

An *in-vivo* herb-drug interaction study of *Tinospora cordifolia* extract on the pharmacokinetics of gliclazide in normal Wistar rats

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ABSTRACT

Background and Aims: *Tinospora cordifolia* (Willd.) Miers (TC), from the *Menispermaceae* family, is a well-known traditional herb used to treat diabetes mellitus and a variety of other ailments, according to traditional Indian literature. Herbal treatments are commonly used as alternatives to medicines. Anti-diabetic herbal medicines containing TC are available in the market. TC has been identified as a powerful CYP2C9 inhibitor, boosting the risk of herb-drug interactions (HDI) when used with medications metabolized via the CYP pathway. The present study evaluated the pharmacokinetic HDI of TC extract with Gliclazide (GL) after oral co-administration in Wistar rats using *in vivo* pharmacokinetic studies.

Methods: A simple, sensitive & accurate RP-HPLC/PDA method was developed and validated. Chromatographic separations were performed on a C₁₈ analytical column with a mobile phase of acetonitrile and 40 mM ammonium acetate buffer (55:45 v/v) pH 3.0 and flow rate gradient programming. The drug concentrations in plasma were measured using the RP-HPLC method after oral co-administration of TC extract (100 mg/kg) with GL (8.3 mg/kg) in Wistar rats.

Results: The pharmacokinetic (PK) interaction studies showed that the bioavailability of GL had significantly increased, with a significant influence on C_{max}, AUC₀₋₄₈, and suppression of volume of distribution (V_d), with no change in T_{max}.

Conclusion: The results obtained from this *in vivo* study proposed that there is a potentially significant PK HDI when GL and TC extract are administered together. This knowledge of potential HDI could be beneficial to healthcare providers and diabetic patients on GL medication. Further research is needed to anticipate this pharmacokinetics HDI of GL in humans.

Keywords: Gliclazide, *Tinospora cordifolia*, Herb-drug interaction, RP-HPLC, Pharmacokinetic

INTRODUCTION

Herbal medicines are now widely used by patients worldwide to treat a wide range of conditions (particularly chronic illnesses that necessitate long-term care) in addition to traditional allopathic drugs. This increases the risk of herb-drug interactions (HDIs), which can have additive, synergistic and antagonistic effects, sometimes resulting in catastrophic clinical outcomes (Fugh-Berman & Ernst, 2001; Hu et al., 2005; Posadzki Watson & Ernst, 2013). Cytochrome P450 (CYP450)-mediated inhibition or induction, as well as transport and efflux proteins are among the key routes postulated for HDIs (Shaikh, Thomas & Chitlange, 2020). Due to the complexity of the herbs used and their ability to modulate multiple targets, the study of HDIs remains a major problem when compared to reporting of drug-drug interactions (Tsai, Lin, Simon Pickard, Tsai & Mahady, 2012; Wills, Bone & Morgan, 2000; Brant-

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ley, Argikar, Lin, Nagar & Paine, 2014). However, if these studies are carried out early in the development of herbal medicine, they can reduce the possibility of HDIs and promote the possibility of using any synergism that might be discovered for drug dose reduction and combination therapy promotion (Prabhakara & Doble, 2008).

