

Research Article

Pharmacokinetic and Pharmacodynamic Interaction of Curcumin with Glimepiride in Normal and Diabetic Rats

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ABSTRACT: Introduction: Herbal antidiabetic preparations are often used as an add-on therapy in diabetes and such herbal preparations often contain curcumin. Hence, in the present investigation the effects of curcumin on the pharmacokinetics and pharmacodynamics of glimepiride in normal as well as diabetic rats was studied. **Methods:** Pharmacokinetic study group I rats were administered with glimepiride (1 mg/kg; p.o.) on 8th day of the study. Group II rats were pretreated with curcumin (80 mg/kg; p.o.) for 7 days and on 8th day with glimepiride (1 mg/kg) followed by curcumin. Blood samples were collected at different time intervals and serum samples were analyzed using High-performance liquid chromatography (HPLC). For the pharmacodynamic study, curcumin alone or in combination with glimepiride was administered to diabetic rats for 28 days and various biochemical parameters were determined. Total antioxidant status was determined by using the DPPH assay. **Results:** In normal and diabetic rats the combination of glimepiride with curcumin increased all the pharmacokinetic parameters including C_{max} , $AUC_{0\text{ to }n}$, AUC_{total} , $t_{1/2}$ and MRT. It also decreased the clearance, Vd markedly as compared to control group. The combination of glimepiride with curcumin provides significant protection against the diabetes induced alterations in the biochemical parameters. In addition, the combination of glimepiride with curcumin also improved the total antioxidant status. **Conclusion:** The results revealed that combination of glimepiride with curcumin led to the enhancement of bioavailability of glimepiride by inhibiting the CYP2C9 enzyme, which suggested that curcumin might be beneficial as an adjuvant to glimepiride in a proper dose, in diabetic patients.

KEYWORDS: curcumin, CYP2C9, glimepiride, pharmacodynamics, pharmacokinetics

INTRODUCTION

A combination of herbal drugs (or isolated phytochemicals) is found to be beneficial in certain diseases when given along with conventional drugs. Glimepiride is a sulphonylurea oral hypoglycemic agent which is widely used for the treatment of type 2 diabetes mellitus. It produces the hypoglycemic effect primarily by stimulating insulin secretion from β -cells of pancreatic islets. The hypoglycemic effect of glimepiride can be altered by co-administration with

other drugs e.g. *Carica papaya* extract.^[1] Thus there is a need to study the interaction between glimepiride and other drugs to avoid adverse effects.

Curcumin, obtained from the dried as well as fresh rhizomes of plant *Curcuma longa* (Zingiberaceae), is widely used as a food additive. Diabecon tablets contain curcumin as one of the ingredients. They can be used by diabetic patients as an alternative medicine along with oral hypoglycemic drugs. Curcumin is reported to have immunomodulatory activity,^[2] cardioprotective activity^[3] and aldose reductase inhibitory activity^[4] and hence may be used to treat diabetic complications. It also reduces hepatic glucose production,^[5] thus there is a possibility that curcumin may have synergistic hypoglycemic activity with glimepiride.

Many drug interactions are a result of induction or inhibition of CYP enzymes. Herbal medicines that modulate intestinal and hepatic CYPs can alter the bioavailability and clearance of co-administered drugs. Several *in vitro* reports of curcumin on inhibition of CYP 450s, especially CYP3A4, CYP1A2 and CYP2C9. Hence, there was possibility of curcumin

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for the metabolic inhibition of glimepiride and is completely metabolized by CYP2C9 microsomal liver enzymes.^[6]

The aim of the present study was to investigate the effect of curcumin on the pharmacokinetics and pharmacodynamics of glimepiride in normal and streptozotocin induced diabetic rats to study the synergistic effects of concomitant treatment with these drugs.

MATERIALS AND METHODS

Drugs and Chemicals

Glimepiride and gliclazide were obtained as gift samples from Dr. Reddy's Laboratories (Hyderabad, India). Methanol (HPLC-grade), potassium dihydrogen orthophosphate and orthophosphoric acid of AR grade (99.5%) were procured from Merck Specialties Pvt. Ltd., Mumbai. Curcumin, α , α - diphenyl- β -picrylhydrazyl (DPPH) and streptozotocin (STZ) were purchased from HiMedia Laboratories Pvt. Ltd, Mumbai. Merck analytical kits were used to estimate the serum biochemical parameters such as glucose, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), total protein, triglycerides and total cholesterol. The water used for analytical purpose was double distilled, filtered by using direct-Quv millipore and sonicated for removing air bubbles. All other chemicals used were of analytical grade.

