ORIGINAL ARTICLE

Influence of *Allium sativum* on Pharmacodynamics and Pharmacokinetics of Gliclazide in Normal Rabbits

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Abstract

Aim: In this chapter, the influence of selected dose of *Allium sativum* (84 mg/1.5 kg bd.wt) on the pharmacodynamics and pharmacokinetics of selected dose of gliclazide (5.6 mg/1.5 kg bd.wt) was studied in normal rabbits. **Materials and Methods:** Materials required were purchased from Sai Chemicals, Visakhapatnam, India. Inbred adult Wistar rabbits of either sex were used for the study. Gliclazide (TD) was administered orally to all the rabbits. After a wash out period of 1 week, the same groups of animals were administered with *Allium sativum* (84 mg/1.5 kg bd.wt.) orally. Again after a further washout period of 1 week, the same group was administered with *A. sativum* (84 mg/1.5 kg bd.wt.) orally, 30 min before the administration of gliclazide (5.6 mg/1.5 kg bd.wt). Blood samples were withdrawn at 0, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 h intervals from marginal ear vein puncture and were analyzed for blood glucose by GOD/POD method in all the experiments and serum gliclazide. **Results:** *A. sativum* has found to enhance the hypoglycemic effect of gliclazide. There was a considerable percent blood glucose reduction with gliclazide (5.6 mg/1.5 kg bd.wt) before and after treatment with *Allium sativum* (104 mg/kg) in rabbits.**Conclusion:** The interaction between *A. sativum* and gliclazide appears to be pharmacodynamic and pharmacokinetic in nature.

Key words: *Allium sativum,* gliclazide, hypoglycaemic, pharmacodynamic, pharmacokinetic

INTRODUCTION

Modern medicine has given us many useful drugs that not only prolong and save lives, but also improve the quality of our lives. However, drugs must be taken properly to ensure that they are safe and effective. The beneficial effects of the drugs can be affected by the ingredients in our food.[1]

Several dietary constituents and photochemical are now identified as important factors affecting drug disposition. Frequently, the underlying mechanism of altered drug concentration is induction or inhibition of drug-metabolizing enzymes or transporters. In addition to dietary constituents leading to reduced plasma concentration of drugs, there are examples of increased plasma concentration by nutrients due to inhibition of drug metabolism, primarily due to inhibition of (intestinal) CYP3A4, resulting in increased plasma concentration.[2]

Many food-drug interactions can be explained by inhibition of P-glycoprotein and/or CYP3A4. Because a broad variety of drugs are substrates for both P-glycoprotein and CYP3A4 and because many compounds are inhibitors of both proteins, elevated plasma concentration of a drug by a concomitantly administered substance can be due to a dual effect on drug transport and metabolism. Since the identification of major drug-metabolizing enzymes in the gut wall mucosa, it became increasingly clear that metabolism in the enterocytes can play an important role for low or variable oral bioavailability of drugs.

Some constituents from herbs may act on the same drug target molecules (e.g., receptors or enzymes), resulting in

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synergistic or antagonistic herb drug interactions. Hence, monitoring drug therapy and study of food-drug interactions have become important to get a clear data about the food-drug interactions. It is very essential to study the food-drug interactions of monitoring of drug therapy in the presence of other drugs in case of some disorders such as diabetes and hypertension.[3]

In some cases like diabetes, hypertension requires monitoring for blood glucose level and blood pressure respectively. Food-drug interaction may alter blood glucose levels in patients with diabetes taking a variety of foods. Hence, blood glucose levels may be increased/decreased with drug-drug interactions and may cause fatal effects in that particular individual.

These are also seen in other disorders such as hypertension and cardiac disorders. Drugs with low therapeutic index (digoxin) also require drug monitoring.[4]

For the study of drug interactions, generally small animals such as mice, rats, and rabbits are used as models. The pharmacodynamic/pharmacokinetic parameters at pre-clinical levels can be conveniently studied in them and results of them can be extrapolated to humans. The above animals can be easily maintained in laboratory conditions and small volumes of blood can be drawn easily at regular time intervals. Hence, in the present study, albino rats (rodent model) and albino rabbits (non-rodent model) were used for studying the mechanisms of drug interactions, since such interaction is likely to happen in human also, if occurs in the above two dissimilar species.