Tinospora cordifolia (TC), also known as Guduchi, belongs to the *Menispermaceae* family and exhibits a variety of pharmacological actions including anti-diabetic, hypo-lipidemic, cardiotoxic, anti-oxidant, anti-inflammatory, and anti-neoplastic properties (Meshram, Bhagyawant, Gautam & Srivastava, 2013). Tinosporone, tinosporaside, tinocordifolioside, and tinosporic acid, as well as berberine, tembetarine, palmatine, magnoflorine, cordifoliosides A to E, syringen, and sitosterol, are some of the key phytoconstituents of TC. Tinosporine, tinosporide, cordifolide, cordifole, and columbinare the phytoconstituents that help to control cholesterol production and glycolysis (Thikekar, Thomas & Chitlange 2021). Berberine is the major active phytoconstituent and was found to inhibit 50% of CYP2C9 activity in a study conducted by Chatterjee *et al.*, 2003. at a concentration of 500 mM According to Singh *et al.*, 2006 TC has the ability to stimulate carcinogen/drug metabolism and antioxidant system enzymes, inhibiting lipid peroxidation in mice, further proving its CYP interaction potential. Similarly, in a study performed by Bahadur *et al.*, 2016 using particular high-throughput screening assays, the researchers revealed that TC inhibits CYP3A4, CYP2D9, CYP29, and CYP1A2 with IC₅₀ values of 136.45, 144.37, 127.55, and 141.82 g/mL, respectively. According to Sahu *et al.*, 2018 the co-administration of TC extract with glibenclamide resulted in higher C_{max}, T_{max}, increased bioavailability (AUC), and decreased glibenclamide clearance (Cl). TC showed potent inhibition of CYP2C9 activity in CYP inhibition assay. This study postulates that concomitant administration of TC extract/preparations containing TC with glibenclamide (metabolized by the CYP2C9 enzyme) can result in significant HDI. The *in vivo* PK study performed in rats by Asha Thomas *et al.*, 2020 strongly suggested the increase in bioavailability of glimepiride and significant alteration of its PK parameters (increase in C_{max}, AUC₀₋₂₄ and MRT₀₋₂₄ with a decrease in V_d and CL) indicating the potential HDI of glimepiride when administered concomitantly with TC extract via the oral route. Also, an *in silico* molecular docking study using CYP2C9 (PDB ID: 1R90) as the target protein and phytoconstituents (isoquinoline alkaloids) of TC, strongly supported the HDI of glimepiride and TC and demonstrated that berberine and accompanying alkaloidal components in TC extract have a good inhibitory potential against CYP2C9.

Gliclazide 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-(p-tolylsulfonyl) urea is a second-generation sulfonylurea used to treat diabetes mellitus type 2, it works as an insulin secretagogue which stimulates pancreatic cells to secrete insulin. It is completely absorbed and has oral bioavailability of 97 % as gastrointestinal absorption is complete with no interference from meals & absence of pre-systemic hepatic metabolism (Sarkar, Tiwari, Bhasin & Mitra, 2011). GL primarily undergoes oxidative biotransformation by means of CYP2C9, and forms methyl hydroxyl gliclazide and 6β-hydroxy gliclazide metabolites in the liver (Yao *et al.*, 2009). A review of

the literature reveals that various methods for GL bioanalysis have been documented. Chien *et al.* reported GL measurement in rat plasma using HPLC with 70mM disodium tetraborate, pH 7.5, and 26.5 percent acetonitrile as mobile phase (Kuo & Wu, 2005). Lopamudra *et al.*, 2014 performed the HPLC analysis of GL in rat plasma using methanol:acetonitrile:water (60:20:15, v/v) as mobile phase. Xu *et al.*, 2008 reported a LC-MS technique for the estimation of GL in rat plasma employing acetonitrile and 40 mM KH₂PO₄ (pH 4.6, 56%) and acetonitrile (44%).

In the present study an effort was made to employ existing LC methods to evaluate plasma levels of GL in rat plasma following a PK based HDI study involving TC extract. But due to the presence of matrix interferences both from plasma and TC extract, the reported methods were not able to effectively estimate GL. For this reason, there was a need to develop a suitable bioanalytical RP-HPLC/PDA method for the estimation of GL in rat plasma and to validate it as per US-FDA guidelines for HDI study.

MATERIAL AND METHODS

Chemicals and reagents

Gliclazide (GL) and Glimepiride (IS) were obtained as a gift sample from Sava Healthcare Ltd, Pune, India. Merck Chemicals in Mumbai, India, supplied HPLC grade acetonitrile. Millipore water filtration technology was used to prepare the distilled water (Millipore, Sigma). All other reagents were of analytical grade.

