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ORIGINAL ARTICLE

Effect of Capsaicin on Pharmacodynamic and pharmacokinetics of Gliclazide in Animal models with Diabetes

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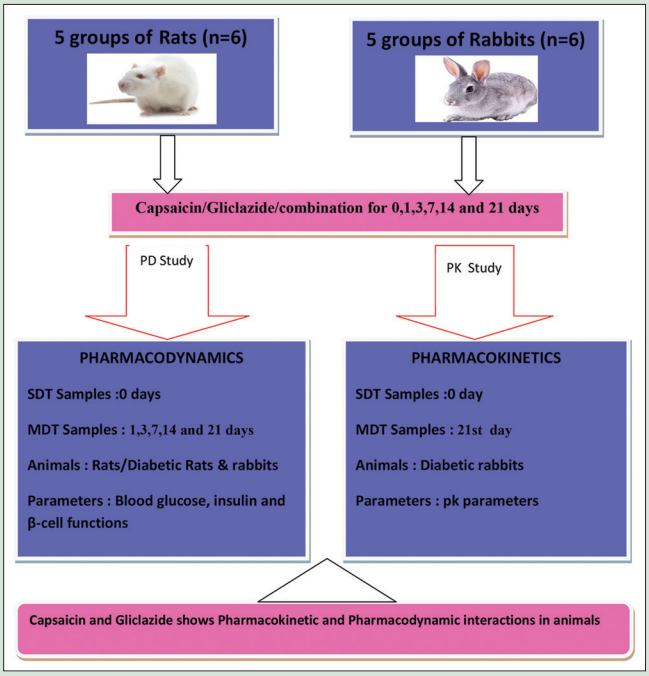
ABSTRACT

Background: Food–drug interactions can have great effect on the adverse effects of many drugs and also on the success of drug treatment. Gliclazide is one of the drugs of choice to treat type 2 diabetes. Capsaicin is present in *Capsicum annuum*, a spice found in regular food. **Objective:** The objective of the present study was to find out the pharmacodynamic (PD) and pharmacokinetic (PK) interactions of capsaicin on gliclazide in animal models using rats and rabbits. **Materials and Methods:** Single- and multiple-dose interaction studies were conducted in rats (normal and diabetic) and rabbits (diabetic) to evaluate the effect of capsaicin on the activity of gliclazide. Blood samples collected at predetermined time intervals from the experimental animals were used for the estimation of glucose and insulin levels using an automated clinical chemistry analyzer and radioimmunoassay method, respectively. β-cell function was determined by homeostasis model assessment. In addition, high-performance liquid chromatography technique was used to analyze the serum gliclazide levels in rabbits. **Results:** Capsaicin did not exhibit any hypoglycemic activity in normal rats, but exhibited significant antihyperglycemic activity in both diabetic rats and rabbits with improvement in insulin levels and β-cell function. Gliclazide showed significant reduction in blood glucose levels in normal and diabetic rats and diabetic rabbits. In addition, it significantly increased insulin levels and β-cell function in diabetic animals. The samples analyzed from all time points in combination with capsaicin showed significantly greater reduction in blood glucose levels and a significant increase in insulin levels and β-cell function in diabetic rats and rabbits. The PK parameters of gliclazide were also altered by capsaicin treatment in rabbits. **Conclusion:** The present study concluded that the interaction of capsaicin with gliclazide on single- and multiple-dose treatment was both PD and PK in nature.

Key words: Capsaicin, diabetes mellitus, drug interactions, gliclazide, pharmacodynamic–pharmacokinetic interactions

SUMMARY

- Human consumption of nutritional richest diets such as fruits and vegetables, and a meteoric rise in the consumption of dietary supplements and herbal products have substantially increased human exposure to phytochemicals. Phytochemicals have a capacity to produce biological activities and have the potential to both elevate and suppress cytochrome P450 activity. Capsaicin shows anti diabetic activity by enhancing insulin and β-cell function in diabetic rats & rabbits. The hypoglycemic effect was enhanced with the presence of gliclazide by elevation of insulin and β-cell functions more prominently also by inhibiting the gliclazide metabolism in animal models.