MATERIALS AND METHODS

Chemicals

Inbred adult Wistar rabbits of either sex were procured from B.N. Ghosh Enterprises, Kolkata, India. The prior permission for the study was obtained from our Institutional Animal Ethics Committee**.** Gliclazide (5g) sample is obtained from Wockhardt, Aurangabad, India. Acetonitrile (HPLC grade) manufactured by Qualigens chemicals, Mumbai, India, was purchased from Sai Chemicals, Visakhapatnam, India. Sodium hydroxide (AR-grade) manufactured by Fine chemicals, Mumbai, India, was purchased from Sai Chemicals, Visakhapatnam, India. Triethylamine (TEA-ARgrade) manufactured by Fine chemicals, Mumbai, India was purchased from Sai Chemicals, Visakhapatnam, India. Ortho phosphoric acid (AR-grade) manufactured by Fine chemicals, Mumbai, India, was purchased from Sai Chemicals, Visakhapatnam, India. Triple distilled water was prepared in the laboratory. Hydrochloric acid (AR-grade) manufactured by Fine chemicals, Mumbai, India, was purchased from Sai Chemicals, Visakhapatnam, India. Blood glucose kits (Auto span) manufactured by Span diagnostics ltd, Surat, India, were purchased from a local pharmacy. Standard animal pellet diet manufactured by Rayan Biotechnologies Pvt. Ltd., Hyderabad, India, was used. Gliclazide solution in distilled water was prepared by dissolving it in a few drops of 0.1N sodium hydroxide then made up to the volume with distilled water.[5]

Experimentation methodology

A group of six normal healthy Wistar rabbits of either sex weighing between 1.35 kg and 1.75 kg were used in the study. Normal healthy rabbits were maintained on uniform diet at room temperature with 12 h/12 h light and dark cycle. They were housed in metallic cages. Rabbits were fed with standard animal pellet diet and water *ad libitum.* Rabbit was placed in rabbit holder and a mouth gauge was placed between the jaws and an infant oral feeding tube is inserted into the GIT slowly. Precaution must be taken while inseting feeding tube into the mouth, such that it should not enter into the tracheal.[6]

The rabbits were fasted for 18 h before the experiment with water *ad libitum*. During the experiment, water was also withdrawn. Gliclazide (TD) was administered orally to all the rabbits. After a wash out period of 1 week, the same group of animals was administered with *Allium sativum* (84 mg/1.5 Kg bd wt.) orally. Again after a further washout period of 1 week, the same group was administered with *A. sativum* (84 mg/1.5 Kg bd wt.) orally, 30 min before the administration of gliclazide (5.6 mg/1.5 kg bd.wt). Blood samples were withdrawn at 0, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 h intervals from marginal ear vein puncture and were analyzed for blood glucose by GOD/POD method in all the experiments and serum gliclazide.[7]

RESULTS AND DISCUSSION

The maximum % fall in blood glucose reduction and peak serum gliclazide concentration in gliclazide treated matching control group were 35.9% and 374 ng/mL at 3 h, respectively [Tables 1-3, Figure 1]. *A. sativum* does not significantly altered blood glucose levels *per se,* [Table 4]. In combination with gliclazide, the % fall in blood glucose reduction was 43.36 ± 0.79 at 3 h [Table 5] and peak serum concentration of gliclazide in blood was 441.9 ± 7.1 ng/mL at 3 h [Tables 6 and 7]. *A. sativum* has found to enhance the hypoglycemic effect of gliclazide. The peak hypoglycemic effect of gliclazide was correlated with the peak concentration of gliclazide in serum.[8] The study indicates that gliclazide levels were high in the blood with peak hypoglycemic effect at 3 h. The percent blood glucose reduction with gliclazide (5.6 mg/1.5 kg bd.wt) before and after the treatment with *A. sativum* (104 mg/kg) in rabbits was shown in Tables 2 and 5, respectively, and the graphical representation is done in Figure 2. The blood glucose levels

