

Pharmacokinetic and Pharmacodynamics Interaction between *Syzygium cumini* and Glipizide: Role of Cytochrome P450 Enzyme

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ABSTRACT

Background: Concomitant administration of herbs and synthetic drugs causes pharmacokinetic and pharmacodynamic interactions. **Objectives:** To investigate pharmacokinetic and pharmacodynamic interactions between *Syzygium cumini* (*S. cumini*, SC) and Glipizide (GZ) and the role of cytochrome P450 (CYP) enzymes in interaction. **Methods:** The effect of the aqueous seed extract of *S. cumini* (50 and 100 µg) on CYP3A was studied using *in vitro* liver microsomes. The interaction of GZ, a second-generation sulphonylurea, with *S. cumini* was examined in Sprague Dawley rats with type 2 diabetes induced through the administration of a high-fat diet, followed by Streptozotocin (STZ) injection. We administered 5mg/kg GZ and 250 and 400 mg/kg *S. cumini* seeds aqueous extract orally. Pharmacodynamic parameters were evaluated by analysing blood glucose, Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) and Alkaline Phosphatase (ALP) levels and by conducting the oral glucose tolerance test. The pharmacokinetics of GZ in combination with *S. cumini* was studied on the 14th day of treatment. Plasma levels were determined through LCMS at various time points (1, 2, 4, 8 and 12 hr after oral administration). **Results:** The hypoglycaemic effect exerted by the combination of GZ and *S. cumini* was significantly higher than that exerted by GZ and *S. cumini* administered alone but not below the normal level. Treatment with GZ and *S. cumini* caused a significant change in ALT and ALP levels compared with treatment with GZ alone. Pre-treatment with *S. cumini* increased the AUC of GZ, which could be due to CYP3A inhibition observed in *in-vitro* analysis. **Conclusion:** Pharmacokinetic and pharmacodynamic interactions occur between *S. cumini* and GZ.

Key words: Herb–drug interactions, Type 2 diabetes mellitus, Pharmacokinetics, LCMS, CYP3A.

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INTRODUCTION

The increasing use of herbal medicinal products in community settings in which allopathic medicine use is common may lead to serious concerns, because nearly all herbal remedies contain multiple, biologically active constituents that may interact with conventional drugs and cause adverse side effects.¹⁻³ Many consumers believe that herbal medicines are natural and are thus safe; however, this is a dangerous over simplification. Some herbal medicines can result in undesirable effects,

which include interactions with prescribed drugs.¹⁻¹¹ A recent survey indicated that 15% of patients who receive conventional pharmacotherapy also use herbal products and potential adverse herb–drug interactions were observed in 40% of these patients.¹² In polypharmacy, determining the prevalence and rate of occurrence of drug interactions is crucial, because these interactions can have serious implications for hospitalised patients. In addition, it is important to identify and detect the major agents in herbal



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products that cause unsafe and harmful interactions.¹³ Interaction of herbs with drugs is well known. Both pharmacokinetic and pharmacodynamic interactions have been reported. Pharmacodynamic interactions between drugs and herbal medicines may be attributed to an additive or synergistic effect, which can result in enhanced effects or toxicity, or to herbal medicines' antagonistic properties, which may reduce drug efficacy and cause therapeutic failure. Pharmacokinetic interactions lead to changes in the absorption, distribution, metabolism and excretion of prescribed drugs. Many drugs, such as drugs that are the substrates of Cytochrome P450 (CYP) enzymes, particularly CYP3A4 and CYP2C9, have been reported to interact with herbs. These enzymes are induced or inhibited by some routinely used herbal medicines. Accordingly, some herbal–drug interactions were reported to be mediated by CYP modulation, resulting in altered drug clearance and therapeutic effects.¹⁴ Glipizide (GZ) is a highly potent second-generation sulphonylurea derivative used to control type II diabetes mellitus. GZ is extensively metabolised in the liver by CYP2C9 and CYP3A4.^{15–19} *Syzygium cumini* (L.) (SC) Skeels (family: *Myrtaceae*) is a herbal drug widely used to treat diabetic conditions and is officially included in The Ayurvedic Pharmacopoeia of India.²⁰ Jamboline, a glycoside present in the seed of SC, is considered to have antidiabetic properties.²¹ The seed extract of *Eugenia jambolana* can reduce blood glucose and glycosylated haemoglobin levels and increase the plasma insulin level.²² The present study examined the effects of the aqueous seed extract of SC on the pharmacokinetics and pharmacodynamics of GZ.