Abbreviations Used: CYP: Cytochrome P450, g: Gram, kg: Kilogram, C: Degree Celsius, %: Percentage, h: Hours, p.o.: Per oral, dL: Deciliter, µ: Micro, IU: International units, mL: milliliter, Cmax: Maximum concentration, Tmax: time to maximum, AUC: Area under the curve, AUMC: Area under the first moment curve, t1/2: Elimination half-life, kel: Elimination rate constant, MRT: Mean residence time, Cl: Clearance, ng: Nanogram, mg: Microgram

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INTRODUCTION

The chances of foods to interact with medications are more, which can lead to serious adverse reactions. When a medication or food is taken orally, both of them travel through the same digestive system simultaneously. Hence, when a drug is mixed with food, it can alter the way the body metabolizes the food or vice versa. Some drugs interfere with the absorption of nutrients. Similarly, some foods can alter the therapeutic efficacy, bioavailability of a drug, and clearance (CL) and increase the risk of side effects. For example, theophylline is a medication used to treat asthma, which is found in tea, coffee, and chocolate. When theophylline is taken along with these

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substances, the risk of drug toxicity increases.[1] Similarly, capsaicin is the active ingredient present in the fruits of *Capsicum annuum,* Solanaceae, which is responsible for the hot pungent taste of chilies. It represents an important ingredient in spicy foods consumed throughout the world. Previous literature reveals that capsaicin decreased the bioavailability of drugs such as galantamine[2] and simvastatin.[3] It also possesses antidiabetic activity[4] and is an inhibitor of CYP2C9 and CYP3A4 enzymes.[5]

Gliclazide, a derivative of sulfonylurea, is an oral hypoglycemic agent and the preferred drug for the treatment of type 2 diabetes. It acts by selectively inhibiting pancreatic K+-ATPase channels.[6] Further, gliclazide was reported to exhibit antioxidant properties, low incidence of severe hypoglycemia, and other hemobiological effects.[7] Gliclazide is primarily metabolized by hepatic microsomal enzymes CYP2C9 and partly by CYP3A4.[6] Hence, the present study was designed to evaluate the pharmacodynamic (PD) and pharmacokinetic (PK) interactions of capsaicin with gliclazide in animal models.

MATERIALS AND METHODS

Drugs and chemicals

Gliclazide was obtained as a gift sample from Dr. Reddy's Laboratories (Bachupally, Hyderabad, Telangana, India). Capsaicin was purchased from Sigma-Aldrich company. Alloxan monohydrate was purchased from LobaChemie (Mumbai, Maharashtra, India). All reagents and chemicals used in the study were of analytical grade.

Preparation of capsaicin solution

Capsaicin solution was prepared in 2% gum acacia solution.

Preparation of gliclazide solution

Gliclazide solution was prepared by dissolving in few drops of 0.1 N sodium hydroxide and the final volume was made with water.[8]

Preparation of alloxan solution

Alloxan monohydrate 110 mg/kg was prepared in sterile saline and given subcutaneously immediately within 5 min to avoid degradation.[9]

Animals

Albino rats of 8–9 weeks old weighing between 170 and 250 g and 3-month-old male albino rabbits weighing between 1 and 1.5 kg were procured from M/s Mahavir Enterprises, Hyderabad. They were maintained under controlled room temperature (24° ± 2°C; relative humidity 60%–70%) in a 12 h light–dark cycle. The animals were given a standard laboratory diet and water *ad libitum*. The animals were acclimatized before the study. The animal experiments were performed after prior approval of the study protocol by the Institutional Animal Ethics Committee (Reg No IAEC/01/GBN/GQ/2014).

Experimental study design

Male albino rats/rabbits were divided into five groups of each consisting of six animals. The doses of 2 and 4 mg/kg body weight were selected for administration in rats and rabbits, respectively, based on the results of gliclazide dose–effect relationship study conducted in normal rats and rabbits. The design of the study is as follows:

- Group I: Normal control
- Group II: Diabetic control
- Group III: Gliclazide (2 mg/kg for rats/4 mg/kg for rabbits) body weight, p.o.
- Group IV: Capsaicin (6 mg/kg) body weight, p.o.
- Group V: Capsaicin (6 mg/kg) + Gliclazide (2 mg/kg for rats/4 mg/kg for rabbits) body weight, p.o.

- Stage 1: PD interaction in normal rats
- Stage 2: PD interaction in diabetic rats
- Stage 3: PD and PK interaction in diabetic rabbits.

