CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4303601

Avalable online at: http://www.iajps.com *Research Article*

STUDY OF PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS OF SITAGLIPTIN WITH KAEMPFEROL IN RATS

Pavani Uppu and Narsimha Reddy Yellu*
University College of Pharmaceutical Sciences, Kakatiya University,
Warangal, Telangana-506009, India.

Abstract:
Kaempferol is a natural flavonoid found in many green leafy vegetable plants and it shoes inhibitory action on P-450 (CYP) enzymes. Most of the antidiabetic drugs were metabolized by different CYP enzymes. The present study was conducted in normal and diabetic rats to know the effect of kaempferol on pharmacokinetics and pharmacodynamics of sitagliptin. The rats were administered with different doses of sitagliptin (25mg/kg), kaempferol (30mg/kg) and combination of both. The peak plasma concentration, AUC was increases whereas volume of distribution, clearance was decreases in both normal and diabetic rats. Pharmacodynamics like blood glucose level was decreased during the study period. This is mainly due to inhibition of CYP3A4 enzyme activity by kaempferol and thereby bioavailability of drug in rat serum was increases. Kaempferol significantly decreases the metabolism of sitagliptin and combination of herb-drug has more beneficial effect in diabetic rats.

Key words: *Kaempferol, CYP enzymes, Sitagliptn, Streptozocin, Pharmacokinetics (pk) and pharmacodynamics (pd).*

Corresponding author:
Narsimha Reddy Yellu*
University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana-506009, India.
E-Mail id: *ynrku@kakatiya.ac.in*

QR code

Please cite this article in press Pavani Uppu and Narsimha Reddy Yellu, ***Study Of Pharmacokinetic And Pharmacodynamic Interactions Of Sitagliptin With Kaempferol In Rats.,*** *Indo Am. J. P. Sci, 2020; 07(11).*

INTRODUCTION:

There are many oral antidiabetic drugs which are used by diabetic patients; along with these some herbal drugs/phytochemicals were also used. Combination of drugs and herbs may cause interactions and those are showing neither beneficiary effect nor adverse effect on the patient[1]. It is important to study the effect of herb-drug interactions and knowing the information of how they alter the pharmacokinetics and pharmacodynamics parameters of drug[2].

Sitagliptin is an oral antidiabetic drug belongs to class of dipeptidyl peptidase-4 (DPP-4) inhibitor which improves glycemic control in patients with type 2 diabetes mellitus. Sitagliptin was mainly metabolized by CYP3A4 and CYP2C8 enzymes[3]. Kaempferol is a natural falvonol, present in variety of plant derived foods like tea, spinach, beans, broccoli, cabbage, capers, cauliflower, chia seeds, chives, cumin, moringa leaves, gooseberries, grapes, kale, strawberries, tomatoes, citrus fruits, apples and grapefruit, endive, fennel, and garlic[4]. Kaempferol proved in having CYP3A4 and CYP2C8 inhibitory action. So it is necessary to study the effect of kaempferol on pk and pd of sitagliptin.

MATERIALS AND METHODS:

Sitagliptin (SG) was obtained as gift sample from Novartis, Hyderabad and Kaempferol (KR) was purchased from yucca enterprises, Mumbai. Streptozocin was supplied from sisco laboratories, Methanol HPLC grade supplied from Merck chemicals, Mumbai. All the chemicals used for the study are of analytical grade.

HPLC analysis of Sitagliptin:

The mobile phase was 20:80 (v/v) mixture of methanol and distilled water (pH adjusted to 3.0 with orthophosphoric acid) delivered at a flow rate of 1 ml/min. The mobile phase was degassed by sonicator and filtered through 0.22 µm membrane filter. The detection was carried out at a wavelength of 266 nm. The injection volume was 20 µl and total run time of the method was set as 10 minutes.[6]

Experimental design

Induction of diabetes in rats

Streptozocin (STZ) at a dose of 55mg/kg was used for induction of diabetes in rats. The required quantity of STZ was dissolved in citrate buffer (pH 4.5) and given through i.p route of administration. After 72 h, blood samples were collected from rats by retro-orbital puncture and the serum was analyzed for glucose levels. Rats with blood glucose level >250 mg/dL were considered as diabetic and were used for the study.[6]

