Pharmacokinetic and Pharmacodynamic interactions of Ferulic Acid with Glibenclamide in Streptozotocin-Induced Diabetic Wistar Rats

PUTTIREDDY SUBRAMANYAREDDY MALATHY AND YELLU NARASIMHA REDDY*

[*]Department of Pharmacology, University College Pharmaceutical Sciences, Kakatiya University, Warangal – 506009, TS, India.

Email: ynrku@kakatiya.ac.in

***Corresponding author**

Prof. Y. Narasimha Reddy

Department of Pharmacology,
University College Pharmaceutical Sciences,
Kakatiya University,
Warangal – 506009,
Telangana, India.
Telephone no: : +91 9440705384
E-mail: ynrku@kakatiya.ac.in

Abstract:

Glibenclamide (GLB), is a sulfonylurea drug prescribed for the treatment of diabetes. GLB is commercially available as an oral dosage form. However, the GLB can still have limitations in the therapeutic efficacy of monotherapy. The coadministration or concurrent administration of synthetic drugs with phytoconstituents showed beneficial effects. Ferulic acid (FA), a phenolic phytoconstituent has antioxidant, anti-inflammatory, and antidiabetic effects. The present investigation is aimed to determine the effect of an FA on pharmacokinetic (PK) and pharmacodynamic (PD) parameters of GLB in normal and streptazocin (STZ) induced diabetes male Wister rats. PK study results confirmed a significant ($p<0.05$) enhancement in oral absorption in the presence of FA, compared with GLB monotherapy. Further, the disease-induced rats showed more PK effect than normal rats after single-dose and multi-dose oral administration. The maximum reduction ($p<0.05$) in glucose levels was observed in normal and disease rats, more effective in disease rats than in normal rats in the presence of FA. The results of PD activity were correlated with the PK behavior in normal and diabetes rats. Therefore, the study demonstrates that the administration of GLB with FA could be beneficial to diabetes patients through oral administration.

Keywords: Glibenclamide, Ferulic acid, Streptazocin, Rats, Pharmacokinetics, Pharmacodynamics.

INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disorder characterized by hyperglycemia, poses a significant global health challenge. (Goyal R, et al 2023). Type 2 diabetes mellitus (T2DM), the most prevalent form, is associated with insulin resistance and impaired insulin secretion. While several therapeutic interventions exist, including oral hypoglycemic agents like Glibenclamide, challenges such as drug resistance and adverse effects persist. (Padhi, S.,2020). Diabetes mellitus (DM) is a disease of inadequate control of blood levels of glucose. It has many subclassifications, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes. (Sapra A, et al 2023).T2DM involves a more complex interplay between genetics and lifestyle. There is clear evidence suggesting that T2DM is has a stronger hereditary profile as compared to T1DM. The majority of patients with the disease have at least one parent with T2DM. (Klein BE, et al.1996).

Natural products offer a promising avenue for developing safe and effective antidiabetic agents.(Alam, Sarker et al. 2022).Ferulic acid (FA), a phenolic compound abundant in plant-based foods, has garnered attention for its diverse pharmacological properties, including antioxidant, anti-inflammatory, and antidiabetic effects (Ye, Hu et al. 2023). Previous studies have demonstrated the potential of FA in ameliorating hyperglycemia and improving insulin sensitivity in diabetic animal models. Glibenclamide, a sulfonylurea drug, enhances insulin secretion by stimulating the closure of ATP-sensitive potassium channels in pancreatic β-cells. By evaluating the combined effects of FA and GLB, we sought to gain insights into potential synergistic or antagonistic interactions and explore the possibility of optimizing glycaemic control and reducing adverse effects.(Hambrock, Löffler-Walz et al. 2002). The study aimed to investigate the impact of FA on the PK/PD profile of Glibenclamide in a streptozotocin (STZ)-induced diabetic rat model.

Materials

Glibenclamide and Glimepiride (internal standard) were purchased from Sigma Aldrich, Hyderabad, India. FA was purchased from Yucca Chemicals Pvt Ltd, Wadala, Maharashtra, India. Methanol (HPLC grade), Acetonitrile (HPLC grade), and potassium dihydrogen phosphate (AR grade), were purchased from Merck Pvt. Ltd. Streptozocin (STZ) was purchased from Hi Media Chemicals, India. Double distilled water was collected from Millipore water system (Direct-Q-UV-3). Chemicals used were of analytical grade.

