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Research Article

Study on consequences for interaction of myricetin with canagliflozin: A special attention to pharmacokinetics and pharmacodynamics of drug

Naga Raju Kandukoori*, Deepika B, Kiranmai Mandava

Department of Pharmaceutics, St. Pauls College of Pharmacy, Turkayamjal, Hyderabad, Telangana, India

ABSTRACT

The metabolism of most antidiabetic drugs is initiated by Cytochrome P-450 (CYP) enzymes present in the human body. The result of this metabolism can be a formation of either active metabolites or inactive metabolites. There is possibility of alteration in the activity of CYP enzymes due to some phytoconstituents which are present in vegetables, fruits and ayurvedic products. In the present research, the effect of myricetin on pharmacokinetics and pharmacodynamics of canagliflozin was studied. Both normal and diabetic rats were used for study. Rats were categorized into different groups. One group received drug alone where as other groups administered a drug in combination with myricetin. Treatment was continued for 8 days and then blood samples were collected and analysed. The pharmacokinetic parameters like C_{max}, t_{max}, AUC, MRT, V_d and Cl_T were estimated for all groups and compared with each other. The mean blood glucose levels were noted before and after treatments and compared among diabetic groups. Results revealed a fact that the myricetin has inhibited the activity of CYP 2C8, CYP 2C9 and CYP 3A4 enzymes, thereby causing to decreased metabolism of drug which ultimately resulted in the increase of C_{max} and AUC. The Myricetin could raise the antidiabetic effect of canagliflozin.

Keywords:
Myricetin, Canagliflozin, Pharmacokinetics, Pharmacodynamics, CYP enzymes

1. INTRODUCTION

Cytochrome-P450 (CYP) enzymes present in human body are deciding factors (to some extent) for the bioavailability of administered drugs. Metabolism of a drug by CYP enzymes may lead to changes in its chemical form. The converted forms may be active or inactive. Being the substrates for CYP enzymes, most of the antidiabetic drugs are metabolized by them. Many phytoconstituents exhibit the role of either inhibiting or inducing activity of CYP enzymes there by affecting the extent of metabolism of antidiabetic drugs. As a result, there will be a remarkable change in pharmacokinetics and pharmacodynamics of antidiabetic drugs[1]. Dietary fruits, vegetables, selected medicinal plants and some antidiabetic ayurvedic products are rich sources of many phytochemicals. These phytoconstituents also show therapeutic activities. If a patient is ingested with phytoconstituents having antidiabetic activity and market available synthetic antidiabetic drug simultaneously, there will be synergistic effect leading to enhanced antidiabetic property due to of alteration of both pharmacokinetics and pharmacodynamics of administered drug. As a result, a great change in final therapeutic efficacy of antidiabetic drug can be observed[2].

Myricetin (3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-4-one) is an active phytoconstituent present in vegetables, fruits, nuts, berries, tea. It is a member of the flavonoid class polyphenolic compounds. It shows antidiabetic activity and inhibits the activity of CYP 2C8, CYP 2C9 and CYP 3A4 enzymes[3]. Till now, research has been done to study the interaction of Myricetin individually with drugs like atomoxetin, docetaxel, carvedilol, tamoxifen and losartan[3-7]. Canagliflozin [2S,3R,4R,5S,6R)-2-{3-[5-[4-fluoro-phenyl)-thiophen-2-ylmethyl]-4-methyl-phenyl}-6-hydroxymethyl-tetrahydropyran-3,4,5-triol] is an oral antihyperglycemic

***Corresponding author:**
*Naga Raju Kandukoori Email: drknr@stpaulscollege.ac.in, kandukooriku@gmail.com

agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to sodium-glucose co-transporter 2 (SGLT2) inhibitor, which act by inhibiting SGLT2 co-transporter which is found in proximal tubules of the kidney[8-9].

