insulin levels (Invitrogen ELISA kit) were estimated.

2.4 Bioanalytical method:

The concentration of gliclazide in plasma was measured using a Waters 2487 High-Performance Liquid Chromatography (HPLC) unit. The unit was equipped with an LC-20AD solvent delivery module, an SPD-20A UV detector, and a Kromasil 100–5C18 column (100 mm × 4.6 mm, 5 µm). The HPLC system was operated at 230 nm. An isocratic mobile phase containing a mixture of acetonitrile, methanol, and water (40:35:25, v/v/v) was used to separate the analyte from the endogenous components. The mobile phase was delivered at a flow rate of 1.00 mL/min. Before mixing, all serum samples were vortexed for 10 seconds. Then, a 100 µl aliquot of the serum sample was mixed with 50 µl of the internal standard working solution (50 µg/ml ibuprofen). To this, 1 ml of methanol was added. After vortexing for 60 seconds, the mixture was centrifuged at 4000 rpm for 15 minutes. The supernatant was transferred to a 5 mL glass tube and evaporated at 45 °C under a gentle stream of nitrogen. The dried extract was reconstituted with 100 µl methanol. Finally, a 50 µl aliquot was injected into the HPLC system. Gliclazide and the internal standard were eluted at 5.7 ± 1 and 8.6 ± 1 minutes, respectively.

2.5 Statistical Analysis:

The results were compared using two-way ANOVA, and Bonferroni post-test to find statistical significance, *** Significant at P<0.001; **Significant at P<0.01; * Significant at P<0.05 compared to control. The pharmacokinetic parameters were analyzed by using Pk solver software.

3. Results

Effect of gliclazide and Foxtail millet diet (FOMD) on blood glucose levels in normal rats. The study was conducted with FOMD at 30% and 60% diet ratios and estimated blood glucose levels are different time points 0hr to 12 hr.

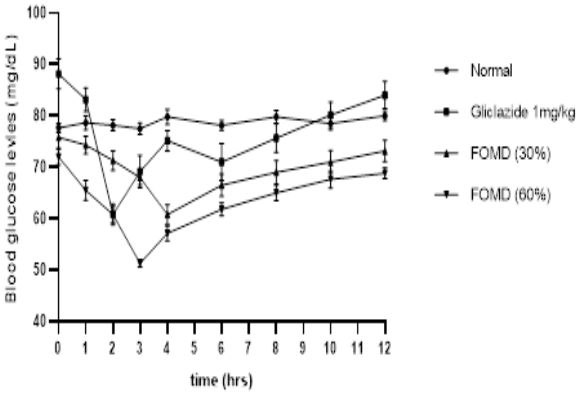

Figure 1. Effect of gliclazide and Foxtail millet diet (FOMD) on blood glucose levels in normal rats

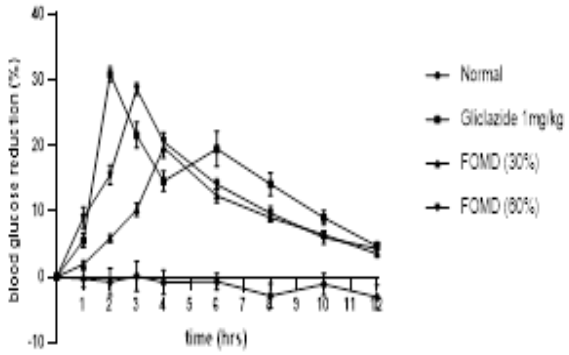

Figure 2. Effect of gliclazide and Foxtail millet diet (FOMD) on % blood glucose reduction in normal rats

The results showed that blood glucose reduction was observed at 2 hr 30.9% and after 6 hours it was 19.53% with gliclazide and supplementation with FOMD 30 and 60 reduced blood glucose levels by 19.74% (4hr) and 28.65% (3hr), respectively (figure 1 and figure 2). With gliclazide, single-dose (SD) and multiple-dose (MD) administrations were designed. When gliclazide was

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administered alone at 1 mg/kg body weight, it produced a 30.90% and 19.53% reduction in blood glucose levels at 1 hour and 6 hours respectively. Table 1 shows that the combination of Gliclazide and FOMD-SD did not result in a significant reduction of blood glucose levels, with reductions of only 33.47% (at 2 hours) and 14.75% (at 6 hours). However, Gli+FOMD-MD showed significant reductions in gliclazide peak levels at 40.66% (1 hour) and 31.40% (8 hours) as shown in Figure 3

Table 1: Effect of gliclazide and combination of Foxtail millet diet (FOMD 60) on blood glucose levels of single and multiple dose study in normal rats