MATERIALS AND METHODS

Chemicals

We purchased glucose (Nice Chemicals Pvt. Ltd., Cochin, India); GZ (Supra Chemicals, Mumbai, India); serum AST, ALT and ALP estimation kits (Randox, Mumbai, India); and streptozotocin (STZ; HiMedia Laboratories Pvt. Ltd., Mumbai, India).

In vitro assessment of CYP3A activity in liver microsomes

After overnight fasting, rats were euthanised and their livers were perfused with 10mL of 0.1M Phosphate-buffered Saline (PBS) and were then isolated. The liver microsomes Preparation was performed as per the method of Chaudhari *et al.*^{23–25}

Erythromycin-N-demethylation assay

Estimation of CYP3A enzyme was optimised by incubating at 5%, 10% 20% and 25% of liver microsome in triplicate. Suspension is incubated with 25µg, 50µg and 100µg in duplicate for selection of concentration of extract. The reaction between these agents was initiated by adding NADPH (0.1mL, 10mM) and terminated after 10 min by adding ice-cold trichloroacetic acid (0.5 mL, 12.5%, w/v) solution. The mixture was then centrifuged (at 2000×g for 10 min) to remove proteins. Subsequently, 1.0mL of Nash reagent (2M ammonium acetate, 0.05 M glacial acetic acid and 0.02 Macetylacetonone) was added to 1.0mL of the supernatant; this mixture was heated in a water bath at 50°C for 30 min. After cooling, absorbance was read at 412nm.

After stabilisation of method a mixture of microsomal suspension (0.1mL, 25%), erythromycin (0.1mL, 10 mM) and potassium phosphate (0.6mL, 100mM, pH7.4) was incubated at 37°C with 0.1mL suspensions containing 50 and 100 µg of SC; Tween 20 (0.1mL, 1%) was used as a negative control and ketoconazole (0.1mL, 5µM) was used as a positive control. The reaction is initiated and the absorbance was read at 412nm.²⁶

CYP3A activity was calculated using standards (1–100 mM formaldehyde) prepared by substituting a sample with a standard solution, which were run in parallel. CYP3A activity is expressed as nM of formaldehyde (CHO) obtained per milligram of protein per hour and was calculated using the following formula:

$$\text{CYP3A activity} = \text{Amount of CHO produced (n/mol)} \times 1/25\text{mg of protein} \times 1/10 \text{ min}$$

Experimental animals

The experimental protocol performed on adult male Sprague–Dawley rats (weighing 180–250g) was approved by the institutional animal ethics committee and animals were maintained under standard conditions (a temperature of 22°C±2°C and a relative humidity of 60% ± 5%) in an animal house approved by the Committee for the Purpose of Control and Supervision on Experiments on Animals (879/PO/Re/s/05/CPCSEA).

Diabetes induced in rats through high-fat diet feeding and STZ administration

Diabetes was induced in adult Sprague–Dawley albino rats through administration of a high-fat diet for 2 weeks, followed by a single intraperitoneal injection of STZ (33mg/kg) in 0.1M citrate buffer (pH 4.5) to overnight-fasted rats (Figure 1). STZ-injected rats were allowed to drink 20% glucose solution to prevent STZ-induced hypoglycaemic mortality. The threshold level

of fasting blood glucose for diagnosing diabetes was set as >200 mg/dL. Animals received drug treatment for 14 days after diabetes induction.^{25,27}

Treatment

Animals were divided into six groups ($n=6$ in each group):

Group I: Vehicle (1 mL/kg, p.o.)