As myricetin is available in common food items, most of the people like diabetic patients unknowingly may consume this phytochemical. Myricetin is existing as active ingredient for many ayurvedic products used in treatment of diabetes. Many diabetic patients may consume these products along with prescribed synthetic drug like canagliflozin. When a diabetic patient is ingested with both canagliflozin and myricetin, there may be a chance of reduced metabolism of drug leading to alteration of bioavailable fraction of active form of drug and also therapeutic activity of drug is affected[5-7]. So, this fact creates a need to study the possible interaction between a phytoconstituent (which alter CYP enzymes activity) and an antidiabetic drug (which is metabolized by CYP enzymes). In this research, the interaction between myricetin and canagliflozin was studied using albino rat models and the changes in pharmacokinetics and pharmacodynamics of drug were reported.

2. MATERIALS AND METHODS

2.1. Drugs and chemicals

Canagliflozin (gifted from Dr. Reddy's Labs, Hyderabad) and metformin (gifted from Glenmark Pharmaceuticals Limited, Mumbai), myricetin and streptozotocin (purchased from Sisco Research Labs), methanol HPLC grade, citric acid, sodium bicarbonate (purchased from Merck Labs). All the used chemicals were related to AR (analytical reagents) grade.

2.2. Animals for *in-vivo* study

The rats were used as animal models in this research after obtaining an approval (IAEC/05/UCPSc/KU/2020) from IAEC (Institutional Animal Ethical committee), University College of Pharmaceutical Sciences, Kakatiya University, Warangal. Male wistar rats weighing 230-260 grams had been supplied by a registered vendor. A controlled environment (12 hrs light and 12 hrs dark) was allowed for rats which were placed in poly propylene cages as per CPCSEA guidelines and standard rat pellet diet and water *ad libitum* were used for rat's feeding. Overnight fasting was maintained for rats before starting the study[9].

2.3. Chromatographic estimation of canagliflozin

Quantification of serum concentration of canagliflozin was done by a validated ultra-fast liquid chromatography (UFLC) method coupled with photodiode array detection (Shimadzu Corporation, Japan). This was a modified reverse phase HPLC system having consisted of binary LC-20AD pumps with a micro gradient mixer. The stationary phase used in this technique was RP C18 column (250 mm × 4.6 mm, 5 µm, Phenomenex Luna). The mobile phase was a mixture of acetonitrile and distilled water (adjusted to pH 3.6) (in the ratio of 50:50 v/v). The flow rate was maintained at 1 mL/min. Degassing of mobile phase was done using ultra-sonicator and filtered through a 0.22 µm membrane filter. The eluent was scanned at a λ_{max} of 214 nm to detect the canagliflozin. Metformin was used as an internal standard. The sample run time for analysis was 10 min. The software used for carrying out of all analysis operations and for interpretation of analyzed data was Lab solutions software[10-11]. The standard graph of canagliflozin was constructed at six concentrations like 5, 10, 15, 20, 25 and 30 µg/ml.

2.3.1. Sample preparations for HPLC analysis:

A mixture of collected test serum (100 µl) and 100 µl of internal standard drug solution (metformin solution with concentration of 10 µg/ml) was prepared in centrifuge tube. After shaking the resultant for 1 min, precipitation of this mixture was enabled by adding 100 µL of acetonitrile. The resultant was vortexed for 1 min and centrifuged for 20 min at 3,000 rpm. Then the supernatant was collected and filtered. The collected filtrate (20 µL) was injected in to HPLC system for analysis[12].

The precision and accuracy of developed HPLC method was tested by analyzing quality control samples at different concentrations like 2, 10, 20, 40, 60, 80 and 100 µg/mL. Analysis was carried out in three replicates. Three sets of quality control samples were analyzed in same day to get intra-day precision data, whereas inter-day precision data was obtained when the samples were analyzed on three consecutive days[12].