Pharmacodynamic interaction in normal rats

Male albino rats were divided into four groups of each six animals. Group I received vehicle, Group III rats were given gliclazide via the oral route at 2 mg/kg body weight, Group IV were administered capsaicin 6 mg/kg, p.o., and Group V received combination treatment with both capsaicin and gliclazide at the previously mentioned doses. After 30 min of capsaicin treatment, the animals were given gliclazide at 2 mg/kg body weight. Blood samples were drawn from the retro-orbital plexus of the rats (fasted for 14 h) under light ether anesthesia. After these single-dose interaction studies, the same groups of animals were given daily treatments with respective drugs for the next 20 days with regular feeding. Blood samples were collected at the predetermined time intervals after treatment with gliclazide alone, capsaicin alone, or combination treatments (single-dose treatment [SDT] and multiple-dose treatment [MDT]). Blood glucose levels were estimated on initial and days 1, 3, 7, 14, and 21 of the treatment.[4,6]

Pharmacodynamic interaction in diabetic rats

Male albino rats weighing 170–250 g were divided into five groups of six animals each. Group I acted as normal control and received vehicle only. Groups II to V were fasted for overnight before challenging with single subcutaneous route of alloxan monohydrate, freshly prepared, and injected within 5 min of preparation to prevent degradation at a dose of 110 mg/kg. To prevent hypoglycemic shock, 5% glucose solution was given for 72 h after administration of alloxan monohydrate. Animals had access to feed and water. Hyperglycemia in animals was confirmed by determining fasting serum glucose (FSG) at 72 h postalloxan monohydrate injection, and the animals were fasted again for 14 h before blood collection from retro-orbital plexus. The rats chosen for the study should have FSG level of above 200 mg/dl at 72 h, which were considered as diabetic. Group II acted as diabetic control. Group III received gliclazide (2 mg/kg, p.o.). Group IV was administered capsaicin 6 mg/kg, p.o., and Group V was administered gliclazide (2 mg/kg, p.o.) after 30 min of capsaicin administration (6 mg/kg, p.o.). Blood samples were drawn from the retro-orbital plexus of the rats under light ether anesthesia. After these single-dose interaction studies, the same groups of animals were given daily treatments with respective drugs for the next 20 days with regular feeding. Blood glucose and insulin levels were estimated using automated clinical chemistry analyzer and radioimmunoassay method, respectively, on initial and days 1, 3, 7, 14, and 21 of the treatment and β-cell function by homeostasis model assessment.[10,11]

Pharmacodynamic and pharmacokinetic interaction in diabetic rabbits

Six rabbits per group were selected. Diabetes was induced similarly as in case of PD interaction in diabetic rats. Group I acted as normal control and Group II acted as diabetic control. Group III rabbits were given gliclazide via the oral route at 4 mg/kg body weight, and their blood was collected at the predetermined time points. Similar procedure was performed with either orally administered capsaicin (6 mg/kg, p.o.) only (Group IV) or combination treatment with both capsaicin and gliclazide (Group V) at the previously mentioned doses. Blood samples were withdrawn from the marginal ear vein of each rabbit. After these single-dose interaction studies, the same groups of animals were given daily treatments with respective drugs for the next 20 days with regular feeding. Blood glucose and insulin

levels were estimated using an automated clinical chemistry analyzer and radioimmunoassay method, respectively, on initial and days 1, 3, 7, 14, and 21 of the treatment and β-cell function by homeostasis model assessment. In addition, serum gliclazide levels were analyzed by high-performance liquid chromatography (HPLC) method. For this, blood samples were withdrawn from the marginal ear vein of each rabbit on day 0 (SDT) and day 21 (MDT) at different time points, i.e., 1, 2, 4, 8, 10, and 12 h.[12]

Determination of β-cell function

β-cell function was assessed by the homeostasis model assessment protocol and was calculated as follows:[8,13,14]

β-cell function = (20 × FSI)/(FSG − 3.5) ×100

where fasting serum insulin (FSI) is expressed in μIU/ml and FSG in mg/dl.

Pharmacokinetic analysis

Various PK parameters of gliclazide such as peak serum concentration (C_{max}), area under the concentration time curve, area under first moment curve, peak time, terminal half-life, elimination rate constant (K_{el}), mean resident time, and CL in rabbit serum were estimated using Kinetica 5.0 software.