Methods

Experimental animals

Prior to the investigation, all experimental animals were reviewed and approved by the Institutional Animal Ethical Committee (IAEC), UCPSc, Kakatiya University, Warangal, India (06/ IAEC /UCPSC/KU/2022). Male albino Wistar rats weighing 180±30 g was purchased from Vyas labs, Hyderabad, India. The animals were housed in standard polypropylene cages and maintained under standard laboratory conditions (12 h light and dark cycle at an ambient temperature of 25 ± 5^0C; 35-60% of relative humidity). The animals were fed with standard rat pellet diet and water *ad libitum.*

Induction of diabetes

Diabetes was induced in overnight-fasted rats by administering single intraperitoneal (i.p) injection of freshly prepared streptozotocin 60 mg/kg/bw in 0.1 M citrate buffer (pH 4.5) in a volume of 0.5 ml/kg/bw, the induction of diabetes was confirmed by measuring fasting blood glucose level on the fifth day of STZ administration. Rats with fasting blood glucose level of more than 250 mg/dl were considered as diabetics and used for the experiment. After 72 h the blood samples were collected by retro orbital puncture and Plasma was analysed for glucose levels. Rats with blood glucose levels of>250mg/dL were considered as diabetic and used for the study (Choudhari VP, et al 2017)

Pharmacokinetic study

This study was conducted in normal and diabetic rats. After overnight fasting, the rats were randomly divided into three groups (each group contains 6).

SDI and MDI study in normal rats

Group I (control) was administered with GLB (10 mg/kg body wt. po), suspended in 0.5% sodium CMC, Group II was pretreated with FA (50mg/Kg Po) followed by GLB **(**10mg/kg/po**)** for single-dose interaction study (SDI), Group III was pretreated with FA (50 mg/kg/po) for 7 days and on the 8thday treated with FA followed by GLB (10 mg/kg) which is known as multiple dose interaction study (MDI).

SDI and MDI study in diabetic rats

Group I (control) was administered with a single dose of GLB (10 mg/kg body wt. po) suspended in 0.5% sodium CMC, Group II was pretreated with a single dose of FA (50mg/Kg Po) followed by GLB(10mg/kg/po), Group III was pretreated with FA (50 mg/kg/po) for 7 days and on the 8^{th,} day treated with FA followed by GLB (10 mg/kg) which is known as multiple dose interaction study(MDI).

Blood samples (about 0.5 mL were collected at predetermined time intervals from retro-orbital vein puncture using heparinized capillary tubes. Plasma samples were separated after centrifugation at 8000 rpm for 15 min and the samples were stored in freezer at -20^0 C further analysis.

HPLC analysis

GLB concentrations were estimated in plasma by RP- HPLC with slight modification by earlier reported methods. The analysis was performed using an ultrafast Liquid Chromatography (Shimadzu, Kyoto, Japan) system with a gradient capillary binary pump (LC-20AD) and the analytical column C18 (2), 250 × 4.6 mm, 5 µ particle size (Luna 5 µ, Phenomenex). The column effluent was measured with a UV-visible dual wavelength absorbance detector (SPD-M20A) at 254nm. The mobile phase is composed of methanol, acetonitrile, and potassium dihydrogen phosphate buffer (20mM, pH 4.5) in a 50:20:30 v/v/v ratio, given isocratically at a flow rate of 1.5mL/min.

Extraction of GLB Plasma samples:

About 100 µL of Plasma sample, added 100 µL of Glipizide at a concentration of 25 µg/mL as IS, and then added 100 µL of cold acetonitrile as a precipitating agent and vortexed for 1 min and further centrifuged at 13000 g for 15 mins. The supernatant was transferred into a clean labeled tube and was stored at -20^{o}C for further analysis. The resultant samples were reconstituted in 200 µL of mobile phase and about 20 µL were injected into HPLC for analysis of GLB.

(Nagaraj B, et al 2018)

Calculation of PK parameters.

Non compartmental pharmacokinetic analysis is performed using Kinetica TM software (version 4.4.1, Thermo Fisher Scientific Corporation, USA). The PK parameters like C_{max}. T_{max}, AUC_{total}, $t_{1/2}$, MRT, V_d and clearance were calculated.