2.4. Experimental design for *in-vivo* studies

2.4.1. Pharmacokinetic interaction study in normal rats

Overnight fasted rats were divided into 3 groups (each group has 6 rats; n=6). Canagliflozin was given to rats (10 mg/kg) in group-1, whereas group-2 rats received myricetin (6 mg/kg) followed by canagliflozin (single dose interaction study). Myricetin alone was given to rats in group-3 for 7 days consecutively and then same rats were administered with myricetin followed by canagliflozin on 8th day (multiple dose interaction study). The blood samples were collected from rats of every group immediately post drug administration. The blood sampling was done from retro orbital plexus using heparinized capillary tubes at particular predetermined time points like 0, 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hrs.

Double the volume of normal saline was ingested orally to each rat after collection of blood sample. The clear supernatant was obtained by subjecting collected blood samples to centrifugation (Heraeus Biofuge Fresco centrifuge, Germany). Then top clear serum samples were separated and stored at -80°C until analysis[12-16].

2.4.2. Pharmacokinetic interaction study in diabetic rats

Induction of diabetes in rats: Streptozotocin solution which was freshly prepared in pH 4.5 citrate buffer, was given to rats (after overnight fasting) through intraperitoneal (IP) route at the dose level of 55 mg/kg. Post 72 hrs of streptozotocin injection, blood samples were collected from retro orbital plexus. After separation of serum from collected samples, all serum samples were scanned using GOD-POD (glucose oxidase-peroxidase) method to estimate glucose levels. The rats were identified as diabetic animals, if their blood glucose levels are more than 250 mg/dL[12].

Diabetic rats were also grouped and treated with drug and phytochemical same as in study protocol with normal rats. Here also the blood samples were collected and separated serum samples were stored at -80°C until analysis.

The data of serum drug concentration values against time points of blood collection, was obtained and used to calculate pharmacokinetic parameters like C_{max}, T_{max}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{1/2}$, MRT, V_d and Cl_T using Kinetica software.

2.4.3. Pharmacodynamic Interaction study in Diabetic rats

Four groups (each consisting of 6 rats; n=6) were created for diabetic rats (after overnight fasting). Only canagliflozin solution was administered to rats in group-1, whereas rats present in group-2 received only myricetin. Oral administration of myricetin followed by canagliflozin was done for rats in group-3 to carry out single dose interaction (SDI) study, whereas multi dose interaction (MDI) study was conducted in group-4 whose animals were administered with myricetin for 7 days and on 8th day given with same phytochemical followed by drug. Retro orbital plexus was used as animal body site from where blood samples were collected at predetermined time points. The blood glucose levels were estimated using GOD-POD method.

The estimation of mean blood glucose levels for each group was done and compared with each other. The percentage reduction in blood glucose was calculated by using following equation[13-14]:

$$\% \text{ Glucose reduction at t hour} = [(G_0 - G_t)/G_0] \times 100$$

Where, G_t = Mean glucose level at t hour

G_0 = Mean glucose level at 0 hour

2.5. Statistical analysis

The format used to express all obtained results was 'mean±SD'. One-way ANOVA (Bonferroni post-test) was used to determine the statistical significance of obtained results using Graph Pad Prism 7.01 software. The values with $p<0.05$ were considered as statistically significant.