Blood Glucose levels (mg/dL)			
	Gliclazide	**Gliclazide + FOMD**	
	Alone	**SD**	**MD**
0	88.17±2.90	84.67±3.48	87.33±1.54
1	83.17±2.32***	75.50±3.16 ns	**51.83**±2.67***
2	**60.83**±**1.53*****	**56.33**±2.41	55.83±1.82***
3	69.17±3.14***	71.67±2.82	60.00±2.53***
4	75.17±1.95***	75.50±2.84 ns	65.67±3.12***
6	**71.00**±**3.58*****	**72.17**±3.00 ns	69.33±3.11***
8	75.67±2.82***	76.50±3.48 ns	**59.83**±1.25***
10	80.17±2.49*	78.67±3.66 ns	62.33±1.71***
12	84.00±2.67 ns	81.83±3.74 ns	67.17±1.48***

ns p>0.05, * p>0.05, ** p<0.01, *** p<0.001, significance followed by 2 WAY ANOVA multiple comparison test with 0 hr

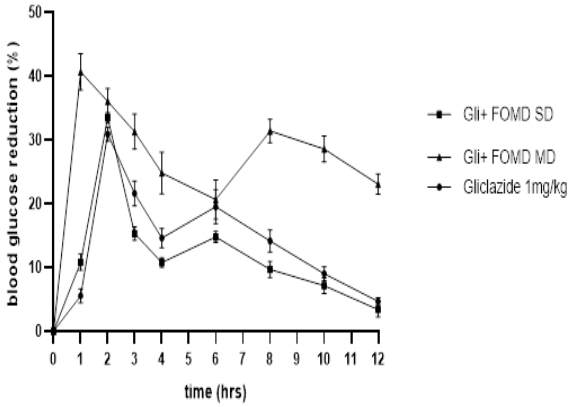

Figure 3. Effect of gliclazide and combination of Foxtail millet diet (FOMD 60) on % blood glucose reduction of single and multiple dose study in normal rats

In this study, we aimed to determine whether the hypoglycemic effects of gliclazide can be enhanced by combining it with millet, either through synergistic activity or pharmacokinetic interaction. We administered varying doses of millet along with gliclazide to estimate the serum gliclazide levels in both SD and MD supplementation. Our findings indicated that there were no significant changes in serum gliclazide levels with the SD of all millets. However, administering gliclazide alone resulted in elevated gliclazide levels, which corresponded to their peak blood glucose reduction hours, with levels of 12.03 µg/ml at 2 hours and 9.04 µg/ml at 6 hours. When combined with FOMD-SD, Gli+FOMD-SD showed a significant enhancement of serum gliclazide to 13.90 µg/ml and 7.88 µg/ml at 2 hours and 6 hours, respectively (table 2). The pharmacokinetic parameters are also assessed to identify the possible food-drug interactions. The results showed an increase in Cmax and a decrease in AUC and MRT from 10 hours to 7 hours (table 3). Table 4 describes the correspondence between HbA1c and insulin with the alterations in the blood glucose levels. It was observed that there is no significant correlation is there between the altered glucose in the combined administration of FOMD and gliclazide.

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Table 2: Serum gliclazide levels of rats treated with gliclazide and combination of Foxtail millet diet (FOMD 60) in single and multiple dose studies in normal rats

Serum Gliclazide levels			
	Gliclazide	**Gliclazide + FOMD**	
	Alone	**SD**	**MD**
0	0.00±0.00	0.00±0.00 ^{ns}	0.00±0.00 ^{ns}
1	7.90±0.25	8.23±0.28 ^{ns}	**15.08**±0.37**
2	**12.03±0.34**	**13.90**±0.37 ^{ns}	13.23±0.34 ^{ns}
3	10.76±0.19	7.30±0.39**	11.42±0.21 *
4	7.77±0.52	5.76±0.43 ^{ns}	10.82±0.32**
6	**9.04±0.33**	**7.88**±0.28*	8.65±0.26*
8	6.89±0.28	5.68±0.24 ^{ns}	**10.90**±0.33**
10	5.33±0.42	4.15±0.51 ^{ns}	8.41±0.45*
12	4.89±0.17	3.40±0.46	7.05±0.23 *

^{ns}p>0.05, *p>0.05, **p<0.01, ***p<0.001, significance followed by 2 WAY ANOVA multiple comparison test with Gliclazide

Table 3: Pharmacokinetic parameters of rats treated with gliclazide and combination of Foxtail millet diet (FOMD 60) in single and multiple dose studies in normal rats

Parameter	**Pharmacokinetic Parameters**			
	Unit	**Gliclazide**	**FOMD-SD**	**FOMD-MD**
Lambda_z	1/h	0.11±0.002	0.14±0.002	0.22±0.001
t1/2	h	6.60±0.005	4.89±0.004	6.38±0.007
Tmax	h	2.00±0.011	2.00±0.015	1.00±0.001
Cmax	µg/ml	12.03±0	13.90±0	15.08±0
Tlag	h	0.00±0.02	0.00±0.07	0.00±0
Clast_obs/Cmax		0.41±0.003	0.24±0.004	0.46±0.003
AUC 0-t	µg/ml*h	89.76±0.11	76.89±0.15	119.44±0.22
AUC 0-inf_obs	µg/ml*h	136.32±1.7	100.87±1.44	183.84±1.12
AUC 0-t/0-inf_obs	µg/ml*h	0.66±0.004	0.76±0.003	0.64±0.002
AUMC 0-inf_obs	µg/ml*h^2	1497.17±31.31	858.66±27.15	2042.09±36.1
MRT 0-inf_obs	h	10.98±0.07	8.51±0.04	11.12±0.06
Vz/F_obs	(mg)/(µg/ml)	0.70±0	0.70±0	0.49±0.07
Cl/F_obs	(mg)/(µg/ml)/h	0.07±0	0.10±0	0.08±0