Pharmacodynamic (PD) study:

These studies were conducted in diabetes-induced rats. After overnight fasting the diabetic rats were randomly divided into 5 groups containing six rats in each group. The single-dose and multi-dose treatments given for the rats were as follows:

Group I: Control (diabetic control), Group II: GLB **(**10mg/kg/po**)** 8 days per orally suspended in 0.5% sodium CMC, Group III: Administered FA (50mg/Kg/ Po) suspended in 0.8 ml of DMSO for 8 days, Group IV: pretreated with FA (50mg/Kg/Po) followed by GLB **(**10mg/kg/po**)** for single dose interaction study, Group V: pretreated with FA (50mg/Kg Po) for 7days on 8th day FA followed by GLB **(**10mg/kg/po**)** for multiple dose interaction study.

Blood samples were withdrawn from the retro-orbital plexus of the rats at 0,0.5,1, 2, 4, 6, 8, 12 and 24 h after the treatment. The samples were analysed for blood glucose using GOD-POD method. The mean blood glucose levels and percentage reduction in blood glucose levels were determined and applied for statistical studies. (Shaker G, et al 20239)

Statistical analysis:

All the PK and PD Parameters were expressed as mean ±SD. The data were statistically evaluated using Student's unpaired t-test using Graph pad prism 5.03.2011 software. Values corresponding to ($p<0.05$) were considered as significant.

RESULTS AND DISCUSSION:

The effect of phytoconstituents on the pharmacological activity of synthetic drugs was improved in the current scenario. The current work mainly focused on the PK and PD behaviour of GLB when co-administered or concurrently administered with FA, a phytoconstituent after the oral route of administration. The study was conducted on normal and diabetic rats

The diabetes in wister rats was induced by streptozotocin at 60 mg/kg/bw. During the induction, the weight of the rats was monitored and a significant reduction in the weight loss of the rats was observed. The rats with more than 250 mg/dL of glucose level were considered diabetic and used for the study.

PK study in normal and STZ-induced diabetic rats.

The PK studies of GLB, and GLB+FA after an SD and MD oral administration were conducted in normal and diabetes-induced rats. The mean plasma concentration and time profiles of GLB and GLB with FA in normal and diseased rats were presented in Figures 1 and 2, respectively. PK parameters of the normal and diseased rats are shown in Table 1 and 2, respectively.

PK parameters in normal rats:

From the results, C_{max}, t_{max}, AUC_{tot}, $t_{1/2}$, and MRT in normal rats were 3.81±0.60µg/mL, 2.0h, 10.36 ±1.5µg/mL.h, 2.51±0.37h and 3.58 ±0.57 h, respectively in GLB treated group. GLB plus FA SD treated group, no significant ($p>0.05$) difference was observed in t_{max} (2.0 h) compared with the GLB treated group. The PK parameters showed 1.07, 1.49, 2.5 and 1.84 folds improvement in C_{max} (4.10 µg/mL), AUC_{tot} (15.44 µg.h/mL), $t_{1/2}$ (6.30 h), and MRT (6.59 h) respectively compared with GLB group. In the case of the GLB plus FA MD treated group, similar PK profile behavior was observed in the GLB plus FA SD treated group. But, 1.04, 1.55, 2.52, 1.8, folds in Cmax (12.10±1.72 µg/mL), AUC_{tot} (42.15±8.43 µg.h/mL), $t_{1/2}$ (3.81±0.95 h) and MRT (3.52±1.22 h), respectively in GLB plus FA MD treated group compared with GLB treated group.

PK parameters in diabetic rats: In diabetic rats, C_{max}, t_{max}, AUC_{tot}, $t_{1/2}$ and MRT of GLB treated group was 6.2 ±0.99 µg/mL, 2.0 h, 20.8 ±3.6 µg/mL.h, 3.81±1.01 h and 3.49 ±0.79 h, respectively. In GLB plus FA SD treated group, no significant difference ($p<0.05$) was observed in t_{max} (2.0 h), compared with the treated group. However, about 1.85 and 1.87, folds improvement in the Cmax (11.53±1.26 µg/mL) and AUC_{tot} (38.94±6.84 µg/mL) respectively was observed compared with the GLB group. In case of GLB plus FA MD treated group, similar PK profile behaviour was observed like GLB plus FA SD treated group. However, about 1.93 and 2.02 folds increment ($p<0.05$) in the C_{max} (12.10 ±1.72 µg/mL) and AUC_{tot} (42.15±8.43µg/mL.h), respectively was observed. No significant difference in $t_{1/2}$ (3.81±0.95) and MRT (3.52±1.22) was observed in comparison with GLB treated group.