Plant extract

TC extract was supplied as a gift sample by Kisalaya Herbal Ltd., Indore, India.

A phytochemical analysis revealed the description (free flowing brown powder with a bitter taste), identification test was positive for bitters, solubility in water: 85.6 %, in 50 v/vethanol: 64.6%, pH of 1% solution (5.11), test for heavy metals: arsenic (0.35 ppm), lead (1.47 ppm), mercury and cadmium (not detected); total ash (5.46%), acid insoluble ash (0.38%), moisture content (3.52 %) and microbiological analysis were within specified limits. The extract contained 3.87 % w/w bitters. For HPTLC fingerprinting of TC extract, the mobile phase used was chloroform: methanol: water (8:2:0.2 v/v/v), and densitometric measurements were performed at 366 nm (Fig 1) (Choudhary, Siddiqui & Khatoun, 2014).

Reverse Phase - High Performance Liquid Chromatography RP-HPLC method and validation

The Shimadzu (LC20AD) HPLC system (Kyoto, Japan) composed of a quaternary pump, manual rheodyne injector with 20μL fixed loop along with the photodiode array (PDA) detector were used for the study. LC solution software was used for processing of data. A Kromasil 100 C₁₈ analytical column (250 mmx4.6 mmx5 μm) was used for chromatographic separations. Mixtures of different solvents with variable polarity and different gradients were employed to find the best chromatographic conditions for generating sharp and well-resolved GL (API) and glimepiride (IS) peaks with minimal tailing. After numerous variations and combinations, in comparison to other mobile phases, it was observed that the mixture of acetonitrile (ACN) and 40mM am-

monium acetate buffer pH 3.0 gave acceptable results. Finally, ACN: 40mM ammonium acetate buffer pH 3.0 adjusted with 1% ortho-phosphoric acid (55:45 v/v) was selected as the mobile phase. The flow rate gradient was set to 0.8 mL/min from 0 to 2 minutes and 1.0 mL/min from 2 to 20 minutes. At 228 nm, the chromatogram was measured. The optimized RP-HPLC/PDA method was validated as per the USFDA bioanalytical method validation guidelines for industry (FDA, 2018).

Animals

The Institutional Animal Ethics Committee (DYPIPSR/IAEC/19-20/P-29), Pune, India, approved the experimental protocol. Wistar rats (Crystal Biological Solutions, Pune, India) with body weights ranging between 250 and 300 g, aged between 6 and 7 weeks were used in this study. The animals were housed in polypropylene cages with solid bottoms and bedding made of autoclaved clean rice husk. The temperature was kept at 22–23°C with a relative humidity of 30–70 % and a 12 hours light/dark cycle with a minimum of 15 air changes *per* hour. All animals were acclimatized to laboratory settings one week previous to the commencement of the experiment. The animals were fasted overnight before the research began but were given *water ad libitum*.

Preparation of calibration standard and quality control standards

Standard stock solutions of GL and IS (100 µg/mL) were prepared separately and subsequently diluted with ACN to obtain working standard solutions of GL (0.5 µg/mL to 32 µg/mL) and IS (50 µg/mL) respectively.

The calibration control standards (CC) of GL-50 ng/mL to 3200 ng/mL and IS-5 µg/mL were prepared by suitably spiking 100 µL of drug free rat plasma with a fixed volume of working standards of GL (100 µL each) and IS respectively. The Quality Control standards (QC); Lower Quality Control (LQC) 150 ng/mL, Middle Quality Control (MQC) 1600 ng/mL and Higher Quality Control (HQC) 2560 ng/mL standards were also prepared.