Group II: GZ (5 mg/kg, p.o.)

Group III: SC (250 mg/kg, p.o.) (SC 250)

Group IV: SC (400 mg/kg, p.o.) (SC 400)

Group V: SC (250 mg/kg, p.o.) + GZ (5 mg/kg, p.o.) (SC 250 + GZ)

Group VI: SC (400 mg/kg, p.o.) + GZ (5 mg/kg, p.o.) (SC 400 + GZ)

The seed extract of *S. cumini* was dissolved in 0.2% CMC for administration. To prevent any physicochemical effect on GZ absorption, GZ was administered to all animals an hour later after SC administration through gavage.

Pharmacodynamic assessment

Blood glucose, AST, ALT and ALP levels were determined on the 14th day of drug treatment by collecting blood samples from the retro-orbital sinus under anaesthesia.

Pharmacokinetic Assessment

Plasma samples were collected after treatment with GZ at 1, 2, 4, 8 and 12 hr 10% of total blood volume was withdrawn. Plasma samples preparation and LCMS analysis of these samples was performed (SI-CART Labs, Gujarat, India) as per the method Chaudhari *et al.*²⁵ The blood was mixed with a required amount of anti-coagulant (3.8% sodium citrate) and centrifuged at $3,000 \times g$ for 7 min to collect the plasma and stored at -20°C for quantification of GZ by LC-MS. In 500ul plasma 2ml of ethyl acetate was added. After 2 min centrifugation, upper layer in the test tube was evaporated to dryness in nitrogen dryer. 1ml acetonitrile was added

and 100 μl of this solution injected in LC-MS. 10mM Ammonium Acetate pH-3.0: Acetonitrile (40:60) was selected as a mobile phase. A 100 μl aliquot of sample was injected into a reverse phase C₁₈ Phenomenex column (250mm \times 4.6mm i.d., 5 μm) pumped with the assigned mobile phase at a flow rate of 1ml/min. The observed peaks were well resolved and therefore the modified method was adopted for quantification of GZ in rat plasma.

Oral glucose tolerance test

The Oral Glucose Tolerance Test (OGTT) was performed in overnight-fasted rats. Glucose (2g/kg p.o.) was fed 30 min after the administration of drugs. Blood samples were collected from the retro-orbital sinus under anaesthesia after 0, 30, 60 and 120 min of glucose administration and serum glucose levels were determined.^{28,29}

Statistical analysis

Results are expressed as mean \pm S.E.M. Statistical significance was determined using one-way analysis of variance, followed by Dunnett's test.

RESULTS

In-vitro assessment of CYP3A activity

Effect of SC seed extract on liver microsomes

The *in vitro* effect of the SC seed extract on CYP3A activity in the liver is presented in Figure 2. We found that 50 μg of the extract did not significantly reduce CYP3A activity, whereas 100 μg of the extract significantly inhibited CYP3A enzyme activity ($p<0.001$), similar to 5 μM ketoconazole.

Assessment of in vivo CYP3A activity

The effect of 250 and 400mg/kg SC on the pharmacokinetic parameters of GZ after 14 days of treatment is presented in Table 1. Compared with treatment with GZ alone, pre-treatment with 250 and 400mg/kg SC resulted in a significant increase in C_{max} ($p<0.001$), AUC ($p<0.05$) and $T_{1/2}$ ($p<0.01$) of GZ but no significant change in Mean Residential Time (MRT).