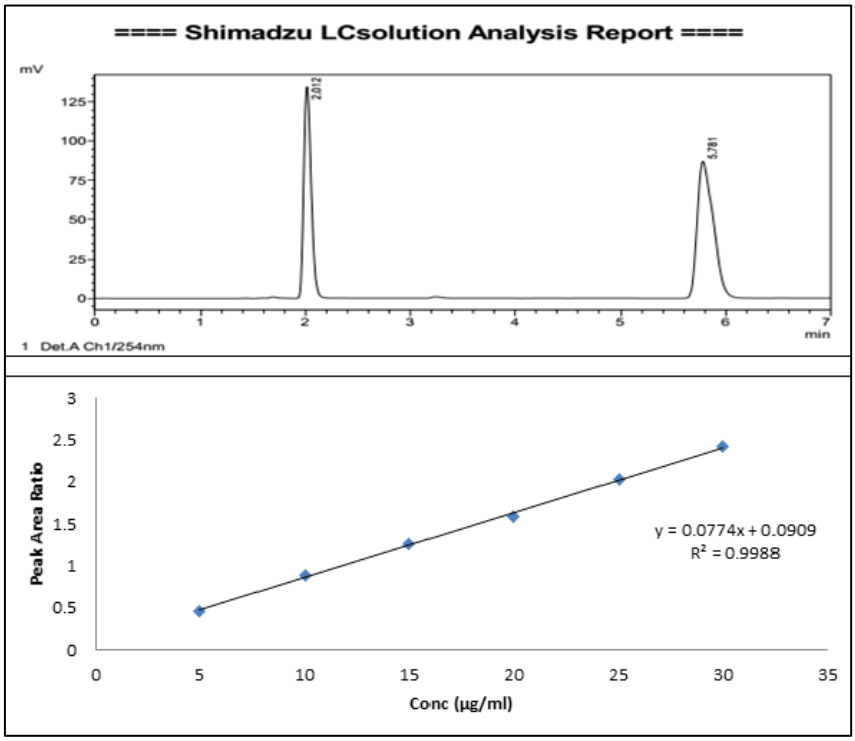

Figure 1. Chromatogram of canagliflozin and standard graph of CGF in rat serum.

3. RESULTS

3.1. HPLC chromatogram and standard curve

The developed HPLC method was found to produce sharp chromatograms for both Canagliflozin and internal standard separately at different retention time points (Figure 1). The chromatogram peak was resulted for Canagliflozin at 2.012 minutes. The internal standard has produced its peak at 5.781 minutes. The consistent accuracy and precision had been noticed with results. So, the developed chromatographic method for Canagliflozin estimation has been proved to give best results with good sensitivity. The plotted standard curve of Canagliflozin (Figure 1) was found to be obeying Beer-Lambert's law with good linearity (R^2=0.9988).

3.2. Pharmacokinetic interaction study in normal rats

Calculation of all the pharmacokinetic (PK) parameters was done using Kinetica software. Table 1 provides all the values of estimated PK parameters. There was an increase in C_{max} by 24.83% (SDI) and 40.1% (MDI) in myricetin pretreated groups compared to control (canagliflozin alone treated) group. The increase in AUC_{0-24} was observed in SDI and MDI groups by 20.5% and 39.2% respectively. $AUC_{0-\infty}$ was also increased by 13.71% (SDI) and 32.29% (MDI) in myricetin pretreated groups compared to control group. T_{max} was observed at 4.0 hr after drug administration in to body. MRT and $t_{1/2}$ were also increased significantly in Myricetin pretreated groups. The parameters like V_d and Cl_T were decreased in pretreated groups. The serum drug concentration profiles of three treated groups are represented in Figure 2.

3.3. Pharmacokinetic interaction study in diabetic rats

All the pharmacokinetic parameters were calculated using Kinetica software (Table 2). In SDI group, the C_{max} was significantly increased by 25.92%, whereas in MDI group, it was increased by 39.06%. AUC_{0-24} was increased by 19.99% (SDI) and 33.53% (MDI) & $AUC_{0-\infty}$ was also increased by 13.10% (SDI) and 29.20% (MDI) in myricetin pretreated groups. After 4.0 hours (T_{max}) of administration of drug, C_{max} was observed in blood serum. MRT and $t_{1/2}$ were also increased significantly in myricetin pretreated groups. The parameters like V_d and

Table 1. Pharmacokinetic parameters of Canagliflozin in Normal rats.