Extraction procedure

A volume of 0.3 mL of blood from the retro-orbital plexus was collected in Eppendorf tubes (using Gilson micropipettes, P.R. Corporation, Mumbai, India) containing 50 µL of 0.5 M EDTA from individual rats. Blood samples were centrifuged at 3000 rpm for 15 minutes (Bio Era Life Sciences, Pune, India), and the plasma was extracted and stored at -20°C until analysis. The liquid-liquid extraction method (LLE) was then used to extract drugs from plasma. Aliquots of 100 µL of drug-free plasma samples were spiked with 100 µL GL and 100 µL of IS solution (50g/mL) in 2.0 mL eppendorf tubes, to which 1.0 mL of tertiary butyl methyl ether (TBME) was added. The resulting mixture was vortexed for 60 seconds at 2500 rpm (Remi Vortex Mixer, CM-101 Plus) then centrifuged for 10 minutes at 5000 rpm. In a nitrogen evaporator, the organic layer was then separated and evaporated to dryness (Mini-eVap). The leftover mass was reconstituted with 1.0 mL mobile phase, filtered using 0.22 µm syringe filters (Millex-GL), and injected into the RP-HPLC/PDA system for further analysis. The concentration of IS was maintained at 5 µg/mL (Figure 1).

In vivo pharmacokinetic studies in normal Wistar rats

An *in vivo* study was planned to explore the effects of TC extract on the PK of GL in healthy male Wistar rats. Experimental animals weighing 250–300 gm were randomly divided into two groups of 6 animals each.

Group I received a vehicle (1% CMC)

Group II received 100 mg/kg b.w.i.d (bis in die, twice a day) of TC extract for 13 days, by oral route. On the 14th day, group I was treated with GL (8.3 mg/kg, p.o.) and group II was treated with TC (100 mg/kg, p.o.) followed by GL (8.3 mg/kg, p.o.).

A volume of 0.3 mL of blood was collected from individual rats from the retro-orbital plexus in Eppendorf tubes containing 50 µL of 0.5 M EDTA at suitable time intervals (0.25, 0.5, 0.75, 1.0, 2, 4, 6, 8, 24 & 48 hrs.) after drug administration. Blood samples were centrifuged; the plasma was separated and stored at -20°C until analysis. The samples were processed as per the optimized liquid-liquid extraction protocol.

Data analysis

Individual animal plasma concentrations vs time profiles were calculated using WinNonlin software version 5.2. (Pharsight Corporation, Mountain View, CA, USA). The observed individual plasma concentration-time data were used to calculate the peak plasma concentration (C_{max}) and the time it took to achieve C_{max} (T_{max}). The PK parameters evaluated were area under the curve (AUC_{0-48}), clearance (CL), volume of distribution (V_d), elimination rate constant K_{el} , $t_{1/2}$ and mean residence time (MRT). All data were expressed as mean ± SD. Statistical analysis was carried out using t-test on Graph Pad Software, CA, USA. The differences were considered to be significant at * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.001$.

RESULTS AND DISCUSSION

LC method development and validation for pharmacokinetic studies

As per the United States - Food Drug Administration (US-FDA) bioanalytical method validation guidelines, the developed method was validated for selectivity, linearity, precision and accuracy, extraction recovery, matrix interferences, incurred sample reanalysis and stability study.

Selectivity

Representative chromatograms obtained for blank rat plasma, blank rat plasma spiked with a working solution of GL at a concentration of 50 ng/mL, and plasma samples taken after oral administration of GL in rats showed the method's selectivity as shown in Figure 2.

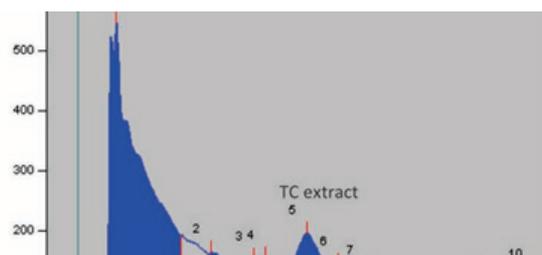


Figure 1. HPTLC densitogram of TC extract.