Pharmacokinetic study in normal and diabetic rats

Overnight fasting, rats were divided into normal and diabetic groups (n = 6). Normal rats (Group-I) was administered with sitagliptin (25mg/kg) and Group II was pretreated with kaempferol (30 mg/kg) for 7 days and on the 8th day with sitagliptin (25 mg/kg) followed by kaempferol. Through retro orbital plexus blood samples were collected by using heparinised capillary tubes, and immediately same volume of normal saline was replaced intra peritoneally[7]. The blood was collected at time intervals of 0.5, 1, 2, 4, 8, and 24 hrs in every group. Serum was separated after centrifugation at 3000 rpm for 20 min and the samples were stored at – 20°C until analysis[8].The pharmacokinetic parameters like C_{max}, T_{max}, AUC_{total}, $t_{1/2}$, MRT, Cl and V_d were calculated. Same procedure was repeated for diabetic rats.

Pharmacodynamic study in diabetic rats

The STZ induced diabetic rats were fasted overnight and divided into 4 groups (n = 6). The rats of group I (diabetic control, normal saline), group II (Sitagliptin, 25mg/kg), group III (Kaempferol, 30mg/kg) and group IV (Sitagliptin, 25mg/kg+ Kaempferol, 30mg/kg) were treated orally. Blood samples were drawn from the retro-orbital plexus of the rats at 0 (Initial fasting blood sample), 0.5, 2, 4, 6, 12 and 24h. The samples were analyzed for blood glucose using glucose oxidase-peroxidase method and percentage reduction in blood glucose concentrations was determined.[9,10]

% glucose reduction at t hour = [(A-B) / A] × 100

A = mean glucose levels at t hour

B = mean glucose levels at 0 hour.

Statistical analysis: The Pharmacokinetic parameters were calculated by using Kinetica TM software (version 4.4.1). All values of pharmacokinetic and pharmacodynamic studies were expressed as Mean±SD. The data were statistically evaluated using one-way analysis of variance (ANOVA). Results were considered to be statistically significant when $p \leq 0.05$.

RESULTS & DISCUSSION:

Pharmacokinetics of sitagliptin in normal and diabetic rats:

In diabetic pretreated rats, compared with the group II (given sitagliptin alone), the co-administration of kaempferol significantly ($p<0.01$) increases C_{max} (1.08 and 1.52 times), AUC_{total} (1.13 and 1.34 times), $t_{1/2}$ (1.06 and 1.22 times), MRT (1.04 and 1.13 times),

whereas, the clearance (1.12and 1.37 times) and volume of distribution (1.14and 1.64 times) of sitagliptin was decreased. The T_{max} was not altered significantly in both normal and diabetic rats. Kaempferol inhibits the CYP3A4, CYP2C8 enzymes involved in the metabolism of the drug and thereby availability of drug was increases.[3] Combination of herb-drug, leads to increase in pharmacokinetic parameters like C_{max}, AUC_{total}, decrease in volume of distribution and clearance due to the changes in metabolism of sitagliptin by inhibitory action of Kaempferol on CYP enzymes.

Table 1: Mean pharmacokinetic parameters of sitagliptin in different groups of normal and STZ-induced diabetic rats.

PK parameter	Sitagliptin		Sitagliptin+Kaempferol	
	Normal	Diabetic	Normal	Diabetic
C_{max}(µg/ml)	4.172±0.51	5.21±0.48	5.74±0.53	7.92±1.68*
T_{max} (h)	2	2	2	2
AUC_{total} (h.µg/ml)	134.59±6.07	153.01±10.44	146.17±5.7	205.6±12.35 **
$t_{½}$ (h)	8.47±3.5	9.03±1.27	9.25±2.40	11.08±4.13 *
MRT (h)	11.55±3.19	13.47±1.95	12.08±2.7	15.3±3.4 *
CL (ml/h/kg)	72.26±74.4	54.81±8.29	64.37±32.5	39.83±7.51*
V_d(ml/kg)	566.06±25.36	439.24±18.7	495.44±10.6	267.70±12.45

All values are expressed as mean ± SD (n=6)
Significant at *p<0.05, **p<0.01 considered as when compared tocontrol groups.