Maintenance of animals

Male Albino rats of Wistar strain weighing 180-250g were purchased from Mahaveera enterprises, Hyderabad, India and used for the studies after obtaining the permission from institutional animal ethical committee (CPCSEA Reg. No.146/1999). The animals were housed in standard polypropylene cages and maintained under standard laboratory conditions (12 h light/dark cycle; at an ambient temperature of $25 \pm 5^\circ\text{C}$; 35-60% of relative humidity). The animals were fed with standard rat pellet diet and water *ad libitum*.

Pharmacokinetic study in normal rats

Grouping of normal rats and pretreatment

Rats were divided into 2 groups ($n = 6$). Group I was administered with glimepiride (1 mg/kg; b.w., p.o.) by suspending in normal saline^[7] on 8th day and group II was pretreated with curcumin (80 mg/kg; b.w., p.o.) in normal saline^[8] for 7 days and on 8th day were treated with glimepiride (1 mg/kg) followed by curcumin (80 mg/kg; b.w., p.o.).

Before the collection of blood samples animals were fasted for 16 h with water *ad libitum*. Blood samples were collected from retro-orbital vein puncture^[9] using heparinised capillary tubes at 0.5, 1, 2, 4, 6, 8, 12 and 24 h. Serum was separated after centrifugation at 8000 rpm for 15 min and stored at -20°C until analysis.

Pharmacokinetic study in diabetic rats

Induction of diabetes in rats

Diabetes was induced by using streptozotocin (55 mg/kg, b.w., i.p.) in citrate buffer (pH 4.5) to the overnight fasted Wistar rats.^[10] After 72 h, blood samples were collected from rats by retro orbital puncture and the serum was analyzed for glucose levels. Animals with blood glucose level > 250 mg/dl were considered as diabetic and were used for the study.

Grouping of diabetic rats and treatment

Diabetic rats were divided into 2 groups ($n = 6$) and were treated same as mentioned in normal rats. Blood samples were collected from retro-orbital vein puncture at time intervals between 0.5, 1, 2, 4, 6, 8, 12 and 24 h using heparinised capillaries. Serum was separated after centrifugation at 8000 rpm for 15 min and stored at -20°C until analysis.

HPLC analysis of glimepiride in normal and diabetic pretreated rats

Serum glimepiride concentration was determined by reverse phase HPLC method.^[7] The solvent delivery system was a Shimadzu pump model LC-10AT (Shimadzu, Japan) and the analytical column used was Lichrosphere 100 RP C₁₈ (125×4.0 mm i.d., 5 μ particle size). Column effluent was monitored with SPD-M10Avp diode array detector at 230 nm. The HPLC system was equilibrated with the mobile phase consisting of methanol: 10mm potassium dihydrogen ortho phosphate (pH 3.0 adjusted with ortho phosphoric acid) (80:20 v/v), at a flow rate of 1.0 ml/min. Serum samples were denatured by methanol and then centrifuged at 8000 rpm for 15 min. 20 μ l of clear supernatant was injected into the HPLC system for quantitation. The samples were detected by isocratic elution. The retention time of glimepiride and gliclazide (internal standard) was found to be 5.5 and 4.0 min and separation was complete in less than 10 min. The method was validated for linearity, accuracy and precision were found to be acceptable over the range of 0.5 - 500 μ g/ml for glimepiride. The method was found suitable to analyze rat serum samples for application in pharmacokinetic, pharmacodynamic, bioavailability/bioequivalence studies.

Pharmacodynamic Studies

Assessment of hypoglycemic activity in STZ-induced diabetic rats

STZ-induced diabetic rats were divided into 4 groups ($n = 6$). The animals of group I (diabetic control, normal saline), group II (glimepiride, 1 mg/kg), group III (curcumin, 80 mg/kg) and group IV [curcumin (80 mg/kg) + glimepiride (1 mg/kg)] were treated orally with the material mentioned in the parenthesis of the respective group. The effect of the curcumin, glimepiride alone and their combinations on fasting blood glucose level was studied up to 24 h. Blood

samples were drawn from the retro-orbital plexus of the rats at '0' (initial fasting blood sample), 2, 4, 6, 8, 12 and 24 h after the treatment. The samples were analyzed for blood glucose using glucose oxidase-peroxidase method.^[11]

Assessment of biochemical parameters in STZ-induced diabetic rats

Overnight fasted STZ-induced diabetic rats were divided into 4 groups (I-IV) and treated in the manner described for the antihyperglycemic study. They were treated once a day for 28 days (sub acute study) and their body weight, fasting blood glucose level, serum insulin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum cholesterol, serum triglyceride and serum total proteins were recorded as previously described.^[12] During the study period, the body weight of the animals and blood glucose levels were recorded after 7, 14, 21 and 28 days of the treatment. Serum insulin, SGOT, SGPT, serum cholesterol, serum triglyceride and serum total protein levels were estimated after 28 days of the treatment.