Linearity

The slopes, intercepts, and correlation coefficients of the GL calibration curve were calculated using the least squares linear regression method in the range of 50-3200 ng/mL. The typical regression equation for GL was $y=0.0024x+ 0.3679$ ($r^2=0.991$) with LLOQ of 50 ng/mL.

Accuracy and precision

At all three QC concentrations, the percent C.V for GL was less than 15% in the intra-day and the inter-day precision of the developed assay method is summarized in Table 1. The accuracy of the method for GL in rat plasma, calculated as relative error (R.E) was within the range of 1.0 to 10%.

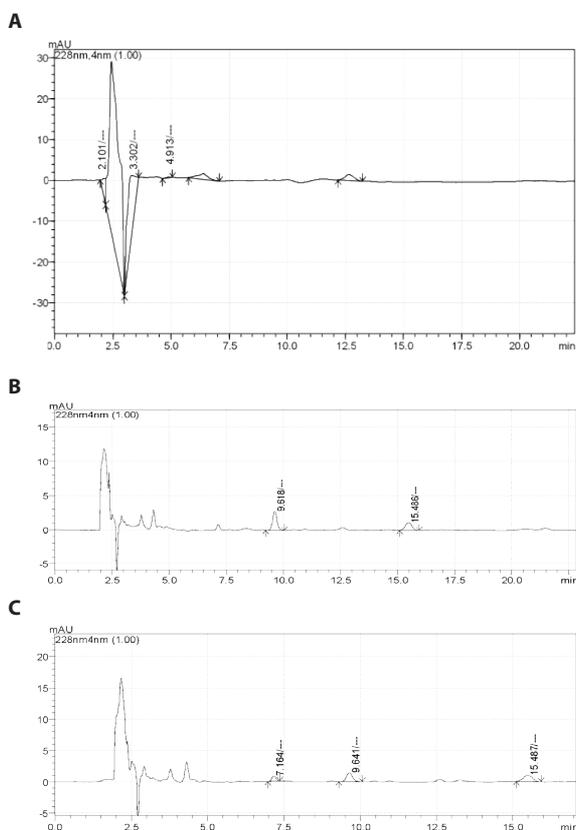


Figure 2. Representative chromatograms of (A) blank rat plasma, (B) blank rat plasma spiked with working solutions at 50 ng/mL of GL and IS and (C) plasma sample collected after oral administration of GL.

Table 2. % Recovery study.

Concentration (ng/mL)	Recovery (%)*		
	Mean	SD	%CV
LQC (150)	89.63	4.34	4.84
MQC (1600)	98.50	0.45	0.46
HQC (2560)	89.74	6.01	6.7

Extraction recovery

As shown in Table 2, the plasma extraction recovery at three concentrations (LQC: 150 ng/mL, MQC: 1600 ng/mL and HQC: 2560 ng/mL) for GL was from 90-95% with % CV below 15%. The mean recovery for Glimepiride (IS) was $90\pm 5\%$.

Stability

The stability of the GL in plasma was studied under various conditions, and the results obtained are reported in Table 3. In rat plasma, GL was found to be stable for 3 hours when held at ambient temperature and for at least 30 days when stored at -20°C with a % CV less than 15% at 2 QC concentrations (LQC and HQC). The % CV of QC samples between the initial concentrations and the concentrations obtained after three freeze-thaw cycles was below 15%. Also, the GL was found to be stable for 24 hrs. at 4°C in the LLE solvent (TBME).

Incurred sample reanalysis, matrix effect

The precision and accuracy of the incurred sample reanalysis of the PK study samples of rats receiving GL (8.3 mg/kg p.o.) were within the acceptance criteria (percent C.V less than 15%, R.E. within the range of 1.0 to 10%) as per USFDA recommendations, as shown in Table 3. In the current method, no significant interference of the matrix at the RT of the GL peak and IS was detected.