PK parameter	CGF	CGF + Myricetin (SDI)	CGF + Myricetin (MDI)
C_{max} (µg/mL)	5.76 ± 0.21	7.19 ± 0.28*	8.07 ± 0.22**
T_{max} (hr)	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
AUC_{0-n} (µg.hr/mL)	57.21 ± 2.02	68.94 ± 1.54*	79.64 ± 1.37**
AUC_{total} (µg.hr/mL)	66.36 ± 1.53	75.46 ± 1.61*	87.79 ± 1.13**
$t_{1/2}$ (hr)	8.12 ± 1.12	9.48 ± 0.46*	10.27 ± 0.49*
MRT (hr)	12.34 ± 0.81	13.69 ± 0.83*	14.97 ± 0.71*
V_d (mL)	1157.12 ± 2.14	1022.45 ± 2.96*	931.74 ± 2.19**
Cl_T (mL/min)	107.35 ± 1.58	96.54 ± 2.01	89.67 ± 1.28*

All Values expressed as Mean±SD; *Significant with p<0.05; **Significant with p<0.01; CGF: Canagliflozin; SDI: Single Dose Interaction; MDI: Multiple Dose Interaction.

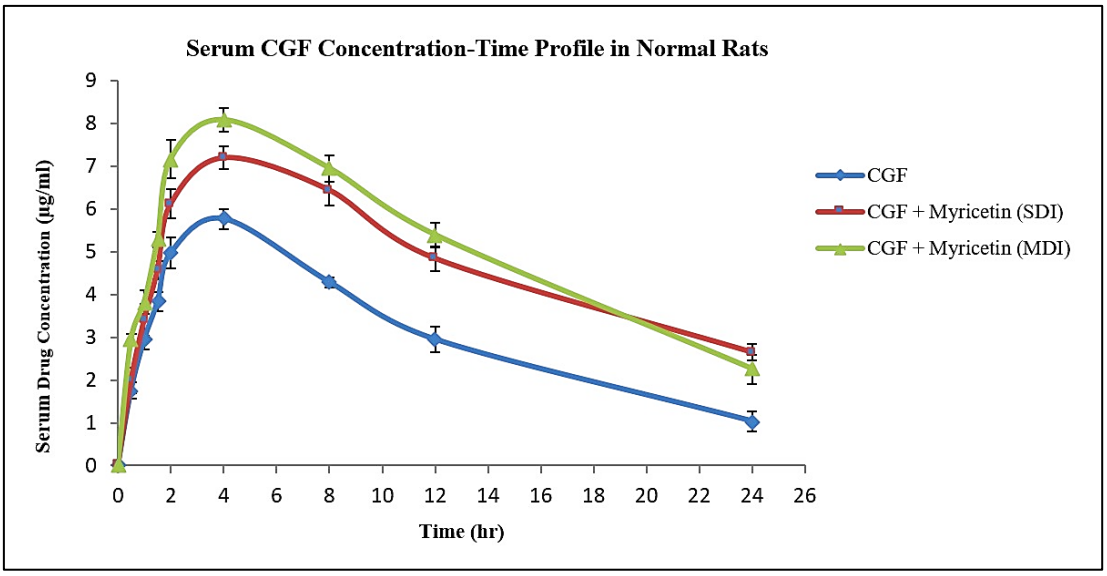

Figure 2. Serum drug concentration versus time plots in normal rats.
CGF: Canagliflozin; SDI: Single Dose Interaction; MDI: Multiple Dose Interaction

Table 2. Pharmacokinetic parameters of Canagliflozin in Diabetic rats.