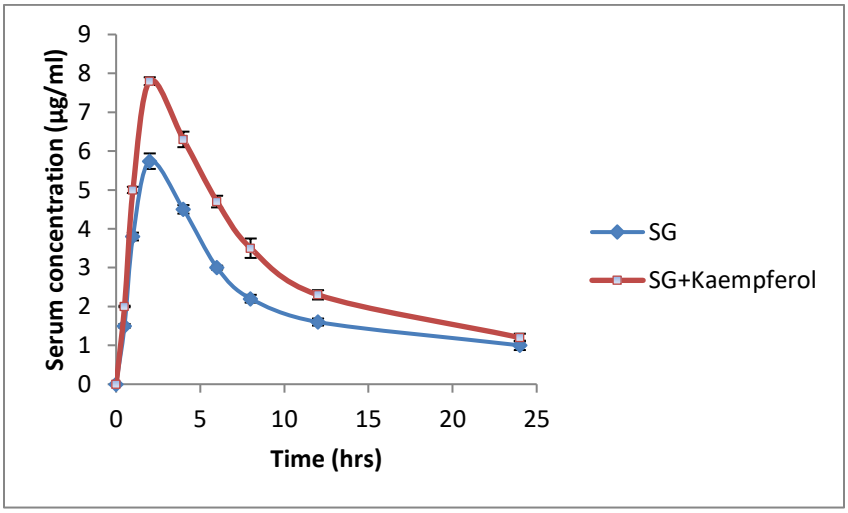

Figure.1: Mean serum concentration of sitagliptin in different groups of diabetic rats.

Pharmacodynamics (Blood glucose reduction) in different groups of diabetic rats

In diabetic rats mean serum glucose level and percentage glucose reduction were calculated. The data indicates that there is a maximum reduction of serum glucose level observed in groups treated with combination of sitagliptin and kaempferol (41.81%), when compared with sitagliptin (38.12%), Kaempferol (28.8%) groups. However, combination of kaempferol with sitagliptin showed significant decrease ($p \leq 0.001$) in serum glucose level at different time intervals. Sitagliptin blocks the dipeptidyl peptidase enzyme which destroys incretin hormone and there by blood glucose levels were decreased.[11]The result suggests that glucose reduction ability of sitagliptin increases upon co-administration with kaempferol in diabetic rats.

Table.2: Comparison of mean serum glucose level and percentage glucose reduction indifferent groups of diabetic rats.

Group	Treatment	Blood glucose level (mg/dl) at different time intervals							
		0 h	0.5 h	1 h	2 h	4 h	6 h	12 h	24 h
I	Control	301±2.38	298±2.17 (0.99%)	299±1.82 (0.66%)	298±2.84 (0.99%)	297±2.83 (1.32%)	298±3.6 (0.99%)	297±2.8 (1.32%)	299±3.3 (0.66%)
II	SG	312.67±4.6	273.32±7.4 (12.5%)	235.73±13.4 (24.6%)	193.46±8.3 (38.12%)**	222.4±4.7 (26.34%)	253.93±10.9 (18.36%)	292.99±7.4 (6.4%)	305.67±9.6 (2.24%)
III	KR	298.53±5.8	280.69±4.71 (6.06%)	264.3±5.73 (11.4%)	212.5±4.6 (28.8%)**	243.36±5.82 (18.4%)	251.25±6.94 (15.7%)	262.06±3.76 (12%)	270.5±4.51 (9.3%)
IV	SG + KR	311.35±5.8	280.65±7.26 (12.83%)*	248.07±5.2 (20.31%)**	181.05±6.77 (41.81%)**	214.80±8.50 (31.04%)	236.65±8.04 (19.54%)*	283.14±5.6 (9.03%)*	299.35±5.8 (3.85%)*

SG: Sitagliptin, KR: Kaempferol. All values are expressed as mean ± SD (n=6)
*p<0.05, **p<0.01 considered as significant when compared with control groups.