Effect of seed extract of *S. cumini* on the blood glucose level of STZ-induced diabetic rats

The blood glucose level was recorded 1, 2, 4 and 8 hr after treatment with GZ. SC oral administration at 250 and 400 mg/kg for 14 days caused a significant ($p<0.001$) hypoglycaemic effect. SC250+GZ has SC400+GZ shown a significant ($P<0.05$) decrease in blood glucose level at 1 hr with SC 250+GZ as well as at 8 hr with SC250+GZ ($P<0.05$) and SC400+GZ ($P<0.01$) when

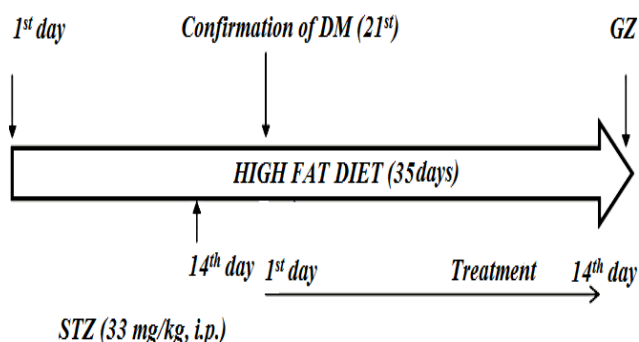


Figure 1: Schematic representation of the experimental.

compared to glipizide alone. In addition, administration of GZ (5mg/kg) for 14 days caused a significant reduction ($p < 0.001$) in the blood glucose level of STZ-diabetic rats compared with diabetic untreated rats (Figure 3).

Effect of seed extract of *S. cumini* on the OGTT

The treatments with GZ in combination with SC resulted in a significant decrease in the serum glucose level compared with the control treatment. The com-

bination of both doses of SC with GZ caused a significant decrease in serum glucose levels compared with GZ alone (Figure 4).

Effect seed extract of *S. cumini* on ALP, AST and ALT levels

The effects of SC alone as well as in combination with GZ on the serum AST, ALT and ALP levels of rats in all treatment groups are shown in Figure 5. SC in combination with GZ caused a dose-dependent significant ($p < 0.001$) reduction in the AST level. Compared with

Table 1: Pharmacokinetic parameters of Glipizide in *S. cumini* pre-treated rats.

Parameter	Glipizide control	SC250+GZ	SC400+GZ
C_{max} (ng/ml)	77.96±4.26	113.6±11.65 *	164.2±6.11***
AUC_{0-t} (ng /ml*h)	570.82±10.38	576.98±33.21	907.73±14.78***
$T_{1/2}$ (h)	2.56±0.16	2.16±0.05	3.46±0.07**
T_{max} (h)	4±0	4±0	4±0
MRT (h)	6.41±0.09	5.6±0.11	6.95±0.11

C_{max} : peak plasma concentration; AUC : area under the plasma concentration curve; $T_{1/2}$: half-life; T_{max} : time to reach C_{max} ; MRT: mean residence time. All values are standard error mean. a $P < 0.05$, b $P < 0.02$, c $P < 0.002$ when compared with Glipizide group (one-way ANOVA followed by Dunnett post hoc test) (n=3)

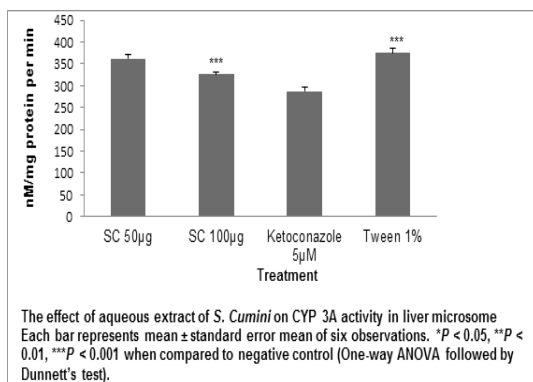


Figure 2: The effect of aqueous extract of *S. cumini* on CYP 3A activity in liver microsome