PK parameter	CGF	CGF + Myricetin (SDI)	CGF + Myricetin (MDI)
C_{max} (µg/ml)	5.94 ± 0.22	7.48 ± 0.29*	8.26 ± 0.19**
T_{max} (hr)	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
AUC_{0-n} (µg.hr/ml)	58.12 ± 2.08	69.74 ± 1.07*	77.61 ± 1.09**
AUC_{total} (µg.hr/ml)	67.63 ± 1.35	76.49 ± 2.06*	87.38 ± 1.79**
$t_{1/2}$ (hr)	8.16 ± 1.23	9.83 ± 0.54*	10.49 ± 0.46*
MRT (hr)	13.19 ± 0.96	14.12 ± 0.91*	15.63 ± 0.57*
V_d (ml)	1196.12 ± 2.04	1067.80 ± 2.37*	964.34 ± 1.87*
Cl_T (ml/min)	108.53 ± 1.58	91.44 ± 1.34*	82.94 ± 1.61*

All Values expressed as Mean±SD; *Significant with $p<0.05$; **Significant with $p<0.01$; CGF: Canagliflozin; SDI: Single Dose Interaction; MDI: Multiple Dose Interaction.

Table 3. Pharmacodynamic parameters in Diabetic rats.

Time (hr)	CGF		Myricetin		CGF + Myricetin (SDI)		CGF + Myricetin (MDI)	
	Mean Glucose Level (mg/dL)	% G R	Mean Glucose Level (mg/dL)	% G R	Mean Glucose Level (mg/dL)	% G R	Mean Glucose Level (mg/dL)	% G R
0	287.32 ± 1.39	0	282.69 ± 1.21	0	301.98 ± 1.39	0	303.97 ± 1.73	0
0.5	270.34 ± 0.75	5.91	280.34 ± 0.51	0.83	272.58 ± 0.26	9.74	271.68 ± 0.18	10.62
1	250.17 ± 0.81	12.93	268.14 ± 0.29	5.15	254.81 ± 0.34	15.62	253.49 ± 0.34	16.61
1.5	235.13 ± 0.56	18.16	261.74 ± 0.36	7.41	246.31 ± 1.06	18.43	245.61 ± 0.18	19.20
2	223.17 ± 1.01	22.33	258.94 ± 0.49	8.40	234.19 ± 0.58	22.45	221.31 ± 1.04	27.19
4	195.12 ± 0.73	32.09	251.37 ± 0.64	11.08	187.64 ± 0.88	37.86	176.35 ± 0.91	41.98
8	182.34 ± 0.53	**36.54**	246.12 ± 0.59	12.94	181.56 ± 0.64	**39.88**	169.14 ± 0.83	**44.36**
12	182.31 ± 0.79	36.55	240.19 ± 0.22	15.03	182.97 ± 0.69	39.41	169.41 ± 0.76	44.27
24	182.36 ± 1.06	36.53	239.49 ± 0.49	**15.28**	182.89 ± 1.01	39.44	169.58 ± 0.49	44.21

All Values expressed as Mean±SD; *Significant with $p<0.05$; **Significant with $p<0.01$; CGF: Canagliflozin; SDI: Single Dose Interaction; MDI: Multiple Dose Interaction.