Estimation of total antioxidant status in diabetic pretreated rats

The serum samples from the sub acute study were also used to determine the total antioxidant status by using DPPH method.^[13] Ascorbic acid was used as a reference standard. The standard graph was prepared using different concentrations of ascorbic acid in water ($y = 0.0018x + 0.0116$, $r = 0.9953$) and the antioxidant status values were expressed in terms of nM of ascorbic acid.

Statistical analysis

The pharmacokinetic parameters were calculated by using Kinetica TM software (version 4.4.1, Thermo Electron Corporation, USA). All values of pharmacokinetic and pharmacodynamic studies were expressed as mean $\pm$ SD (standard deviation). The data were statistically evaluated using one way analysis of variance (ANOVA) followed by post hoc Dunnet's t-multiple comparison test using Graph Pad Prism 4 computer software. Values corresponding to $p \leq 0.05$ were considered as significant.

RESULTS

Pharmacokinetics of glimepiride pretreated with curcumin in normal rats

In normal rats the C_{max} (peak serum concentration) of glimepiride significantly increased in curcumin-glimepiride group by 1.13 times, $AUC_{0 \text{ to } n}$ (area under serum concentration/time plot until the last quantifiable value) by 1.12 times, AUC_{total} (area under serum concentration/time plot extrapolated to infinity) by 1.16 times, $t_{1/2}$ (terminal half life) by 1.26 times, MRT (average mean residence time) by

1.06 times, whereas the clearance and volume of distribution of glimepiride was decreased by 0.9 and 0.8 times when compared with control group. Mean pharmacokinetic parameters of glimepiride in different groups of normal rats are shown in Table 1.

Pharmacokinetics of glimepiride pretreated with curcumin in diabetic rats

In STZ-induced diabetic rats the C_{max} of glimepiride significantly increased in curcumin-glimepiride group by 1.37 times, $AUC_{0 \text{ to } n}$ by 1.16 times, AUC_{total} by 1.29 times, $t_{1/2}$ by 1.68 times and MRT by 1.29 times, whereas the clearance and volume of distribution of glimepiride was decreased by 0.68 and 0.61 times when compared with control group. The T_{max} of glimepiride in both normal and diabetic groups was not altered by concurrent administration of curcumin. Mean pharmacokinetic parameters of glimepiride in different groups of diabetic rats are depicted in Table 2.

Table 1: Mean pharmacokinetic parameters of glimepiride in different groups of normal rats

PK parameter ^a	Glimepiride	Glimepiride + Curcumin
C_{max} ($\mu\text{g/ml}$)	18.66 $\pm$ 0.84	21.25 $\pm$ 1.21**
T_{max} (h)	4	4
AUC_{0-n} ($\mu\text{g/ml h}$)	161.67 $\pm$ 4.40	180.87 $\pm$ 11.10**
AUC_{tot} ($\mu\text{g/ml h}$)	170.51 $\pm$ 6.66	199.34 $\pm$ 8.72**
$t_{1/2}$ (h)	5.58 $\pm$ 0.99	7.05 $\pm$ 0.88**
MRT (h)	10.68 $\pm$ 0.95	11.36 $\pm$ 0.85**
CL (ml/min)	325.12 $\pm$ 12.53	295.23 $\pm$ 10.78**
Vd (ml)	56.3 $\pm$ 5.65	45.1 $\pm$ 8.98**

All values are expressed as mean $\pm$ SD (n=6).

* $p < 0.05$; ** $p < 0.01$ considered as significant when compared with glimepiride control

^aDefinitions of the parameters:

C_{max} : Peak serum concentration; **T_{max} :** Time to reach peak serum concentration; **AUC_{0-n} :** Area under serum concentration/time plot until the last quantifiable value; **AUC_{total} :** Area under serum concentration/time plot extrapolated to infinity; **$t_{1/2}$:** Terminal half life; **MRT:** Average mean residence time; **CL:** Total clearance; **Vd:** Volume of distribution.