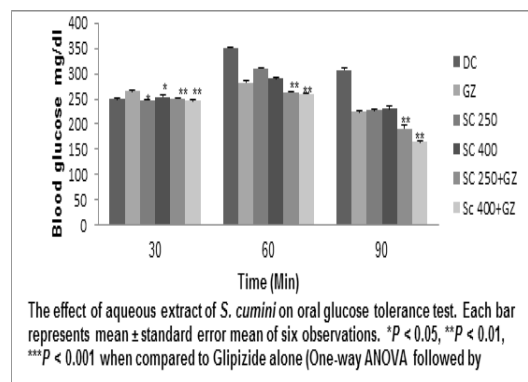


Figure 4: The effect of aqueous extract of *S. cumini* on oral glucose tolerance test.

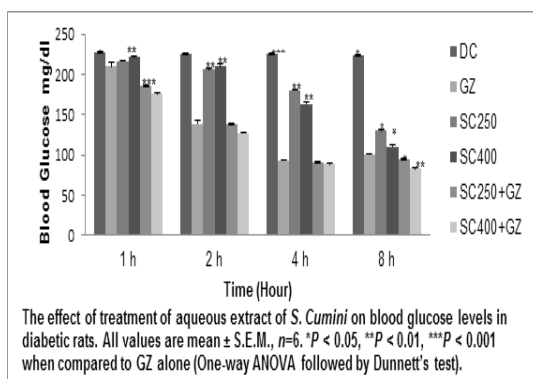


Figure 3: The effect of treatment of aqueous extract of *S. cumini* on blood glucose levels in diabetic rats.

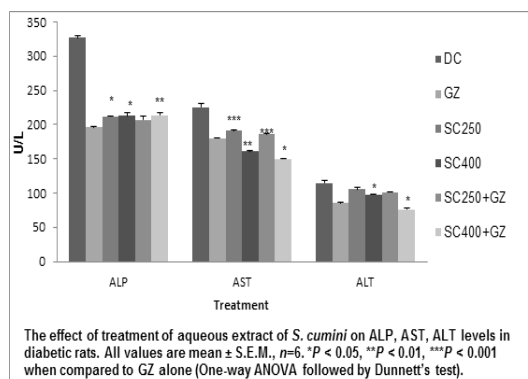


Figure 5: The effect of treatment of aqueous extract of *S. cumini* on ALP, AST, ALT levels in diabetic rats.

GZ alone, the ALT level was significantly reduced by 400 mg/kg SC in combination with GZ. Furthermore, compared with GZ alone, 400 mg/kg SC in combination with GZ resulted in a significant ($p < 0.01$) reduction in the ALP level (Figure 5).

DISCUSSION

The use of complementary therapies for the treatment of diabetes is ever increasing and often remains unnoticed by physicians.³⁰ Because most clinically used drugs are metabolised by CYP enzymes, changes in CYP activity initiated by herbal medications can alter the pharmacokinetics of co-administered drugs. This can subsequently reduce the pharmacological effects of co-administered drugs or cause toxicity.³¹ In the present study, the pharmacokinetic profile of GZ was evaluated considering that GZ is a substrate of CYP3A. We investigated the effect of SC on erythromycin-N-demethylation, which is an indicator of CYP3A activity, by using liver microsomes. The SC extract exhibited dose-dependent inhibitory effects on liver CYP3A. Ketoconazole was used as the reference standard in this study because of its reported *in vitro* and *in vivo* inhibitory effects on CYP4503A activity.³² Treatment with 250 and 400 mg/kg SC for 2 weeks altered the pharmacokinetic parameters of GZ. The plasma concentration (ng/mL)–time profile of GZ orally administered after SC administration increased. CYP3A inhibition through SC pre-treatment led to an increase in the C_{max} and AUC of GZ in diabetic rats. Pre-treatment with SC also increased the half-life compared with the administration of GZ alone, confirming the occurrence of interaction between SC and GZ during metabolism. In previous studies, the aqueous seed extract of SC exerted a hypoglycaemic effect on STZ-induced diabetic rats.^{33,34} The seeds of SC contain glucosides, jamboline and ellagic acid, which have the ability to control the conversion of starch into sugar in case of excess production of glucose.³⁵ In the present study, compared with GZ alone, both 250 and 400 mg/kg doses of SC in combination with GZ caused a significant decrease in the blood glucose level but no hypoglycaemia. In the OGTT test, 250 and 400 mg/kg SC in combination with GZ resulted in a significant decrease in the blood glucose level. A high plasma GZ level due to pre-treatment with the SC seed extract might have shown significant alteration in glucose level in presence of combination of GZ with SC. SC seeds possess antioxidant properties.³⁶ Treatment with 400 mg/kg SC in combination with GZ reduced the elevated AST and ALT levels in diabetic rats compared with diabetic control rats, thereby suggesting beneficial effects of SC on altered liver function in diabetes. The results