PK parameters comparison in normal vs disease rats: From the comparison of PK parameters of GLB treated between normal and disease-treated rats were showed 1.6, 2.0, 1.5 folds enhancement in the C_{max}, AUC_{tot}, $t_{1/2}$ respectively. GLB plus FA SD group showed 2.8 and 2.5-fold enhancement in the C_{max} and AUC_{tot} respectively. Similarly, the GLB plus FA MD treated group showed 3.0 and 2.6-fold enhancement in the C_{max} and AUC_{tot}, respectively. But the t_{max} in both normal and diabetic rats was found to be 2.0 h. This indicates that the co-administration of FA does not alter the absorption of the GLB. In comparison to normal rats, 2.52- and 2.62-fold improvement after SD and MD administration, respectively was observed in the oral bioavailability of GLB in diabetic rats when pretreatment with FA. Several studies evidenced improvement in the PK parameters when phytoconstituents or plant extracts are used along with synthetic drugs (Devi PR,. et al 2015, Kandukoori Naga Raju,. et al 2020, Vora A, et al 2020).

Pharmacodynamic study in diabetic rats.

In pharmacodynamic study the mean plasma glucose levels were determined using glucose oxidase-peroxidase method and the percent glucose reduction at each time point were compared with initial (considered as baseline value) mean glucose levels. The glucose levels of the study were shown in (Table 3 and 4) and Figure 3 and 4. The blood glucose levels were significantly ($p<0.05$) reduced (10.0 and 12. % after SD and MD of GLB + FA treatment, respectively) compared to GLB alone treated diabetic rats during a period of 24 h were noticed from PD studies. The maximum reduction was observed at 2 h (43.9 and 45.6 % after SD and MD of GLB + FA treatment, respectively) when compared with standard GLB treatment (33.2 %). Maximum hypoglycemic activity (6.8 % reduction) was observed at 2 h in UMB treated group. The increased hypoglycemic activity with coadministration of GLB and FA are compared with alone drug FA treated groups and suggested that enhanced glucose reduction activity of GLB in diabetic rats was only with pretreatment of FA.

Conclusion

The in vivo pharmacokinetic and pharmacodynamic effects of GLB with FA, a phenolic phytoconstituent, were investigated in normal and diabetic male Wister rats. PK trial results revealed a considerable increase in the rate and duration of oral absorption in the presence of FA compared to GLB monotherapy. Furthermore, disease-induced animals demonstrated greater PK effects than normal rats. The PK activity correlates with the PD activity. The greatest drop in glucose levels was observed in both normal and disease rats, with disease rats outperforming normal rats in the presence of FA.

Conflict of interest

The authors do not have any conflict of interest.

Acknowledgement

The authors would like to thank the AICTE New Delhi for supporting this work.

Table 1: Pharmacokinetic parameters of GLB in different groups of normal rats (mean±SD, n=6)

PK parameters	GLB	GLB+FA (SDI)	GLB + FA (MDI)
C_{max} (µg/mL)	3.81±0.60	4.10±0.61	4.00±0.72
T_{max} (h)	2.0	2.0	2.0
AUC_{total} (µg.h/mL)	10.36±1.5	15.44±2.77	16.11±3.21
$T_{1/2}$ (h)	2.51±0.37	6.30±0.69	6.34±0.82
MRT (h)	3.58±0.57	6.59±0.72	6.45±0.83
CL (mL/h/kg)	0.96±0.14	0.60±0.18	0.62±0.21
V_d (mL/kg)	3.75±0.61	5.40±0.97	5.40±1.08
K_e (h-1)	0.26±0.03	0.11±0.05	0.110±0.06

*p < 0.05; **p < 0.01 considered as significant when compared with GLB control.
GLB – Glibenclamide; FA – Ferulic acid.