Chromatography

The instrument used for HPLC analysis was YOUNG LIN ACME 9000 (Korea) with Autochrome 3000 integrator and ultraviolet-visible detector.

Chromatographic parameters

- Column: Xbridge-Extend C18 (250 mm × 4.6 mm, packed with 5 μm)
- Wavelength: 210 nm
- Injection volume: 20 μl
- Elution: Isocratic
- Flow rate: 1.2 ml/min
- Run time: 8 min.

Preparation of mobile phase

Dissolved 2.7218 g of potassium dihydrogen orthophosphate in 1000 ml of water and mixed, pH adjusted to 3.5 with orthophosphoric acid, and filtered through 0.4 μm membrane filter. Mixed methanol and buffer (0.02 M) in the ratio of 50:50 V/V and sonicated up to 15 min to degas the mobile phase.[15]

Extraction procedure

To 0.3 ml of serum in 1.5 ml Eppendorf tube, 0.3 ml of methanol was added to precipitate proteins and for extraction of gliclazide. The tubes were vortexed for 3 min and centrifuged at 3000 rpm for 5 min. The supernatant was separated and filtered through 0.45 μm nylon membrane filter.

Data and statistical analysis

The data were analyzed using one-way analysis of variance, followed by Dunnett's test and $P < 0.05$ was considered statistically significant. The data were expressed as mean ± standard deviation.

RESULTS

Pharmacodynamic interaction in normal rats

Gliclazide produced significant hypoglycemic activity in normal rats with maximum percentage blood glucose reduction of 45.0% [Table 1], whereas in combination with capsaicin, the maximum percentage blood glucose reduction was 45.8%. Capsaicin does not have any effect on blood glucose levels in normal rats. That is why the mean percentage blood glucose reduction in combination treatment and gliclazide alone was almost same.

Pharmacodynamic interaction in diabetic rats

Capsaicin produced significant antihyperglycemic activity in diabetic rats on the 21st day with peak percentage blood glucose reduction of 61.9% whereas gliclazide produced 57.4% and combination showed 72.0% [Table 2]. Capsaicin showed maximum insulin levels of 22.24 on the 21st day [Table 3]. Gliclazide also showed maximum insulin levels of 20.87 on the 21st day, and in combination with capsaicin, it showed peak insulin levels of 27.98 on the 21st day [Table 3]. In both single and multidose studies, the combination exhibited significant and progressive changes in blood glucose, insulin levels, and β-cell function in animal models. In multidose study, the combination produced a significantly greater reduction in blood glucose levels in diabetic rats when compared to diabetic control. Overall, capsaicin enhanced the activity of gliclazide [Tables 3 and 4].

Pharmacodynamic and pharmacokinetic interaction in diabetic rabbits

Capsaicin produced significant antihyperglycemic activity in diabetic rabbits on the 21st day with peak percentage blood glucose reduction of 54.0% [Table 5]. Gliclazide also produced peak percentage blood glucose reduction of 49.3% on the 21st day whereas the combination produced 61.2% [Table 5]. Capsaicin showed maximum insulin levels of 25.75 on

Table 1: Mean percentage blood glucose reduction of gliclazide in the presence and absence of capsaicin in single- and multiple-dose study for normal rats (*n*=6)

Group	Treatment	Mean percentage blood glucose reduction					
		Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
III	Gliclazide (2 mg/kg)	40.5**	41.0**	42.1**	43.0**	44.2**	45.0**
IV	Capsaicin (6 mg/kg)	0.8	0.8	1.7	1.7	1.7	1.7
V	Capsaicin (6 mg/kg) + gliclazide (2 mg/kg)	41.3**	41.8**	43.0**	43.8**	45.0**	45.8**

**P<0.01 statistically significant when compared with normal control

Table 2: Mean percentage blood glucose reduction of gliclazide in the presence and absence of capsaicin in single- and multiple-dose study for diabetic rats (*n*=6)

Group	Treatment	Mean percentage blood glucose reduction					
		Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
III	Gliclazide (2 mg/kg)	45.5**	46.7**	47.4**	48.5**	51.0**	57.4**
IV	Capsaicin (6 mg/kg)	51.5**	53.3**	54.7**	56.1**	59.7**	61.9**
V	Capsaicin (6 mg/kg) + gliclazide (2 mg/kg)	54.5**	56.3**	59.2**	62.4**	67.2**	72.0**