of the present study demonstrated that aqueous extract of seeds of SC interact with GZ through CYP3A inhibition by enhancing the systemic bioavailability of GZ.

CONCLUSION

The results of *in vitro* and *in vivo* studies indicated that drug interactions occurred after the co-administration of the SC extract with the CYP3A substrate agent GZ. This pharmacokinetic interaction caused a significant increase in the GZ level, resulting in pharmacodynamic interactions. Therefore, future studies should isolate different constituents of the seed extract of SC and examine their interaction with GZ.

ACKNOWLEDGEMENT

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ABBREVIATIONS

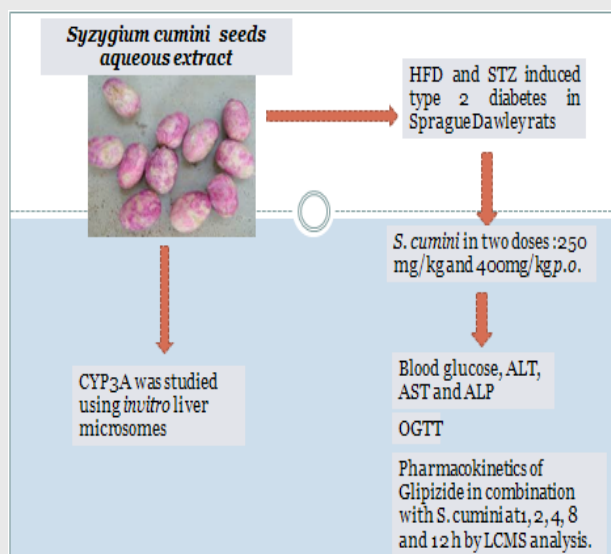
ALT: Alanine aminotransferase; **ALP:** Alkaline Phosphatase; **AUC:** Area under Curve; **AST:** Aspartate aminotransferase; **C_{max} :** Maximum Measured Blood Concentration; **$T_{1/2}$:** Terminal Elimination Half-Life; **T_{max} :** Time of Maximum Measured Plasma Concentration.

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PICTORIAL ABSTRACT



SUMMARY

The use of complementary therapies for the treatment of diabetes is ever increasing and often remains unnoticed by a physician. In present study glipizide pharmacodynamic and pharmacokinetic alteration was studied in combination with *Syzygium cumini*. Inhibition of CYP3A activity in *in-vitro* analysis on liver microsomes was obtained due to *S. cumini*. In high fat diet and STZ induced diabetic model, the hypoglycaemic effect observed with combination of glipizide and *S. cumini* was significantly high as compared to either of the drugs given alone but was not below the normal level. There was a significant decrease in ALT and ALP level compared to glipizide alone. *S. cumini* pre-treatment shown significant increase in AUC of glipizide, which could be due to CYP3A inhibition observed in *in-vitro* analysis. Data revealed that there was a pharmacokinetic and pharmacodynamic interaction between *S. cumini* with glipizide.

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