Table 1: Effect of gliclazide (2 TD) on blood glucose levels in normal rabbits (*n*=6)

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
0	97	91	85	110	106	95	97.33±3.8
1	75 (22.68)	71 (21.98)	71 (16.47)	83 (24.55)	68 (35.85)	79 (16.84)	74.50±2.3
2	69 (28.87)	59 (35.16)	63 (25.88)	70 (36.36)	65 (38.68)	68 (28.42)	65.67±1.7
3	55 (43.30)	47 (48.35)	43 (49.41)	54 (50.91)	55 (48.11)	48 (49.47)	50.33±2.1
4	69 (28.87)	59 (35.16)	63 (25.88)	70 (36.36)	65 (38.68)	68 (28.42)	65.67±1.7
6	78 (19.59)	67 (26.37)	70 (17.65)	80 (27.27)	71 (33.02)	79 (16.84)	74.17±2.2
8	81 (16.49)	76 (16.48)	76 (10.59)	86 (21.82)	72 (32.08)	85 (10.53)	79.33±2.3
12	87 (10.31)	78 (14.29)	80 (5.88)	89 (19.09)	77 (27.36)	91 (4.21)	83.67±2.5
16	92 (5.15)	86 (5.49)	89 (–4.71)	94 (14.55)	82 (22.64)	91 (4.21)	89.00±1.8
24	95 (2.06)	85 (6.59)	87 (-2.35)	101 (8.18)	87 (17.92)	90 (5.26)	90.83±2.5

Table 2: Effect of gliclazide (TD) on blood glucose levels in normal rabbits (*n*=6)

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
0	99	88	96	104	95	89	95.17±2.5
1	84 (15.15)	75 (14.77)	80 (16.67)	91 (12.50)	79 (16.84)	77 (13.48)	81.00±2.4
2	78 (21.21)	70 (20.45)	75 (21.88)	81 (22.12)	71 (25.26)	73 (17.98)	74.67±1.7
3	60 (39.39)	54 (38.64)	64 (33.33)	72 (30.77)	56 (41.05)	62 (30.34)	61.33±2.6
4	69 (30.30)	58 (34.09)	67 (30.21)	77 (25.96)	60 (36.84)	67 (24.72)	66.33±2.8
6	77 (22.22)	64 (27.27)	74 (22.92)	85 (18.27)	67 (29.47)	71 (20.22)	73.00±3.1
8	82 (17.17)	71 (19.32)	81 (15.63)	93 (10.58)	75 (21.05)	78 (12.36)	80.00±3.1
12	86 (13.13)	78 (11.36)	87 (9.38)	97 (6.73)	80 (15.79)	81 (8.99)	84.83±2.8
16	92 (7.07)	83 (5.68)	91 (5.21)	99 (4.81)	87 (8.42)	84 (5.62)	89.33±2.4
24	94 (5.05)	86 (2.27)	92 (4.17)	101 (2.88)	88 (7.37)	87 (2.25)	91.33±2.3

Table 3: Effect of gliclazide (1/2 TD) on blood glucose levels in normal rabbits (*n*=6)

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
0	100	102	107	97	90	101	99.50±2.3
1	95 (5)	89 (12.75)	91 (11.21)	95 (2.06)	83 (7.78)	95 (5.94)	91.33±2.0
2	88 (12)	80 (21.57)	82 (17.76)	89 (8.25)	71 (21.11)	85 (15.84)	82.50±2.7
3	75 (25)	79 (22.55)	83 (29.91)	70 (27.84)	65 (27.78)	80 (20.79)	75.33±2.8
4	81 (19)	83 (18.63)	85 (24.30)	85 (12.37)	65 (27.78)	84 (16.83)	80.50±3.2
6	88 (12)	90 (11.76)	90 (17.76)	89 (8.25)	69 (23.33)	89 (11.88)	85.83±3.4
8	88 (12)	97 (4.90)	89 (17.76)	90 (7.22)	75 (16.67)	93 (7.92)	88.67±3.0
12	93 (7)	95 (6.86)	98 (13.08)	91 (6.19)	81 (10.00)	97 (3.96)	92.50±2.5
16	97 (3)	96 (5.88)	104 (9.35)	95 (2.06)	87 (3.33)	98 (2.97)	96.17±2.2
24	97 (3)	98 (3.92)	103 (9.35)	99 (2.06)	89 (1.11)	97 (3.96)	97.17±1.9