Table 2: Mean pharmacokinetic parameters of glimepiride in different groups of STZ-induced diabetic rats

PK parameter ^a	Glimepiride	Glimepiride + Curcumin
C_{max} ($\mu\text{g/ml}$)	21.43 $\pm$ 1.33	29.36 $\pm$ 1.92**
T_{max} (h)	4	4
AUC_{0-n} ($\mu\text{g/ml h}$)	177.90 $\pm$ 9.73	207.35 $\pm$ 7.93**
AUC_{tot} ($\mu\text{g/ml h}$)	198.17 $\pm$ 14.49	256.83 $\pm$ 23.11**
$t_{1/2}$ (h)	6.13 $\pm$ 0.71	10.27 $\pm$ 2.49**
MRT (h)	10.84 $\pm$ 0.88	13.99 $\pm$ 2.55**
CL (ml/min)	306.23 $\pm$ 12.35	209.67 $\pm$ 8.98**
Vd (ml)	51.45 $\pm$ 7.56	31.43 $\pm$ 7.89**

All values are expressed as mean $\pm$ SD (n=6)

* $p < 0.05$; ** $p < 0.01$ considered as significant when compared with glimepiride control.

^aDefinitions of the parameters:

C_{max} : Peak serum concentration; **T_{max} :** Time to reach peak serum concentration; **AUC_{0-n} :** Area under serum concentration/time plot until the last quantifiable value; **AUC_{total} :** Area under serum concentration/time plot extrapolated to infinity; **$t_{1/2}$:** Terminal half life; **MRT:** Average mean residence time; **CL:** Total clearance; **Vd:** Volume of distribution.

Effect of curcumin on the hypoglycemic action of glimepiride

The mean serum glucose level and percentage glucose reduction determined in the antihyperglycemic study of pretreated diabetic rats is shown in Table 3. The data reveals that there is a maximum reduction of serum glucose level 56.57% in curcumin-glimepiride pretreated group, when compared to standard (glimepiride, 53.87%) and curcumin (45.21%) alone pretreated groups at 6th hr, respectively.

Effect on different biochemical parameters in STZ-induced diabetic rats

There was a gradual diminution in body weight of animals in diabetic control group. The animals of the curcumin, curcumin-glimepiride and standard drug treated groups showed a gradual and significant ($p < 0.01$) increase in the body weight from 7 days onwards. The increase in the body weight was observed till the end of the study (28 days). The significant ($p < 0.01$) effect of curcumin and curcumin-glimepiride on body weight of the animals was comparable to that of the standard drug, glimepiride at each time interval of the study (Figure 1).

The effect of the combination of curcumin-glimepiride in reducing the blood glucose levels was maximum after 28 days showing 57.5%. The antihyperglycemic effect of curcumin-glimepiride was comparable to that of the standard drug, glimepiride (51.2%) at all time intervals of the study. Curcumin (46.8%) alone treated group also showed significant ($p < 0.01$) effect in reduction of blood glucose levels and was 0.77 times less when compared with curcumin-glimepiride treated group (Figure 2).

Curcumin-glimepiride treated group shown significant effect ($p < 0.01$) in reducing serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) levels was maximum after 28 days showing 39.5% and 51.3% respectively and well comparable to that of the standard drug, glimepiride (29.2%, 26.5%). In curcumin alone pretreated group also found maximum diminution in serum GOT and GPT levels after 28 days showing 35.9% and 36.9%. The percentage reduction in serum GOT, GPT levels compared with the curcumin-glimepiride after 28 days was greater than that of the standard and curcumin alone treated groups (Figures 3 and 4).

The reduction in serum triglyceride level of curcumin-glimepiride treated group was 63.0%, while it was 51.4% for the standard group (glimepiride). For curcumin alone, the pretreated group also showed decreased serum triglyceride levels after 28 days, showing 58.9%. However, the percentage reduction in serum triglyceride levels compared with the curcumin-glimepiride after 28 days was greater than that of the standard drug and curcumin alone treated groups (Figure 5).