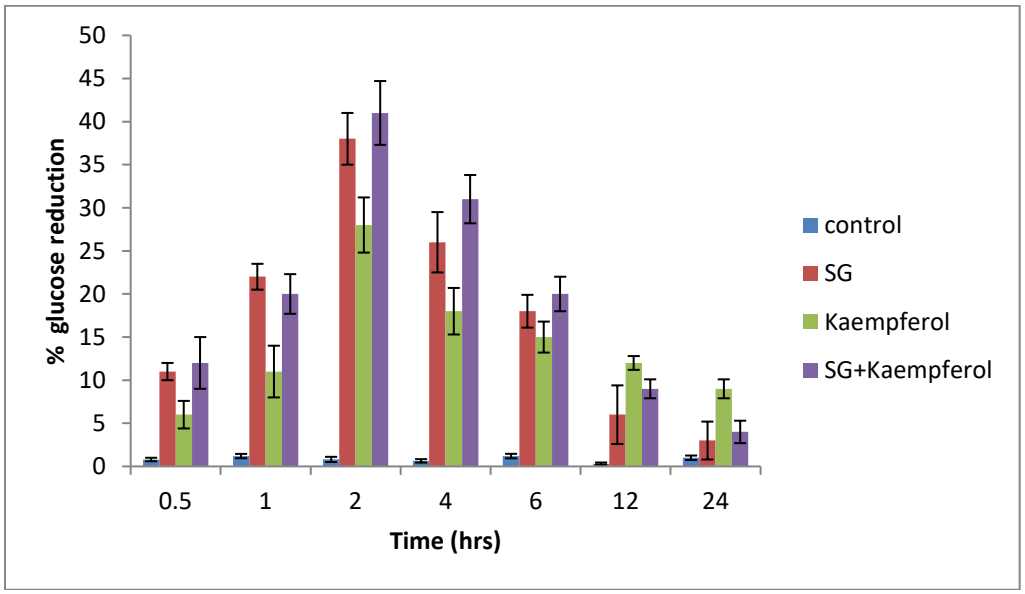

Figure.2: Comparison of percentage glucose reduction in different groups of diabetic rats.

CONCLUSION:

Kaempferol alters the metabolism of sitagliptin by showing inhibitory action on CYP3A4 and CY2C8 enzymes. As a result drug metabolism was decreases and availability of sitagliptin was improved. The interaction was beneficial in terms of reduction in blood glucose level in diabetic rats. Diabetic patients may require special attention in dose adjustment while administering sitagliptin along with kaempferol.

REFERENCES:

1. Tripathi P, Gupta PP and Lal VK. Interaction of Momordica charantia with metformin in diabetic rats. American Journal of Pharmacology Toxicology; 2013, 8: 102- 106.
2. Saurabh Nimesh, Ravi Tomar and Shubham Dhiman. Medicinal Herbal Plants and Allopathic Drugs to Treat Diabetes Mellitus: A glance; Advances in Pharmacology and Clinical Trials; 2019, 4(1).
3. Vincent SH, Reed JR, Bergman AJ, et al. Metabolism and excretion of the dipeptidyl peptidase 4 inhibitor. Sitagliptin in humans. Drug Metabolism and Disposition; 2007, 35(4):533-538.
4. Zang, Y.; Sato, H.; Igarashi, K. Anti-diabetic effects of a kaempferol glycoside-rich fraction from unripe soybean (Edamame, Glycine max L. Merrill. 'Jindai') leaves on KK-A(y) mice. Bioscience, Biotechnology, and Biochemistry; 2011, 75(9),1677-1684.
5. Sujani PV, Phanindra SS, Reddy PY, Deevena N. Vlidated RP-HPLC method for the estimation of simvastatin and sitagliptin. Scholars Academic Journal of Pharmacy; 2014, 3, 265-270.
6. Kuhad A, Chopra K. The mechanism of alloxan and streptozocin action in B cells of the rat pancreas. Physiological research; 2007, 50: 537-546.
7. Trinder P. Determination of blood glucose using 4- amino phenazone as oxygen acceptor. Journal of Clinical Pathology 1969; 22: 246.
8. Jyothi P, Thirupathi G and Narsimhareddy Y. Pharmacokinetic and pharmacodynamic interaction study of curcumin with repaglinide in normal and diabetic rats. Journal of global trends in pharmaceutical sciences; 2017, 8(3): 4130 – 4137.
9. Prasad N, ravikiran M and jagat R. Influence of curcumin on pioglitazone metabolism and Pk/Pd: Diabetes mellitus. Journal of diabetes and metabolism, 2012;https://doi.org/10.4172/2155-6156.S6-003.
10. Cheguri S, Ajmera RR and CiddiV.Pharmacokinetic and Pharmacodynamic Interaction of Quercetin with Saxagliptin in Normal and Diabetic Rats. Pharmacologia; 2017,8 (3): 90-94.
11. Joseph A. Davis, Shuchita Singh, SachinSethi, Subhasis Roy, Shivani Mittra, GeetavaniRayasam, Vinay Bansal, Jitendra Sattigeri, and Abhijit Ray. Nature of action of Sitagliptin, the dipeptidyl peptidase-IV inhibitor in diabetic animals. Indian Journal of Pharmacology; 2010, 42(4): 229–233.