Table 2: Pharmacokinetic parameters of GLB in different groups of Diabetic rats (mean±SD, n=6)

PK parameters	GLB	GLB+FA (SDI)	GLB + FA (MDI)
C_{max} (µg/mL)	6.20±0.99	11.53±1.26	12.10±1.72
T_{max} (h)	2.0	2.0	2.0
AUC_{total} (µg.h/mL)	20.8±3.6	38.94±6.84	42.15±8.43
$T_{1/2}$ (h)	3.81±1.01	3.58±0.71	3.81±0.95
MRT (h)	3.49±0.79	3.58±0.87	3.52±1.22
CL (mL/h/kg)	0.48±0.12	0.25±0.11	0.23±0.53
V_d (mL/kg)	2.63±0.61	1.18±0.81	1.16±1.32
K_e (h-1)	0.18±0.32	0.19±0.63	0.21±0.72

*p < 0.05; **p < 0.01 considered as significant when compared with GLB diabetic.
GLB – Glibenclamide; FA – Ferulic acid.

Table 3. Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Normal rats (mean±SD, n=6)

Group	Treatment	Dose (mg/kg)	Blood glucose level (mg/dl) at different time points						
			0 h	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**	**24 h**
I	C	NT	**97.33± 7.26**	**97.64± 6.82**	**97.89± 6.53**	**98.53± 6.63**	**98.87± 6.19**	**99.38± 6.76**	**99.61± 6.98**
II	GLB	10	**84.33± 6.94**	**62.25± 4.22**	**54.30± 4.13**	**58.70± 3.29**	**61.90± 3.68**	**64.00± 4.62**	**80.80± 6.12**
III	FA	40	**96.23± 8.21**	**90.98± 5.87**	**89.34± 6.24**	**90.89± 5.93**	**91.54± 8.10**	**93.54± 7.24**	**95.89± 6.29**
IV	GLB+ FA (SDI)	10+40	**84.89± 4.52**	**58.85± 3.55**	**51.72 ±4.51**	**55.91± 2.93**	**58.90± 4.91**	**62.98± 5.13**	**79.61± 7.73**
V	GLB+ FA (MDII)	10+40	**82.55± 6.52**	**55.85± 5.12**	**48.83 ±4.21**	**52.35± 3.54**	**54.62 ± 5.51**	**60.63± 6.13**	**78.91± 7.19**

**p<0.001, *p<0.01 indicates statistically significant when compared to control group, Diabetic control, GLB-Glibenclamide, FA – Ferulic acid.

Table 4: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Diabetic rats (mean±SD, n=6)

Group	Treatment	Dose (mg/kg)	Blood glucose level (mg/dl) at different time points						
			0 h	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**	**24 h**
I	DC	NT	**287.27 ± 8.64**	**289.51 ± 8.26**	**290.13 ± 7.82**	**292.32 ± 8.14**	**293.57 ± 6.82**	**296.34 ± 6.79**	**297.21 ± 7.52**
II	GLB	10	**286.31 ±7.01**	**240.90 ±5.40**	**191.20 ±3.45**	**226.80 ±4.29**	**225.30 ±5.52**	**246.13 ±6.21**	**276.12 ±6.82**

III	FA	50	**292.43 ± 7.64**	**279.08 ± 5.0**	**272.04 ± 4.06**	**261.89 ±3.71**	**269.26 ±5.98**	**276±6.14**	**281.89 ±7.25**
IV	GLB+ FA (SDI)	10+50	**289.13 ±5.75**	**233.14 ±4.40**	**162.62 ±4.19**	**236.50 ± 3.60**	**246.19 ±5.91**	**262.13 ±6.69**	**283.51 ±7.41**
V	GLB+ FA (MDI)	10+50	**285.09 ±5.29**	**221.08 ±6.61**	**155.21 ±4.09**	**227.40 ± 3.49**	**239.81 ±5.15**	**248.61 ±6.34**	**269.12 ±7.15**

**p<0.001, *p<0.01 indicates statistically significant when compared to control group. Control – Diabetic control, GLB – Glibenclamide, FA – Ferulic acid.

Figure 1: Pharmacokinetic parameters of Glibenclamide in different groups of normal rats (mean±SD, n=6).