Table 3: Comparison of mean serum glucose levels and percentage reduction of serum glucose level of group II, group III and group IV with group I in STZ-induced diabetic rats

Group no	Treatment	Dose (mg/kg)	Blood glucose level (mg/dl) at different hours						
			0h	2h	4h	6h	8h	12h	24h
I	Control	---	441.02 ± 2.30	442.5 ± 2.48 (0.33%)	442.50 ± 0.86 (0.23%)	442.05 ± 3.92 (0.23%)	442.02 ± 2.10 (0.22%)	442.87 ± 2.28 (0.42%)	442.72 ± 2.51 (0.38%)
II	Glimepiride	1 mg/kg	463.7 ± 2.58	382.25 ± 4.40 (17.56%)**	298.58 ± 3.66 (35.6%)**	213.87 ± 4.92 (53.87%)**	315.08 ± 13.1 (32.05%)**	384.28 ± 33.17 (17.12%)**	434.58 ± 8.50 (6.2%)**
III	Curcumin	80 mg/kg	433.0 ± 1.65	355.43 ± 4.62 (17.91%)**	302.38 ± 5.19 (30.16%)**	237.23 ± 7.85 (45.21%)**	314.15 ± 5.71 (27.44%)**	396.91 ± 8.39 (8.3%)**	426.18 ± 4.43 (1.57%)*
IV	Curcumin + Glimepiride	80 mg/kg + 1 mg/kg	411.48 ± 2.39	327.13 ± 6.00 (20.49%)**	258.23 ± 5.92 (37.24%)**	178.68 ± 6.94 (56.57%)**	249.68 ± 6.60 (39.32%)**	302.10 ± 6.45 (26.58%)**	314.58 ± 9.06 (23.54%)**

All values are expressed as mean ± SD (n=6)

* $p < 0.05$; ** $p < 0.01$ considered as significant when compared with group I at respective time interval

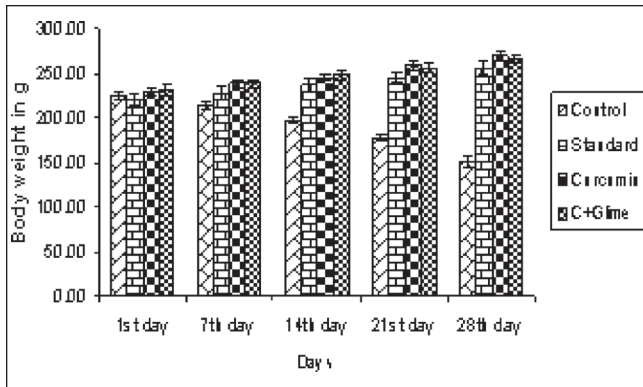


Figure 1: Effect of sub acute pretreatment of curcumin and glimepiride on body weights of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

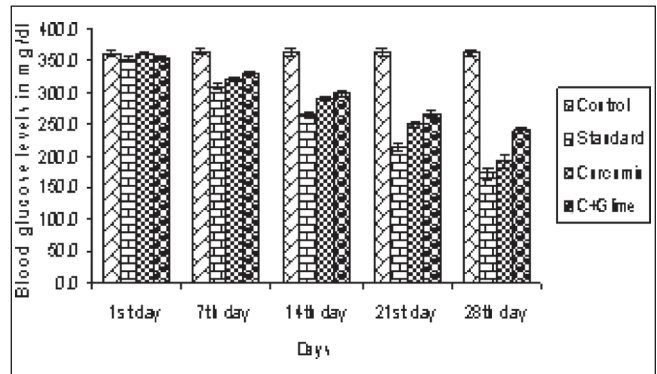


Figure 2: Effect of sub acute pretreatment of curcumin and glimepiride on blood glucose levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

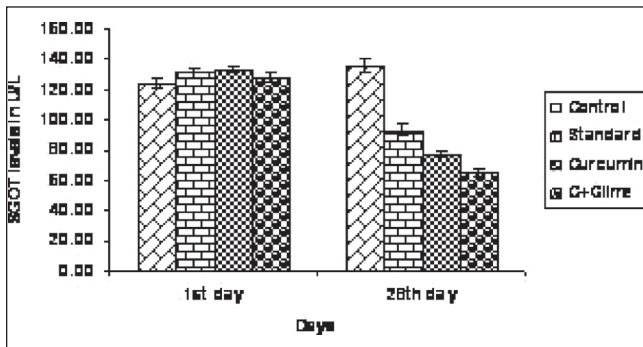


Figure 3: Effect of sub acute pretreatment of curcumin and glimepiride on SGOT levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