**P<0.01 statistically significant when compared with diabetic control

the 21st day whereas gliclazide showed 29.43 and combination showed 36.03 on the 21st day [Table 6]. In both single- and multidose studies, the combination exhibited significant and progressive changes in blood glucose, insulin levels, and β-cell function in diabetic rabbits [Tables 6 and 7]. In multidose study, the combination produced a significantly greater reduction in blood glucose levels in diabetic rabbits when compared to diabetic control. The PK parameters of gliclazide alone and in the presence of capsaicin following single- and multiple-dose administrations are given in Table 8. C_{max} of gliclazide in Group III (gliclazide alone) was found to be 367.22 ng/ml whereas in Group V (combination treatment) was found to be 375.64 (SDT) and 420.36 (MDT) [Table 8]. Capsaicin was found to increase serum levels of gliclazide. It also altered the PK parameters of gliclazide in rabbits. Overall, capsaicin enhanced the activity of gliclazide.

DISCUSSION

Food–drug interactions can lead to toxic effects of drug therapy and also to a loss of therapeutic efficacy.[16] Although animal models can never replace the need for comprehensive studies in human subjects, they help in understanding the mechanisms of drug interactions. Gliclazide is the choice of drug for treating diabetes mellitus which is primarily metabolized by hepatic microsomal enzymes CYP2C9 and partly by CYP3A4.[6] Capsaicin is the active ingredient found in the fruits of *C. annuum*, Solanaceae. Literature survey reveals that capsaicin possesses antidiabetic activity[4] and is an inhibitor of CYP2C9 and CYP3A4 enzymes[5] which are responsible for the metabolism of gliclazide. Widespread exposure of population to capsaicin occurs through the means of food and topical medicines. Due to the current therapeutic applications of capsaicin and its frequent consumption, the correct assessment of this compound and its interactions with other drugs is important from a public health standpoint.

Hence, the present study was designed to assess the PD and PK interactions of capsaicin on the activity of gliclazide in animal models. Animal model using normal rats was used to identify the interaction whereas that of diabetic rats was used to validate the interaction. Rabbit model was

Table 3: Effect of capsaicin on insulin levels in diabetic rats (*n*=6)

Group	Treatment	Insulin (μIU/mL)					
		Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
III	Gliclazide (2 mg/kg)	14.61±1.15	15.08±0.74	16.11±1.02	17.53±1.21	18.78±1.01	20.87±0.92
IV	Capsaicin (6 mg/kg)	18.02±0.62	18.45±1.10	19.03±1.02	19.86±0.95	20.95±1.14	22.24±1.15
V	Capsaicin (6 mg/kg) + gliclazide (2 mg/kg)	21.12±1.22	21.99±1.11	22.85±1.18	24.04±0.92	26.08±0.87	27.98±0.96

Data are expressed as mean±SD. SD: Standard deviation

Table 4: Effect of capsaicin on β-cell function in diabetic rats (*n*=6)

Treatment	β-cell function					
	Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
Gliclazide (2 mg/kg)	165.55±1.00	173.83±0.88	188.97±1.22	210.57±0.30	234.02±0.48	299.21±0.71
Capsaicin (6 mg/kg)	230.29±0.29	243.56±0.71	259.80±0.66	280.71±0.53	318.63±0.79	357.27±1.51
Capsaicin (6 mg/kg) + gliclazide (2 mg/kg)	288.33±0.55	310.81±0.69	347.53±0.50	399.00±0.52	489.77±0.74	618.34±0.73

Data are expressed as mean±SD. Calculated by homeostasis model assessment. SD: Standard deviation

Table 5: Mean percentage blood glucose reduction of gliclazide in the presence and absence of capsaicin in single- and multiple-dose study for diabetic rabbits (*n*=6)

Group	Treatment	Mean percentage blood glucose reduction					
		Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
III	Gliclazide (4 mg/kg)	38.8**	40.3**	41.7**	43.6**	46.2**	49.3**
IV	Capsaicin (6 mg/kg)	42.4**	43.3**	44.7**	47.0**	50.5**	54.0**
V	Capsaicin (6 mg/kg) + gliclazide (4 mg/kg)	45.5**	47.5**	50.2**	53.0**	55.9**	61.2**

**$P<0.01$ statistically significant when compared with diabetic control

Table 6: Effect of capsaicin on insulin levels in diabetic rabbits (*n*=6)