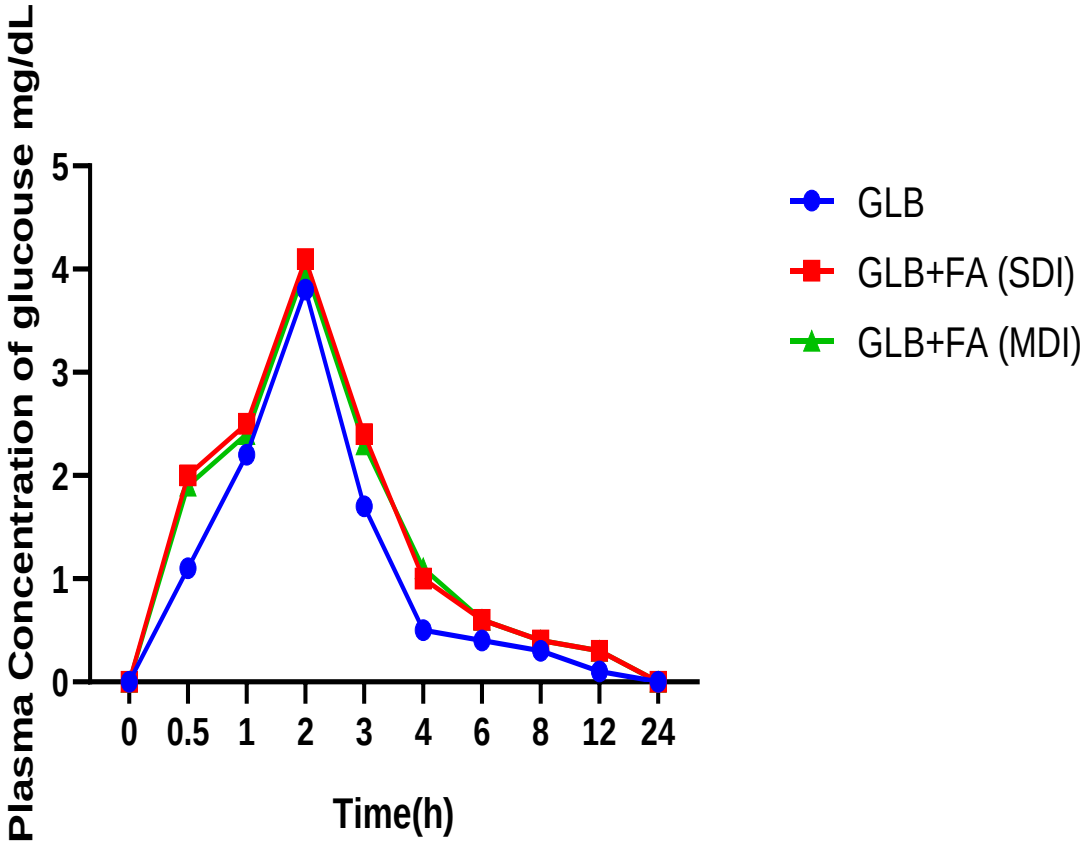


Figure 2: Pharmacokinetic parameters of Glibenclamide in different groups of Diabetic rats (mean±SD, n=6)