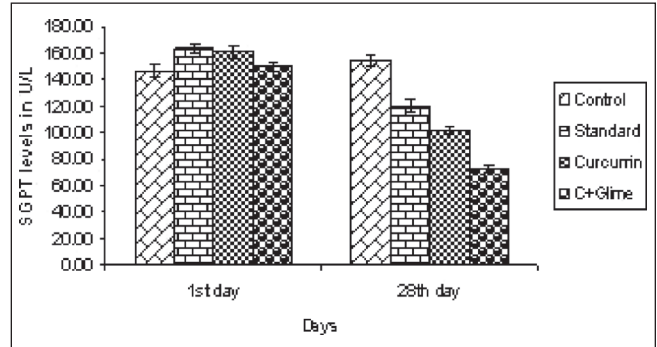


Figure 4: Effect of sub acute pretreatment of curcumin and glimepiride on SGPT levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

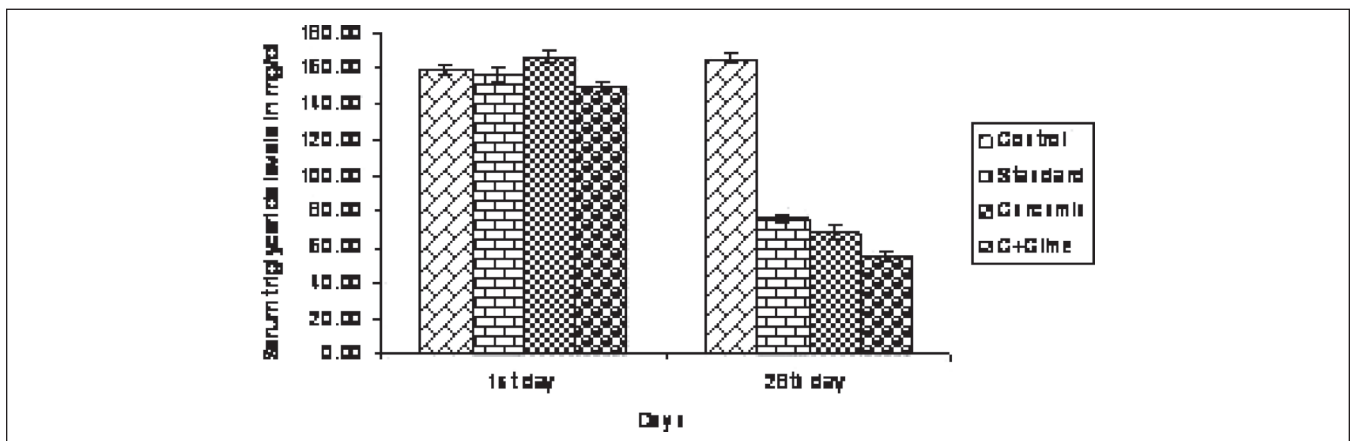


Figure 5: Effect of sub acute pretreatment of curcumin and glimepiride on serum triglyceride levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

The percent reduction in serum cholesterol levels of curcumin-glimepiride group was 59.8%, whereas it was 55.8% in standard group (glimepiride) and curcumin (57.8%) alone treated groups (Figure 6).

The effect of the curcumin-glimepiride treated group on serum total protein levels was maximum after 28 days,

showing a 78.13% increase. This was comparable to that of the standard (51.96%) and curcumin (69.6%) alone pretreated groups (Figure 7). The significant increasing effect ($p < 0.01$) of the curcumin-glimepiride group on serum insulin levels was maximum after 28 days showing 84.5%, was comparable to that of the standard glimepiride (55.4%) and curcumin (61.03%) alone pretreated groups (Figure 8).

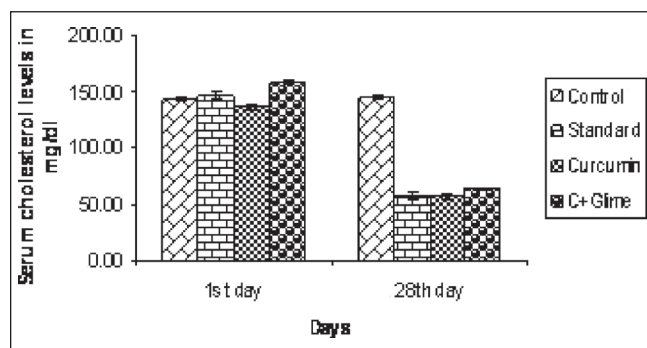


Figure 6: Effect of sub acute pretreatment of curcumin and glimepiride on serum cholesterol levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