and the percent blood glucose reduction with *A. sativum* (104 mg/Kg) were shown in Table 4. The serum gliclazide concentration with gliclazide (5.6 mg/1.5 kg bd.wt) before and after the treatment with *A. sativum* (104 mg/Kg) in rabbits was shown in Tables 6 and 7 respectively and graphical representation is done in Figure 3. The pharmacokinetic parameters of gliclazide observed with gliclazide (5.6 mg/1.5 kg bd.wt) before and after *A. sativum* treatment (104 mg/Kg) were shown in Tables 8 and 9, respectively. The mean values of different pharmacokinetic parameters of

gliclazide (5.6 mg/1.5 kg bd.wt) with and without *A. sativum* (104 mg/kg) treatment were shown in Table 10.

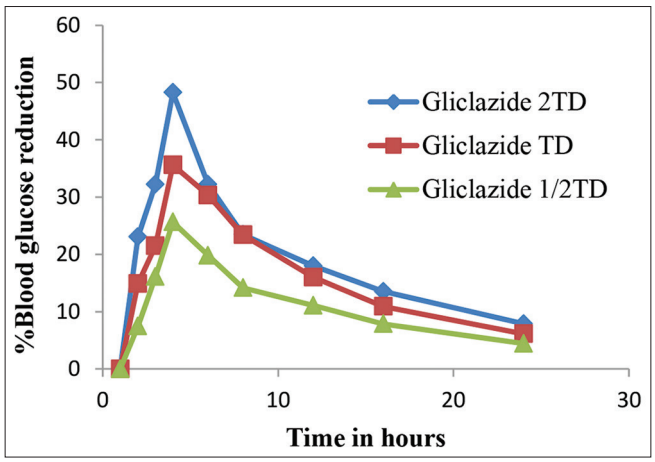

Figure 1: Percent Blood Glucose reduction with different doses of Gliclazide in Normal rabbits (*n*=6)

The Student's paired *t*-test was applied to the data and statistical significant change was observed in parameters such as $AUC_{0\text{-}t(24)}$, $AUC_{0\text{-}\infty}$, AUMC, C_{max}, Ke, and elimination t½ of gliclazide when given in combination with *A. sativum* which shown in Table 10.

The AUC and AUMC of gliclazide were significantly altered in combination group from 3188.99 ng/mL*h and 35538.51 ng/mL*h*h to 3758.56 ng/ml*h and 42889.56 ng/mL *h*h, respectively, compared to gliclazide treated group. The Cmax is significantly increased from 346.74 to 441.88 ng/ml indicating that there is change in availability of gliclazide in the presence of *A. sativum*.[9] The Vd was nearly same 16.73 and 15.65 L. The Tmax remained unchanged. The absorption half-life (t 1/2(a)) and absorption rate constant (Ka) remained unchanged, indicating that the absorption was not altered. The elimination half-life (t ½) and elimination rate constant (Kel) were significantly altered or in excretion of gliclazide in the presence of *A. sativum*. The mean residence time (MRT)

Table 4: Blood glucose levels (mg/dL) with *Allium sativum* in normal rabbits

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
0	56	75	119	60	71	77	76.3±3.54
1	68 (–21)	53 (29.3)	90 (24.3)	72 (–20)	49 (30.9)	67 (12.9)	66.5±3.25
2	72 (–28)	61 (18.6)	98 (17.6)	76 (–26.6)	57 (19.7)	71 (7.8)	72.5±3.1
3	61 (–8.9)	56 (25.3)	101 (15.1)	65 (–8.3)	52 (26.76)	67 (13)	67±2.45
4	46 (17.8)	60 (20)	120 (–0.8)	50 (16.6)	56 (21.12)	65 (15.58)	66.2±2.14
6	54 (3.5)	64 (14.6)	114 (4.2)	58 (3.3)	60 (15.5)	70 (9.1)	70±1.86
8	51 (8.9)	60 (20)	120 (0.8)	55 (8.3)	56 (21.12)	67 (12.9)	68.2±2.35
12	44 (21.4)	57 (24)	119 (0)	48 (20)	53 (25.35)	64 (16.8)	64.2±2.04
16	49 (12.5)	59 (21.3)	117 (1.6)	52 (13.3)	64 (9.8)	72 (6.6)	68.83±2.99
24	47 (16)	52 (30.6)	101 (15.1)	57 (5)	54 (23.9)	61 (20.8)	62±3.00