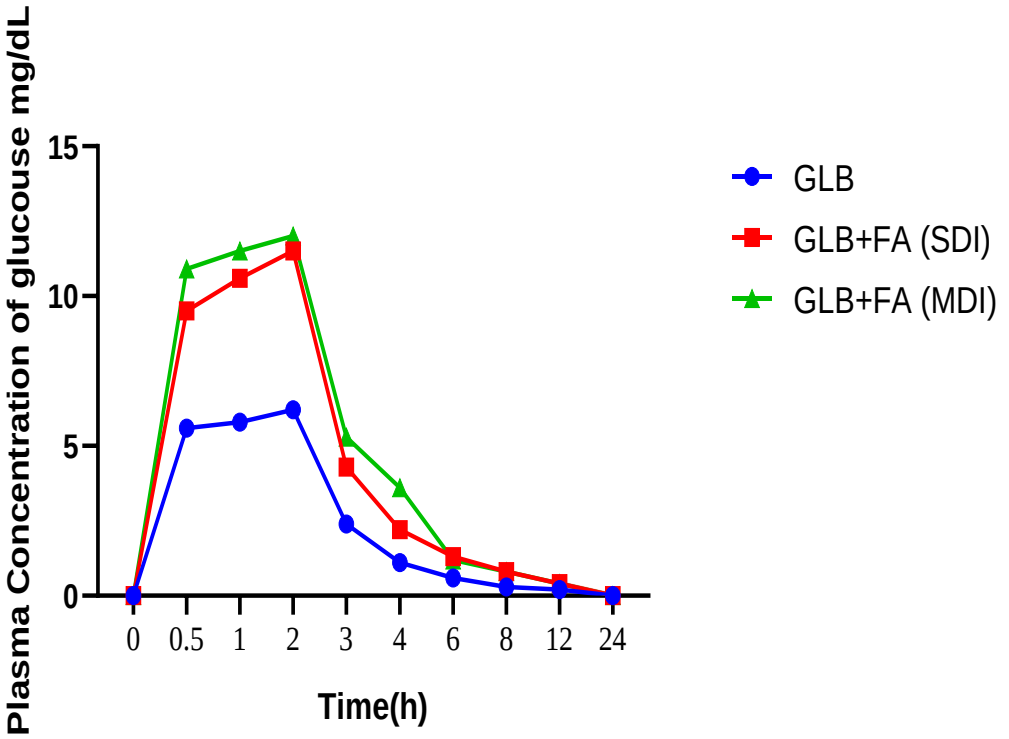


Figure 3: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Normal rats (mean±SD, n=6)

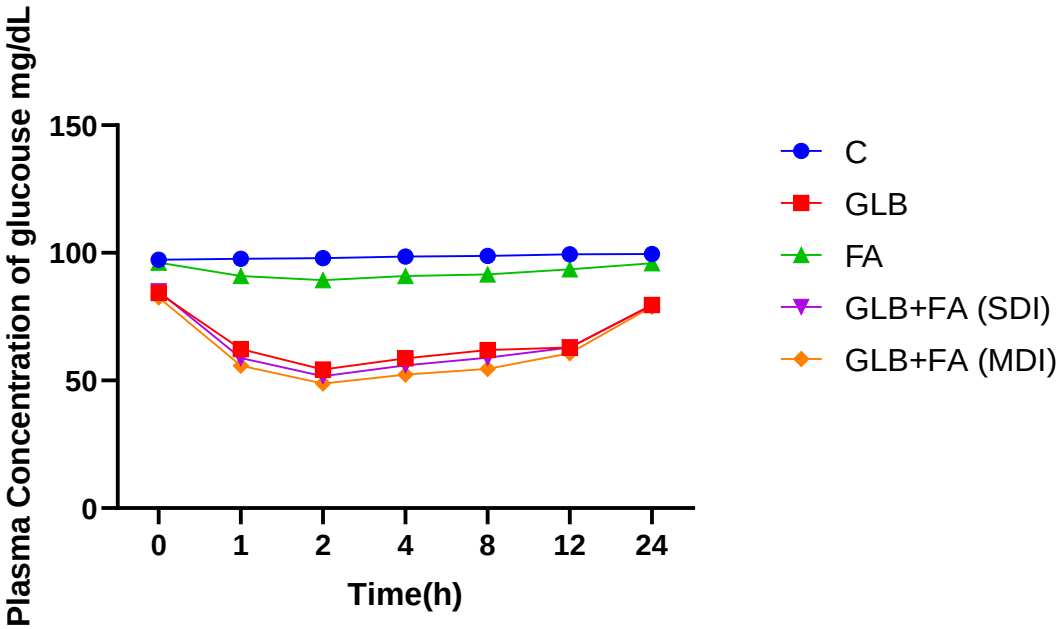
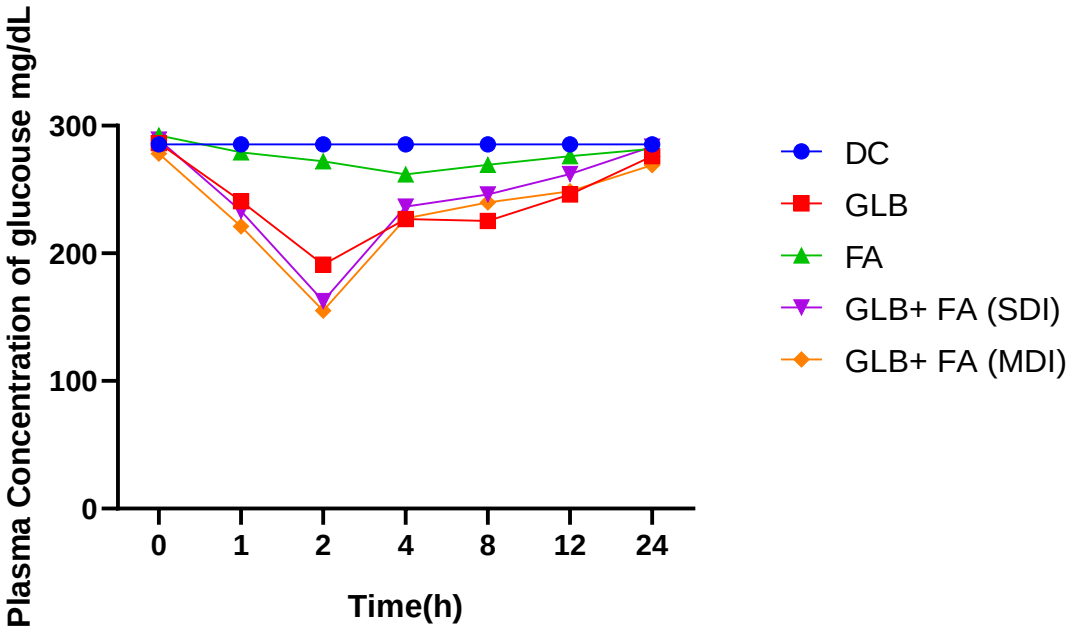