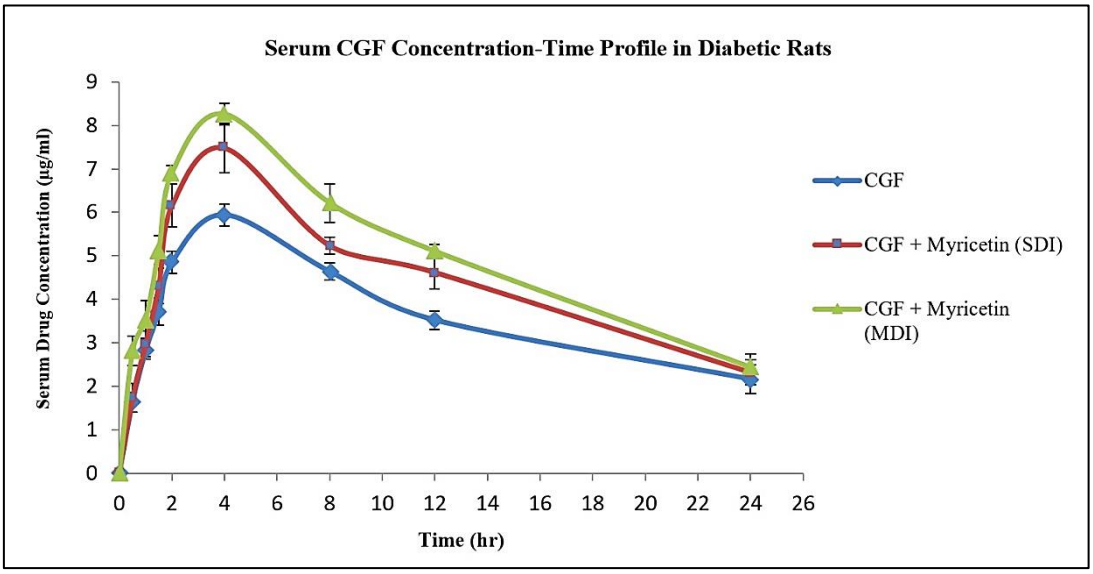

Figure 3. Serum drug concentration versus time plots in diabetic rats.
CGF: Canagliflozin; SDI: Single Dose Interaction; MDI: Multiple Dose Interaction

Cl_T were decreased in pretreated groups. The serum drug concentration profiles of three treated diabetic groups are represented in Figure 3.

3.4. Pharmacodynamic interaction study in diabetic rats

The more glucose reduction (44.36% after 8 hours) was observed in group-4 compared to other groups. The % glucose reductions (after 8 hours of drug administration) were 36.54% and 39.88% in control and SDI groups, respectively. In group-2, myricetin alone also decreased the glucose levels at minimal level (15.28% after 24 hours of CGF administration) in diabetic rats.

4. DISCUSSION

The developed HPLC method was found to have accuracy and precision. The limit of detection (LOD)