Table 5: Blood glucose levels (mg/dL) with gliclazide (5.6 mg/1.5 kg body weight) in combination with *Allium sativum* in normal rabbits

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
0	84	88	120	106	92	113	100.5±2.01
1	53 (36.9)	57 (35)	85 (29)	71 (33)	61 (33.69)	78 (36.9)	67.5±1.81
2	57* (32.14)	62 (29)	100 (16.6)	8.6 (18)	67 (27)	93 (17.7)	77.5±2.56
3	40 (52.3)	45 (48)	75 (37.5)	61 (36)	50 (45.6)	68 (39.8)	56.5±1.8
4	49 (41.6)	55 (37.5)	85* (29)	70 (34)	61 (33.69)	77* (31.8)	66.16±1.38
6	69 (17.8)	71 (19.3)	70 (41.6)	60* (43)	74 (19.56)	65 (42)	68.16±2.02
8	64 (23.8)	67 (23.8)	102 (15)	97*** (8.5)	71 (22.8)	109 (3.5)	85.00±2.22
12	61 (27)	64 (27.27)	109 (9.1)	94 (11.3)	69 (25)	101 (10.6)	83.00±2.02
16	75 (10.7)	72*** (18.18)	111 (7.5)	89 (17)	68 (26)	100 (11.5)	85.8±1.29
24	77 (8.3)	75 (14.7)	104 (13.3)	87 (16)	70 (24)	95 (15.9)*	84.6±1.67

*Significant at *P*<0.05 compared to gliclazide (5.6mg/1.5kg) matching control. ***Significant at *P*<0.001 compared to gliclazide (5.6mg/1.5kg) matching control.

Table 6: Serum gliclazide levels (ng/mL) with gliclazide (TD) oral, without *Allium sativum* (TD) in normal rabbits

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
1	86	72.8	79	80.2	86.5	74.1	79.77±2.3
2	206.8	211.8	224.8	223.5	221.8	237.8	221.08±4.4
3	372.8	359.8	399.8	397.8	343.8	371.2	374.20±8.9
4	302.8	311.8	343.5	312	334.2	308.8	318.85±6.6
6	280.8	277.8	259.3	250.8	240.4	228.3	256.23±8.4
8	217.8	216.8	239.7	237.2	212.5	239	227.17±5.2
12	130.8	120.5	106.5	125.8	122.5	123.2	121.55±3.3
16	96.5	97.2	94.7	95.2	97.7	102.2	97.25±1.1
24	85.9	74.1	69.5	64.4	62	72.5	71.40±3.5

Table 7: Serum gliclazide levels (ng/mL) with gliclazide (TD) oral, in combination with *Allium sativum* (TD) in normal rabbits

Time	Rabbits						Mean±SEM
(h)	R1	R2	R3	R4	R5	R6	
1	110.8	107.5	106.5	141.8	127.5	101.2	115.83±2.6
2	272.5	314.14	292.8	285.28	311.9	249.34	287.66±5.0
3	440.8	472.08	464.74	451	427.7	395.4	441.95±7.1
4	348.46	370.9	354	361.7	317	298.7	341.79±4.5
6	284.7	270.7	265	291.15	259	247.4	269.65±9.6
8	141	169.14	154	157.4	152.43	124.7	149.77±6.9
12	109.7	121.4	148.6	115.8	131.4	124	125.15±8.8
16	97	104.9	123.4	101.8	114.6	92	105.61±3.9
24	59	74	94.76	64.8	68.8	54.7	69.34±3.0