Figure 4: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Diabetic rats (mean±SD, n=6)



References

1. Goyal R, Singhal M, Jialal I. Type 2 Diabetes. [Updated 2023 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513253/
2. Padhi, S., Nayak, A. K., & Behera, A. (2020). Type II diabetes mellitus: a review on recent drug-based therapeutics. Biomedicine & Pharmacotherapy, 131, 110708.
3. Sapra A, Bhandari P. Diabetes. [Updated 2023 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551501/
4. Klein BE, Klein R, Moss SE, Cruickshanks KJ. Parental history of diabetes in a population-based study. Diabetes Care.1996;19(8):827-30.
5. Alam S, Sarker MMR, Sultana TN, Chowdhury MNR, Rashid MA, Chaity NI, Zhao C, Xiao J, Hafez EE, Khan SA, Mohamed IN. Antidiabetic Phytochemicals From Medicinal Plants: Prospective Candidates for New Drug Discovery and Development. Front Endocrinol (Lausanne). 2022 24;(13): 800714.
6. Ye, L., P. Hu, L.-P. Feng, L.-L. Huang, Y. Wang, X. Yan, J. Xiong and H.-L. Xia (2023). "Protective Effects of Ferulic Acid on Metabolic Syndrome: A Comprehensive Review." Molecules **28**(1): 281.
7. Hambrock, A., C. Löffler-Walz and U. Quast (2002). "Glibenclamide binding to sulphonylurea receptor subtypes: dependence on adenine nucleotides." Br J Pharmacol **136**(7): 995-1004.
8. Choudhari VP, Gore KP, Pawar AT. Antidiabetic, antihyperlipidemic activities and herb-drug interaction of a polyherbal formulation in streptozotocin induced diabetic rats. J Ayurveda Integr Med. 2017 ;**8**(4):218-225.

9. B, Nagaraj & Veeresham, Ciddi. (2018). Effect of ashwagandha on pharmacokinetic and pharmacodynamic parameters of glimepiride in streptozotocin-induced diabetic rats. Asian Journal of Pharmaceutical and Clinical Research. 2018 ;**11**(4): 207–210.
10. Shaker G, Swift CJ. Peroxidase-Coupled Glucose Method. [Updated 2023 Aug 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK594277/
11. Devi PR, Reddy AG, Rao GS, Kumar CS, Boobalan G. Pharmacokinetic interaction of curcumin and glibenclamide in diabetic rats. Vet World. 2015 ;**8**(4):508-11
12. Kandukoori Naga Raju, Uppu Pavani and Yellu Narsimha Reddy. Study of alterations in pharmacokinetics and pharmacodynamics of Saxagliptin in the presence of Rutin: An interaction study in rats. J App Pharm Sci 2020; **10**(11): 81-86.
13. Vora A, Varghese A, Kachwala Y, Laddha AP, Bhaskar M, Akhtar J, et al.. Pharmacokinetic and pharmacodynamic interactions of Tinospora cordifolia aqueous extract and hypoglycemic drugs in streptozotocin-induced diabetes in rats. Pharmacognosy Magazine. 2020;16(68):47-56.