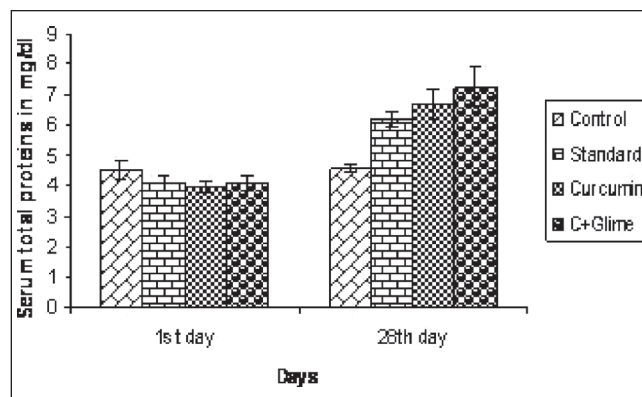


Figure 7: Effect of sub acute pretreatment of curcumin and glimepiride on serum total protein levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

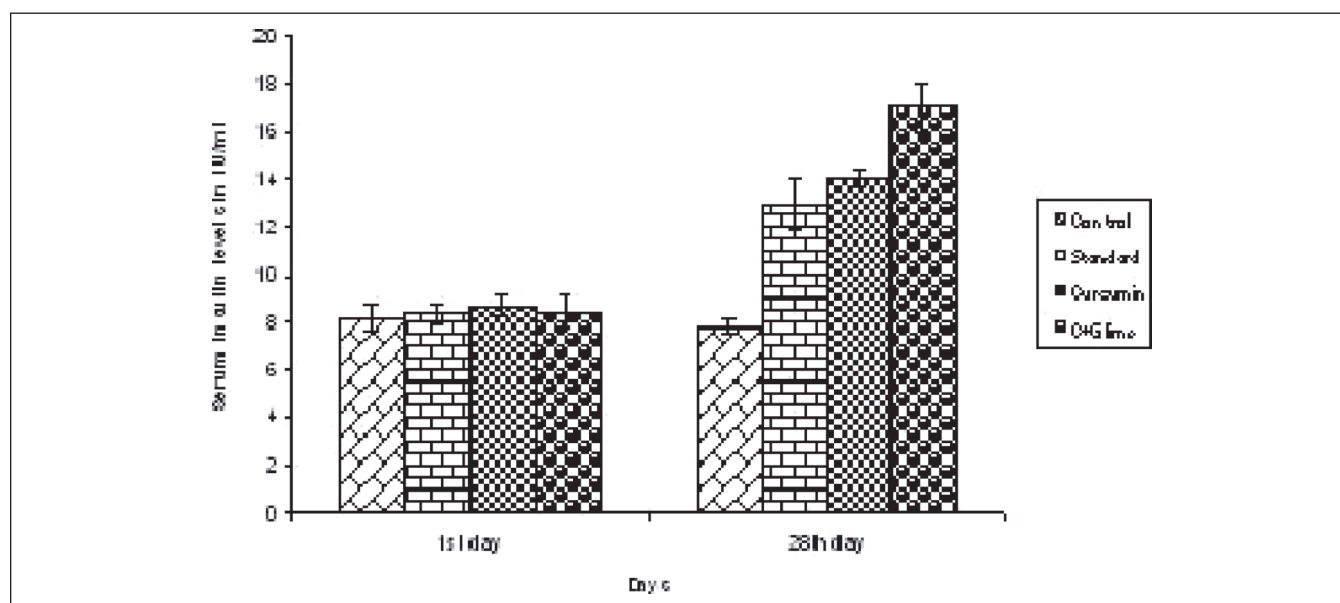


Figure 8: Effect of sub acute pretreatment of curcumin and glimepiride on serum insulin levels of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

Total antioxidant status of groups of diabetic rats

The serum total antioxidant status of the control, standard, curcumin-glimepiride and curcumin alone pretreated groups of diabetic rats are shown in Figure 9. The curcumin-glimepiride group gradually increased ($p < 0.01$) in total antioxidant status when compared with curcumin, glimepiride alone pretreated and with control group at all time intervals of the study.