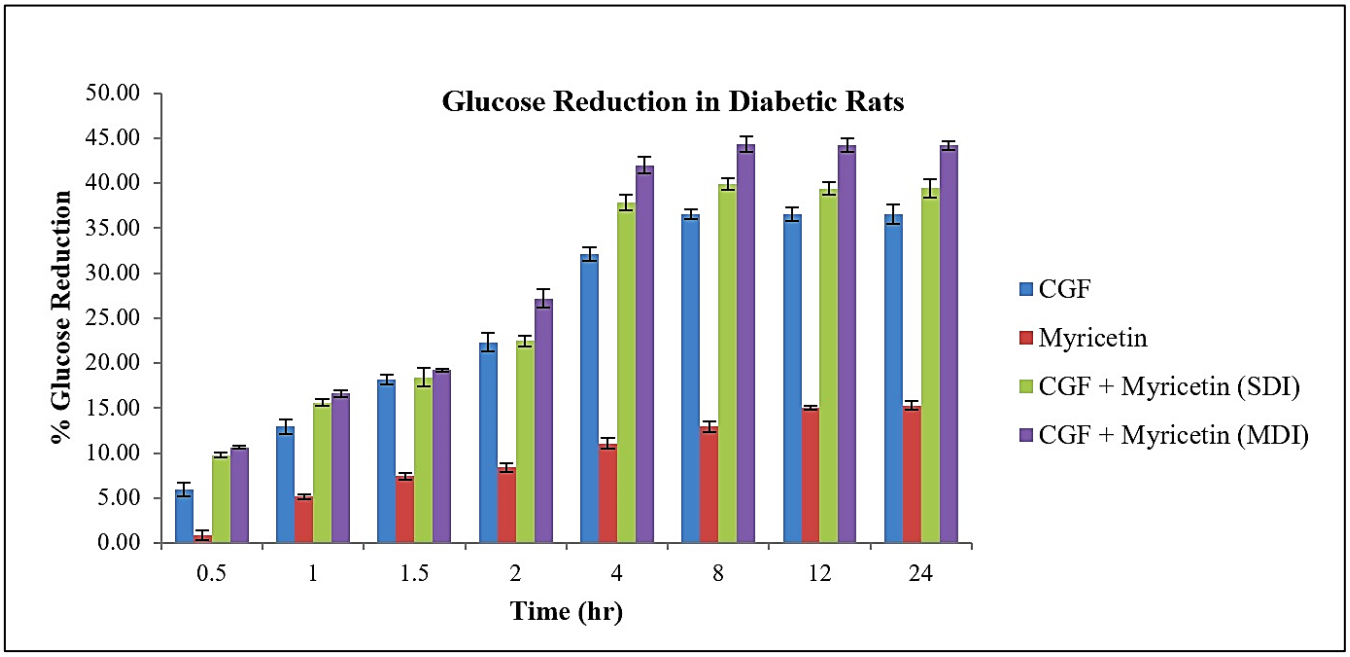

Figure 4. Glucose reduction profile in diabetic rats.
CGF: Canagliflozin; SDI: Single Dose Interaction; MDI: Multiple Dose Interaction

and limit of quantification (LOQ) of the analysis were found to be 0.28425 µg and 0.87455 µg, respectively. These LOD and LOQ were found to be within the range of the analyzed levels in serum samples[12].

In both normal and diabetic groups (group-2 and group-3), there was an increase in C_{max} and AUC values. It has clearly indicated that the bioavailability of canagliflozin was increased in myricetin pretreated rats. It may be because of inhibition of CYP 2C8, CYP 2C9 and CYP 3A4 activity by myricetin, which resulted in decreased metabolism of canagliflozin[17]. There was no alteration in T_{max} value in all 3 groups, which indicated that the rate of drug absorption was not affected in the presence of myricetin. The $t_{1/2}$ and MRT were slightly increased in myricetin pretreated rats compared to control group. It may be due to hiked drug amount in body fluids[17-19]. There was a decrease in volume of distribution and total body clearance in myricetin pretreated groups which indicated that myricetin could affect the protein binding of drug with body fluid proteins. Canagliflozin has more protein binding capacity. When there was an increase in available drug fraction in body fluids (due to myricetin effect), the bound fraction of drug has also increased. This reduced the free drug fraction which affected drug distribution and drug clearance[20-21]. Thus altered PK parameters of drug in presence of myricetin lead to a great change in therapeutic activity of canagliflozin.

The hikes in glucose reductions were observed in myricetin pretreated rats. This may be because of increased pharmacokinetic parameters (C_{max} and AUC) of canagliflozin due to its reduced metabolism[12-14]. It clearly understood that there was more availability of drug at tissue receptors to elicit the therapeutic activity. This caused to the enhancement of antihyperglycemic activity of canagliflozin[19-21]. Myricetin (as an antidiabetic agent) was responsible for synergistic antidiabetic activity in SDI and MDI groups[2,7]. The effect of myricetin on antidiabetic property of canagliflozin was more significant in multiple dose interaction (MDI) groups of both normal and diabetic rats.

5. CONCLUSION

A phytochemical like myricetin could greatly affected the pharmacokinetic and pharmacodynamic parameters of canagliflozin. Decreased metabolism of canagliflozin thereby enhancing drug's bioavailable fraction was brought about by myricetin which was proved to be an inhibitor of CYP 2C8, CYP 2C9 and CYP 3A4 in previous literature. Increase of C_{max} and AUC of drug in the presence of myricetin was responsible for the hiked antidiabetic activity of canagliflozin. From the results of this research it could be concluded that the myricetin has shown significant interaction with canagliflozin and altered its therapeutic activity. So it is suggestable to stay away from taking vegetables, fruits and ayurvedic products containing myricetin while patient is on antidiabetic therapy with canagliflozin. This research reveals the importance of dose adjustment of any antidiabetic drug, if it is to be administered along with a phytochemical that can modify its metabolism.

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Conflict of Interest

All the authors involved in this research work declare no conflict of interest for the results of study and publication of the manuscript.

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