Table 4: Mean Serum insulin (µIU/mL) and HbA1C with mean serum glucose level (mg/dL) in Gliclazide, FOMD and single and multiple dose Combinations at peak hours of blood glucose reduction

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Groups	Time (hrs)	Mean serum glucose levels (mg/dL)	Serum Insulin (µU/mL)	HbA1C
Gliclazide	2 hr	61.80±1.66	**10.20±0.23**	**5.01±0.12**
	6hr	71.22±3.58	9.10±0.87	5.45±0.22
FOMD 60	3hr	51.33±0.73	10.07±0.34	5.21±0.14
Gliclazide+ FOMD (SD)	2 hr	56.33±2.41	7.72±0.29	5.22±0.21
	6hr	72.17±3.00	9.10±0.18	5.67±0.08

4. Discussion

Dietary fiber is essential for maintaining good health. It swells in the intestine, which slows down the movement of food 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 (Cronin P., 2021). The fiber's high viscosity, glycemic index, and water-holding capacity also help lower blood glucose and insulin response (Giuntini EB., 2022). In addition, dietary fiber components bind bile salts, thereby promoting the excretion of cholesterol 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 (Nie Y., 2021).

However, different foods can have different effects on blood sugar levels. It is very important to monitor your blood glucose levels regularly, especially when adding new foods to your diet. Changes in your diet can affect the effectiveness of antidiabetic drugs such as gliclazide (Ogura J., 2022). If you are taking gliclazide, be aware of the possibility of interactions with certain foods, such as millet. These foods may slow down the absorption of gliclazide, which is usually taken with food. If you have a high-fiber diet, this may further affect the absorption of the medicine. To better understand the effects of co-consumption of gliclazide and millet, a study will be conducted in healthy rats. This study aims to verify the potential risks and benefits of the combination, as well as gain a more comprehensive understanding of its efficacy and safety in diabetes models and ultimately in patients. The study was designed in such a way as to understand the pharmacodynamics and pharmacokinetic interactions in both single-dose and multiple-dose administrations.

In this study, normal rats were used to investigate the interaction between gliclazide and Millet in terms of blood glucose levels. They selected a dose of 1 mg/kg based on previous studies conducted by various authors on herb-drug interaction studies in rats (Umachandar L., 2018). Previous research has shown that this dose was effective in lowering blood glucose levels in normal rats. The results of the study showed that gliclazide lowered blood glucose levels in two phases. After 2 hours the reduction was 30.9% and after 6 hours it was 19.53% as shown in Figures 1 and 2 and the FOMD 60 supplementation showed 28.65% reduction. The initial rapid release of insulin (phase I), stimulated by gliclazide, which may be responsible for the maximal reduction observed at 2 hours. Gliclazide also increased the sensitivity of pancreatic β-cells to glucose, contributing to this reduction. However, gliclazide did not affect the sustained release of insulin (phase II) (Al-Omary FAM., 2017). After 6 hours, the observed decrease can be attributed to the ability of gliclazide to increase the sensitivity of peripheral tissues to insulin. Gliclazide is metabolized to several metabolites by hepatic cytochrome P450 isoenzymes 3A4 and 2C9 and is eliminated in the urine (Kang P., 2023). Part of them is eliminated by the biliary route, which includes enterohepatic circulation in rats (Rama Narsimha Reddy A., 2017). Reabsorption of biliary-eliminated gliclazide may be responsible for the second peak of its hypoglycemic effect in normal rats.

The study aimed to assess the effects of gliclazide on blood glucose levels in both single and multiple-dose studies conducted over seven days. The results indicated that while the single-dose administration showed no significant improvement in blood glucose reduction, the

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multiple-dose administration led to a significant reduction in blood glucose levels (table 1). It needs to estimate the kinetic parameters underlying drug metabolism by CYP enzymes in the liver to predict drug effects, which is essential for drug development. Because of the dosing requirements of potent drugs, the amount of CYP enzyme may greatly exceed the amount of drug in the liver (Choi B., 2017). Moreover, the study also found that combining millets with gliclazide resulted in a significant increase in the level of gliclazide in the bloodstream, both in single and multiple-dose studies. However, it did not affect the peak hours of gliclazide, and the levels of gliclazide varied at different time points of co-administration with FOMD (Table 3). The results showed changes in t1/2, Tmax, Cmax, AUC, and MRT corresponding to the serum levels of gliclazide in GLI+FOMD60-MD (table 4).

5. Conclusions

According to the study, when foxtail millet and gliclazide are taken together, there are remarkable interactions between them. These interactions may occur due to their combined pharmacodynamic activity and metabolic pharmacokinetic interactions. Therefore, physicians must be cautious and aware of these interactions to avoid potential hypoglycemia. They should adjust the dosage of gliclazide accordingly to ensure patient safety.

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