DISCUSSION

In normal and STZ-induced diabetic rats, a combination of glimepiride with curcumin increased all the pharmacokinetic parameters including C_{max} , $AUC_{0 \text{ to } n}$, AUC_{total} , $t_{1/2}$ and MRT. This may be due to alteration in the metabolism of glimepiride, either by enhancing absorption or by inhibiting CYP2C9

which is responsible for glimepiride metabolism. In the curcumin treated group, there was no change in T'_{max} of glimepiride in both normal and diabetic rats, indicating that there is no alteration in rate of absorption of glimepiride and the serum affinity of glimepiride for albumin is 99.5% bound. Acidic drugs can displace ionic binding of sulfonylureas from serum proteins to a far greater extent than the non-ionic bound glimepiride.^[14] This indicates that the decreased volume of distribution may not be due to displacement of glimepiride by curcumin. The decreased volume of distribution may be due to metabolic inhibition of glimepiride by curcumin. This metabolic inhibition decreases metabolic clearance of glimepiride and the decreased metabolic clearance may leads to the decreased total clearance. The present investigations are in accordance with the earlier *in-vitro* studies of curcumin metabolic inhibition on CYP2C9 enzyme in human liver microsomes.^[15-17]

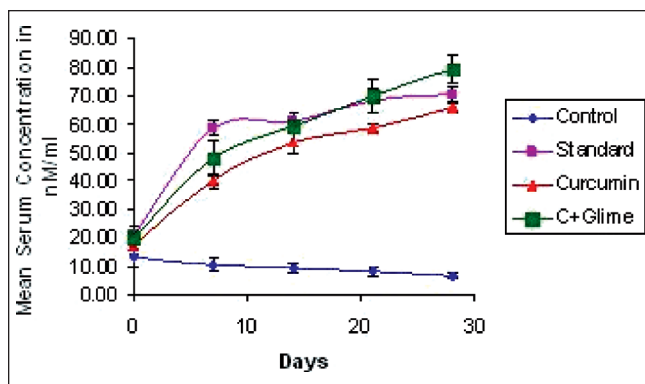


Figure 9: Effect of sub acute pretreatment of curcumin and glimepiride on total antioxidant status of STZ-induced diabetic rats. All values are expressed as mean $\pm$ SD (n=6).

The hypoglycemic effect of concomitant administration of glimepiride with curcumin was more in diabetic rats compared to alone the treatment with single drugs, and with control group in antihyperglycemic study. This suggests that there is an enhancement of glucose reduction capacity of glimepiride with curcumin in diabetic rats. In the sub acute study, the concomitant administration of curcumin with glimepiride produced more beneficial changes on body weight and serum biochemical parameters in STZ-induced diabetic rats when compared with glimepiride, curcumin alone treated groups and control group. A significant improvement in body weight indicates the ability of combination of drugs and individual drugs to prevent loss of body weight in diabetic rats. It reveals that these drugs do not have any effect on degradation of depot fat to maintain the body weight.^[18] Combination of glimepiride with curcumin and curcumin alone pretreated groups reduced significantly ($p < 0.01$) the blood glucose levels after 7 days to till the end of the study (28 days). This phenomenon clearly indicates that these drugs in combination control the hyperglycemic state of type 2 diabetes more effectively than alone treated drugs. The significant ($p < 0.01$) reduction in SGOT and SGPT levels further strengthens the antidiabetogenic effect because increased gluconeogenesis and ketogenesis occur in diabetes, which may be due to high levels of SGOT and SGPT.^[19] Combination of curcumin with glimepiride exhibited more antihypertriglyceridemic and antihypercholesterolemic activity than the curcumin alone pretreated groups and with control group. Further, the increased serum total protein level brought out by these drugs explains its antidiabetogenic effect as the reduction in protein level takes place in diabetes due to deficiency of insulin, which stimulates uptake of aminoacids into muscle and increases protein synthesis.^[20] The significant ($p < 0.01$) increase in serum insulin levels after 28 days of the study indicates that curcumin might have exhibited the antihyperglycemic effect like glimepiride, i.e. by insulin secretagogue activity.^[21]

The serum total antioxidant status data suggests that the pretreatment of diabetic rats with curcumin alone leads to a significant increase in free radical scavenging capacity when compared to control group. However the total antioxidant status of rats pretreated with curcumin-glimepiride was maximum when compared with the rats pretreated with curcumin alone. This suggests that the combination of these drugs may stimulate the antioxidant mechanisms and interfere with pharmacokinetics and pharmacodynamics.

CONCLUSION

The present study indicated that curcumin affects the metabolism of glimepiride in STZ-induced diabetic rats, possibly by the inhibition of CYP2C9. The combination of glimepiride with curcumin considerably enhances the glucose-lowering effect of glimepiride. Hence, glimepiride doses may require special attention if used along with curcumin containing herbal preparations to avoid the complications.

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