In vivo pharmacokinetic studies of Gliclazide after oral administration and co-administration with TC extract

The developed RP-HPLC/PDA method was effectively used to analyze the PK HDI on concomitant administration of GL and TC extract, the latter of which is known to be a powerful CYP2C9 inhibitor. After oral administration of TC, the plasma concentration vs. time profiles of GL are shown in Figure 3. The PK parameters are summarized in Table 4. As per the PK profile obtained; the administration of GL (8.3 mg/kg, p.o.) resulted in C_{\max} of 19129.85 ± 501.96 $\mu\text{g/mL}$ at the T_{\max} 1hr of the study. The value for V_d was found to be $0.000977878\pm$ L with CL of

Table 1. Precision and Accuracy study.

Concentration (ng/mL)	Intraday precision*			Interday Precision*		
	Estimated conc. (ng/mL)	Precision* (%CV)	Accuracy* (%RE)	Estimated conc. (ng/mL)	Precision* (%CV)	Accuracy* (%RE)
LQC (150)	133.85	6.19	10.76	138.71	2.9	7.5
MQC (1600)	1370.94	0.52	14.31	1382.29	0.3	13.6
HQC (2560)	2262.76	7.1	11.61	2219.41	5.6	13.3
Mean of six determinations						

Table 3. Statistical data for stability and other validation parameters.

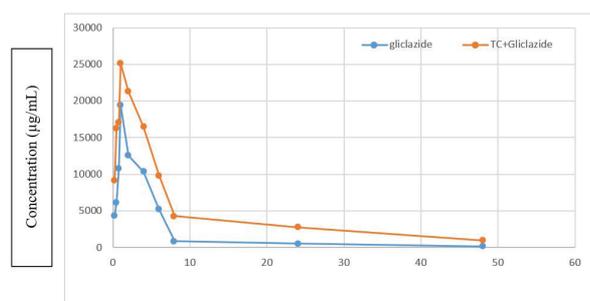
Validation Parameter	Nominal Conc. (ng/mL)*	Determined conc. (ng/mL)*	%CV*
Short term stability	LQC (150)	137.15	1.1
	HQC (2560)	2077.5	2.3
Freeze thaw stability	LQC (150)	135.43	7.5
	HQC (2560)	1901.54	6.4
Long term stability	LQC (150)	121.079	1.1
	HQC (2560)	1659.77	6.2
Incurred sample reanalysis	LQC (150)	128.77	3.41
	HQC (2560)	2260.31	8.68
Matrix effect	-	Nil	-

*Mean of six determinations

Table 4. Pharmacokinetic parameters of Gliclazide after oral administration in rats (n=6).

Group	T _{max} (h)	C _{max} (µg/mL)	AUC ₀₋₄₈ (h*µg/mL)	K _e (hr ⁻¹)	t _{1/2} (hr)	V _d (L)	CL (L/hr)	MRT (hr)
Group-1 (GL)	1	19129.85±501.9	203371.12±11258.4	0.086	8.34	0.00098	0.000081	12.04±1.19
Group-2 (GL+TC)	1	25020.40±295.98****	435102.20±27361.52***	0.067*	10.41±0.85*	0.00052****	0.0000351***	15.03±1.23*

Data are expressed as mean ± SD. **significant with respect to the GL group.


Figure 3. Plasma conc. (ng/mL) vs. time in hrs. profile of Gliclazide before and after administration of TC extract.

0.000081 L/hr, K_e 0.083606486 hr⁻¹, $t_{1/2}$ 8.34 ± 0.82 hr and a MRT of 12.04 ± 1.19 hr. Co-administration of TC at a dose of 100 mg/kg, p.o. in rats resulted in a significantly ($p < 0.001$) increased C_{max} 25020.40 ± 295.9 µg/mL, AUC_{0-48} (203371.12 ± 11258.44 to 435102.20 ± 27361.52 h*µg/mL, $t_{1/2}$ 10.41 ± 0.85 hr and MRT 15.02 ± 1.2 hr as shown in Table 4. Consequently a decrease in V_d 0.000525375 L, CL 0.0000351 L/hr, K_e 0.06685169 hr⁻¹ was observed.