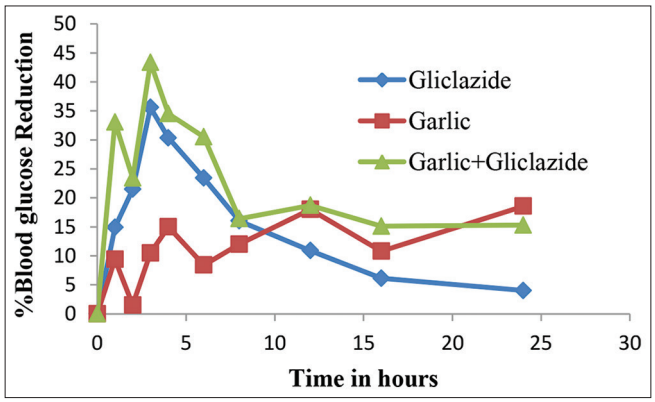

Figure 2: Effect of *Allium sativum* on the hypoglycemic activity of gliclazide in normal rabbits (*n*=6)

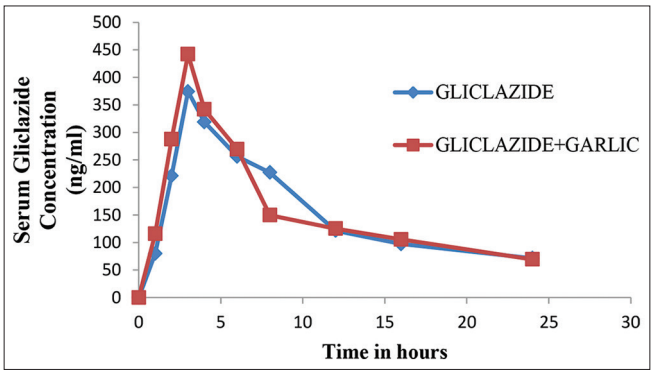

Figure 3: Serum gliclazide concentration versus time in normal rabbits treated with and without *Allium sativum* (*n*=6)

of gliclazide before and after the treatment was 15.67 h and 15.76 h, respectively.[10]

The increased in the AUC, AUMC, Ke, t½ indicate that there is interaction at metabolism or excretion of gliclazide. Since there is no change in the clearance the interaction may not be at excretion level. The active constituent of *A. sativum and S-allyl cysteine* was reported to inhibit CYP 2C9 enzyme in rat model. The same enzyme is also responsible for the partial metabolism of gliclazide.[11] Hence, the raise in the serum levels and changes in the pharmacokinetic parameter of gliclazide in the presence of *A. sativum* might be due to interaction at metabolic site.

Garlic enhanced the mean percent blood glucose reduction of gliclazide in rabbits; this interaction may be due to either pharmacokinetic or pharmacodynamic nature.[12] The overall

Table 8: Different pharmacokinetic parameters of gliclazide (5.6 mg/1.5 kg body weight) in normal rabbits

Parameter	Rabbits (weights in Kg)						Mean±SEM
	1 (1.35)	2 (1.41)	3 (1.67)	4 (1.48)	5 (1.37)	6 (1.55)	
AUC_{0-24}	2133.48	3520.095	3328.025	3376.16	3356.94	3419.25	3188.99±233.29
$AUC_{0-\alpha}$	2821.53	4049.26	3771.88	4135.08	4125.22	4138.43	3840.23±231.90
$AUMC_{0-24}$	37753.11	34592.99	31543.53	36541.8	35998.76	36800.89	35538.51±991.84
$AUMC_{0-\alpha}$	62646.84	53037.07	46872.42	64501.7	63994.88	62995.94	59008.14±3270.31
K_e	0.0672	0.1045	0.0875	0.1012	0.0975	0.0892	0.0911±0.00603
K_a	1.53	1.53	1.53	1.53	1.53	1.53	1.53
$T_{1/2}$ (ke)	10.3	6.6	7.92	6.8	7.1	7.7	7.7±0.293
V_{dss}	34.2	17.21	11.64	12.14	12.61	12.61	16.73±3.93
Cl	1587.79	1382.96	988.895	812.55	848.43	865.06	1080.94±145.57
C_{max}	345.1	356.27	341.36	346.28	336.59	354.89	346.74±3.41
T_{max}	3	3	3	3	3	3	3.00
MRT	22.21	13.09	12.43	15.60	15.51	15.22	15.67±1.55