Group	Treatment	Insulin (μIU/mL)					
		Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
III	Gliclazide (4 mg/kg)	21.25±1.02	21.99±0.31	22.85±0.35	24.09±0.29	26.78±0.47	29.43±0.53
IV	Capsaicin (6 mg/kg)	17.12±0.28	17.93±0.33	19.15±0.39	20.81±0.14	22.52±0.52	25.75±0.78
V	Capsaicin (6 mg/kg) + gliclazide (4 mg/kg)	25.30±0.43	26.53±0.47	28.45±0.29	30.61±0.39	32.11±0.78	36.03±0.68

Data are expressed as mean±SD. SD: Standard deviation

Table 7: Effect of capsaicin on β-cell function in diabetic rabbits (*n*=6)

Treatment	β-cell function					
	Day 0	Day 1	Day 3	Day 7	Day 14	Day 21
Gliclazide (2 mg/kg)	214.11±1.00	223.82±0.68	241.16±0.54	264.00±0.73	305.19±0.57	353.51±0.59
Capsaicin (6 mg/kg)	183.59±1.09	192.28±0.41	213.37±0.86	242.68±0.65	278.89±0.99	342.19±0.81
Capsaicin (6 mg/kg) + gliclazide (2 mg/kg)	286.69±1.15	307.59±0.49	352.32±0.58	404.09±0.72	447.53±0.87	569.64±0.77

Data are expressed as mean±SD. Calculated by homeostasis model assessment. SD: Standard deviation

Table 8: Mean pharmacokinetic parameters of gliclazide in the presence and absence of capsaicin in rabbits (*n*=6)

Pharmacokinetic parameter	Gliclazide (4 mg/kg)	Capsaicin (6 mg/kg) + gliclazide (4 mg/kg) (SDT)	Capsaicin (6 mg/kg) + gliclazide (4 mg/kg) (MDT)
C_{max} (ng/mL)	367.22±5.18	375.64±3.83	420.36±6.38
T_{max} (h)	3±0.00	3±0.00	3±0.00
AUC (h ng/mL)	4039.45±32.52	4306.86±36.14	5891.62±43.21
AUMC (h ng/mL)	38725.54±204.23	41568±184.62	57233±214.33
T1/2	10.39±0.54	10.69±0.62	11.01±0.73
Kel (l/h)	0.066±0.01	0.064±0.01	0.062±0.01
MRT (h)	9.58±0.01	9.65±0.01	9.71±0.01
CL (L/h)	0.083±0.00	0.079±0.00	0.072±0.00

Data are expressed as mean±SD. SD: Standard deviation; SDT: Single-dose treatment; MDT: Multiple-dose treatment

used further to validate the same in a dissimilar species.[17] Diabetes was induced with alloxan monohydrate, since it is more economical and most widely used toxicant to induce diabetes in animal models.

Capsaicin did not exhibit any hypoglycemic activity on normal rats, but it exhibited significant antihyperglycemic activity in diabetic rats. It significantly and progressively reduced blood glucose levels, increased insulin levels, and enhanced β-cell function in diabetic rats and rabbits. The maximum effect of capsaicin was observed on the 21st day. Gliclazide exhibited both hypoglycemic (normal rats) and antihyperglycemic activity (diabetic rats and rabbits) significantly. It significantly and progressively reduced blood glucose levels, increased insulin levels, and enhanced β-cell function in diabetic rats and rabbits. The maximum effect of gliclazide was observed on the 21st day. Capsaicin enhanced the activity of gliclazide and increased the serum levels of gliclazide. It also altered PK parameters of gliclazide. The activity of gliclazide was more in the presence of capsaicin when compared to gliclazide alone. The increased activity of gliclazide in the presence of capsaicin might be due to the inhibition of CYP2C9 and CYP3A4, the enzymes which are responsible for the metabolism of Gliclazide.

CONCLUSION

The present study concluded that the interaction of capsaicin with gliclazide was both PD and PK in nature as the glucose levels in animal models were significantly reduced; insulin levels, β-cell function, and serum gliclazide levels were significantly improved; and the other PK parameters of gliclazide were also altered. Since the interaction was observed in two dissimilar species, it is also likely to occur in humans. As capsaicin is an important ingredient in spicy foods consumed throughout the world, periodic monitoring of glucose levels is necessary when gliclazide is administered in diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

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