CONCLUSION

A simple, sensitive, and accurate HPLC-PDA technique for estimating GL in rat plasma was developed and validated using a simple liquid-liquid extraction method. The developed method was successfully used to study the PK effect of GL in rats *in vivo*. The results of the PK investigation revealed that co-administration of TC extract significantly altered the PK pa-

rameters of GL; co-administration of TC extract resulted in an increase in the C_{max} , AUC_{0-48} , $t_{1/2}$ and MRT, consequently enhancing its bioavailability. As a result, V_d , K_e and CL for GL were reported to be reduced. This shift in PK parameters could be due to the inhibitory ability of berberine and other alkaloids found in high concentrations in TC extract on CYP2C9 activity.

In conclusion, the findings of this evidence-based investigation reveal that GL and TC extract have a considerable HDI. However, thorough clinical PK and pharmacodynamic studies are still required to establish HDI in higher animals. On prolonged administration, increase in bioavailability of GL due to an increase in its plasma concentration in the body may lead to propagation of its toxic manifestation and side effects, which could be fatal. As a result, the concomitant consumption of TC in patients on GL medication must be monitored vigilantly. This information concerning possible HDI of GL and TC may be useful for both physicians and patients on GL therapy.

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Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

- Adhikari, L., Mishra, U. S., & Murthy, P. N. (2014). RP-HPLC determination of gliclazide in rat plasma and its application in pharmacokinetic studies. *International Journal of PharmTech Research*, 6(2), 692–700.
- Bahadur, S., Mukherjee, P., Milan Ahmmed, S., Kar, A., Harwansh, R., & Pandit, S. (2016). Metabolism-mediated interaction potential of standardized extract of *Tinospora cordifolia* through rat and human liver microsomes. *Indian Journal of Pharmacology*, 48(5), 576–581. <https://doi.org/10.4103/0253-7613.190758>
- Brantley, S. J., Argikar, A. A., Lin, Y. S., Nagar, S., & Paine, M. F. (2014). Herb-drug interactions: Challenges and opportunities for improved predictions. *Drug Metabolism and Disposition*, 42(3), 301–317. <https://doi.org/10.1124/dmd.113.055236>
- Chatterjee, P., & Franklin, M. R. (2003). Human cytochrome p450 inhibition and metabolic-intermediate complex formation by goldenseal extract and its methylenedioxyphenyl components. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, 31(11), 1391–1397. <https://doi.org/10.1124/dmd.31.11.1391>
- Choudhary, N., Siddiqui, M. B., & Khatoun, S. (2014). Pharmacognostic evaluation of *Tinospora cordifolia* (Willd.) Miers and identification of biomarkers. *Indian Journal of Traditional Knowledge*, 13(3), 543–550.
- Fugh-Berman, A., & Ernst, E. (2001). Herb-drug interactions: review and assessment of report reliability. *British Journal of Clinical Pharmacology*, 52(5), 587–595. <https://doi.org/10.1046/j.0306-5251.2001.01469.x>
- Hu, Z., Yang, X., Ho, P. C. L., Chan, S. Y., Heng, P. W. S., Chan, E., Duan, W., Koh, H. L., & Zhou, S. (2005). Herb-drug interactions: a literature review. *Drugs*, 65(9), 1239–1282. <https://doi.org/10.2165/00003495-200565090-00005>