Table 9: Different pharmacokinetic parameters of gliclazide (5.6 mg/1.5 kg body weight) with *Allium sativum* in normal Rabbits

Parameter	Rabbits (weights in Kg)						Mean±SEM
	1 (1.5)	2 (1.41)	3 (1.32)	4 (1.46)	5 (1.24)	6 (0.98)	
AUC_{0-24}	3595.99	3910.15	4100.88	3808.33	3806.33	3329.69	3758.562±108.824*
$AUC_{0-\alpha}$	4228.3	4772.08	5451.2	4521.96	4661.24	3946.86	4596.94±210.45*
$AUMC_{0-24}$	37838.11	44210.15	54474.48	40644.55	44416.44	35753.63	42889.56±2706.5*
$AUMC_{0-\alpha}$	59790.6	74948.3	106123	65630.9	75559.6	57529.4	73263.63±7246.2
K_e	0.09	0.085	0.07	0.09	0.08	0.088	0.0838±0.003167
Ka	1.15	1.15	1.15	1.15	1.15	1.15	1.15±0.19
$T_{1/2}$	7.7	8.15	9.9	7.7	8.66	7.87	8.33±0.37
V_{dss}	16.5	16.4	16.7	16.4	15.1	12.8	15.65±0.61
Cl	1324.4	1110.56	898.88	1205.23	986.86	937.45	1077.23±67
C_{max}	440.8	472.08	464.74	451	427.7	395	441.88±11.42***
T_{max}	3	3	3	3	3	3	3
MRT	14.14	15.7	19.46	14.51	16.21	14.57	15.76±0.8

>*Allium sativum* was given 30 min prior to gliclazide, *Significant at $P<0.05$ compared to gliclazide (5.6 mg/1.5 kg) matching control, ***Significant at $P<0.001$ compared to gliclazide (5.6 mg/1.5 kg) matching control

Table 10: Significance of mean pharmacokinetic parameters of gliclazide (5.6 mg/1.5 kg body weight) with and without *Allium sativum* in normal rabbits

Pharmacokinetic parameter	Without *Allium sativum*	With *Allium sativum*	Significance at $P<0.05$
AUC_{0-24}	3188.99±233.29	3758.562±108.824*	Significant
$AUC_{0-\alpha}$	3840.23±231.90	4596.94±210.45*	Significant
$AUMC_{0-24}$	35538.51±991.84	42889.56±2706.5*	Significant
$AUMC_{0-\alpha}$	59008.14±3270.31	73263.63±7246.2	Not significant
K_e	0.0911±0.00603	0.0838±0.003167	Not significant
K_a	1.53	1.15	Not significant
$T_{1/2}$	8.23±0.293	8.22±0.37	Not significant
V_{dss}	16.73±3.93	15.65±0.61	Not significant
Cl	1080.94±145.57	1077.23±67	Not significant
C_{max}	346.74±3.41	441.88±11.42***	Significant
T_{max}	3.00	3	Not significant
MRT	15.67±1.55	15.76±0.8	Not significant

serum gliclazide levels were increased from 1 to 24 h and there was significant change in C max, AUC (0–24), AUC (0-α), AUMC (0–24), Kel and t½. This indicates that *A. sativum* increases bioavailability of gliclazide. The results indicate that the interaction may be at metabolism/excretion phases. Since there was no change in clearance, the possible route of interaction may be at metabolism.[13]

The possible mechanism of action of interaction at the site of metabolism may be due to s-ally cysteine which is one of main active constituent in garlic which has the capacity to inhibit the hepatic microsomal enzyme CYP P450 2C9 the same enzyme also responsible for metabolism of gliclazide.[14]

CONCLUSION

The interaction between *A. sativum* and gliclazide appears to be pharmacodynamic and pharmacokinetic in nature. Hence, diabetic and health-care professional are cautioned about the use of high quantities of garlic while taking antidiabetic medications particularly sulphonylureas.

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