- Kuo, C.-Y., & Wu, S.-M. (2005). High-performance liquid chromatography with electrochemical detection for analysis of gliclazide in plasma. *Journal of Chromatography. A*, 1088(1–2), 131–135. <https://doi.org/10.1016/j.chroma.2004.12.097>
- Meshram, A., Bhagyawant, S., Gautam, S., & Srivastava, N. (2013). Potential role of *Tinosporacordifolia* in pharmaceuticals. *World Journal of Pharmaceutical Sciences*, 2, 4615–4625.
- Posadzki, P., Watson, L., & Ernst, E. (2013). Herb-drug interactions: an overview of systematic reviews. *British Journal of Clinical Pharmacology*, 75(3), 603–618. <https://doi.org/10.1111/j.1365-2125.2012.04350.x>
- Prabhakar, P. K., & Doble, M. (2008). A target based therapeutic approach towards diabetes mellitus using medicinal plants. *Current Diabetes Reviews*, 4(4), 291–308. <https://doi.org/10.2174/157339908786241124>
- Sahu, R., Ahmed, T., Sangana, R., Punde, R., & Subudhi, B. B. (2018). Effect of *Tinospora cordifolia* aqua-alcoholic extract on pharmacokinetic of Glibenclamide in rats: An herb-drug interaction study. *Journal of Pharmaceutical and Biomedical Analysis*, 151, 310–316. <https://doi.org/10.1016/j.jpba.2018.01.010>
- Sarkar, A., Tiwari, A., Bhasin, P. S., & Mitra, M. (2011). Pharmacological and pharmaceutical profile of gliclazide: A review. *Journal of Applied Pharmaceutical Science*, 1(9), 11–19.
- Shaikh, A. S., Thomas, A. B., & Chitlange, S. S. (2020). Herb–drug interaction studies of herbs used in treatment of cardiovascular disorders—A narrative review of preclinical and clinical studies. *Phytotherapy Research*, 34(5), 1008–1026. <https://doi.org/10.1002/ptr.6585>
- Singh, R. P., Banerjee, S., Kumar, P. V. S., Raveesha, K. A., & Rao, A. R. (2006). *Tinospora cordifolia* induces enzymes of carcinogen/drug metabolism and antioxidant system, and inhibits lipid peroxidation in mice. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, 13(1–2), 74–84. <https://doi.org/10.1016/j.phymed.2004.02.013>
- Thihekar, A. K., Thomas, A. B., & Chitlange, S. S. (2021). Herb-drug interactions in diabetes mellitus: A review based on pre-clinical and clinical data. *Phytotherapy Research*, 35(9): 4763–4781. <https://doi.org/10.1002/ptr.7108>
- Thomas, A. B., Shaikh, A. S., Rajee, A., Lokhande, K. B., Swamy, K. V., Nagore, D. H., & Doke, R. (2020). Herb drug interaction of *Tinospora cordifolia* (Willd.) Miers extract and Glimepiride: *In vivo* and *in silico* studies. *Medicinal Plants-International Journal of Phytomedicines and Related Industries*, 12(4), 555–567.
- Tsai, H.-H., Lin, H.-W., Simon Pickard, A., Tsai, H.-Y., & Mahady, G. B. (2012). Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. *International Journal of Clinical Practice*, 66(11), 1056–1078. <https://doi.org/10.1111/j.1742-1241.2012.03008.x>
- Wills, R. B., Bone, K., & Morgan, M. (2000). Herbal products: active constituents, modes of action and quality control. *Nutrition Research Reviews*, 13(1), 47–77. <https://doi.org/10.1079/095442200108729007>
- Xu, H., Williams, K. M., Liauw, W. S., Murray, M., Day, R. O., & McLachlan, A. J. (2008). Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. *British Journal of Pharmacology*, 153(7), 1579–1586. <https://doi.org/10.1038/sj.bjp.0707685>
- Yao, Y., Han, W.-W., Zhou, Y.-H., Li, Z.-S., Li, Q., Chen, X.-Y., & Zhong, D.-F. (2009). The metabolism of CYP2C9 and CYP2C19 for gliclazide by homology modeling and docking study. *European Journal of Medicinal Chemistry*, 44(2), 854–861. <https://doi.org/10.1016/j.ejmech.2008.04.015>