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Evaluation of Pharmacodynamic interaction between Tinospora Cordifolia Alcoholic extract and Gliclazide : An herb-drug interaction study

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ABSTRACT

Many diabetic people today consume herbs or herbal formulations along with prescription and non-prescription medications which may result in the herb-drug interaction

Tinospora Cordifolia, with berberine being one of the most abundant active phytoconstituent widely used as an antidiabetic While Gliclazide is indicated to treat type 2 diabetes mellitus whichacts as an insulin secretagogue .*T. Cordifolia* is a potent inhibitor of CYP2C9 and Gliclazide is known to be metabolized by this enzyme. Potential Pharmacodynamic herb drug interaction might be possible in case of co administration of both.

The pharmacodynamic interaction between TCE and Gliclazide was evaluated on hypoglycemic activity in normal and streptozotocin-nicotinamide-induced diabetic rats. The study was conducted in 2 parts viz. acute study and sub-acute study in both normal and diabetic animals. The serum triglyceride level and histopathology of pancreas was performed to assess effect on glucose metabolism and pancreas. FTIR Analysis was also carried out to evaluate the interaction between functional groups.

The combination showed pharmacodynamic interaction as reduction the time of onset of action and increasing the duration of action of gliclazide when administered in combination with *T. cardiofolia.* In FTIR studies of combination showed no physical interaction between functional groups suggesting both drugs might be acting on the different receptors.

The study concludes that the combination of Gliclazide with TCE showed an increase in the hypoglycemic effect as compared to the gliclazide alone in STZ-NIC induced diabetic rats. This might be utilized clinically as a beneficial drug interaction in patients after thorough investigations in clinical studies.

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Keywords: Herb-drug interaction, Diabetes, antidiabetic drug.

INTRODUCTION

Complementary and alternative therapies, as well as traditional herbal home remedies, are growing they are considered to be free of side effects and generally recognized as safe due to their natural origin.[1] According to the World Health Organization(WHO), approximately 80% of the global population still depends upon herbal medicines as complementary or alternative medicine.[2] Millions of people today use herbs either as food or in the form of medicine along with prescription and nonprescription medications, which sometimes may cause interaction.

herb-drug interactions (HDI) are described as those undesirable adverse reactions that occur as a result of concomitant administration of herbal medicines and conventional drugs. These interactions can be beneficial or harmful. The rate of occurrence of HDI may be more common than that of drug-drug interaction due to the presence of multiple pharmacological active phytoconstituent in herbal medicines, while the classical drugs contain only one active ingredient.[3] HDI was also reported to alter pharmacokinetic and pharmacodynamic parameters.

In developed and developing countries most people consume herbs and their products for acute and sometimes chronic conditions by self-prescribing. Most of the population is unaware of the toxic or potential adverse effects and interactions of herbal products caused when it is co-administered with any conventional medication.[2,4,5,6,7]

Diabetes mellitus (DM) is a complex chronic illness characterized by an increase in blood sugar level and glucose intolerance as a result of deficiencies in either insulin secretion or action, or both. Worldwide it is proving to be a major health problem, especially in urban areas. Diabetes is associated with lots of side effects so most people preferred herbal formulations because they believed that herbs have fewer side effects and low cost. Various oral hypoglycemic drugs are used for the management of diabetes. Gliclazide is one of the oral antidiabetic agents, which acts by[7] blocking ATP-sensitive potassium channels in b-cells of the pancreas. This blocking induces depolarization of

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the cell membrane, which causes voltage-dependent calcium channels to open and causes an increase in intracellular Ca++ in the b-cells to stimulate insulin secretion from the pancreas, thus it is widely used in the treatment of diabetes.

Tinospora cordifolia (Menispermaceae) is commonly known as Gulancha or Tinosporain English and Giloya or Ambervel in Hindi. Evidence suggested that TC is effective in the management of various diseases like cancer,[8,9] diabetes[7,10]etc, when the immune system is depressed,[11,12] increased cholesterol level,[13] liver damage condition,[14] and in diabetic foot ulcer.[15] However, all these findings are far too preliminary to be relied upon. The use of this herb as antidiabetic potential is described in materiamedica and the Ayurvedic pharmacopeia of India.[16] In India, many marketed antidiabetic formulations contained key ingredients of TC which are Diabecon, Diasulin, and Diabeta.[17]The antidiabetic effects of TC are reported to be mediated by insulin mimicking and insulin-releasing effects due to its constituents including palmatine,jatrorrhizine, mangnoflorine, and berberine.

Material & Method

Plant material

The alcoholic extract of Tinospora cordifolia was obtained as a gift sample from the Mprex Research Lab. It was administered in dose of 100 mg/kg of body weight orally as suspension in 0.3% carboxyl methylcellulose(CMC).

Drug & Chemical

Gliclazide was purchased from a local chemical supplier research lab Pune. Streptozotocin was purchased from Sigma- Aldrich lab. All reagents and chemicals used in the study were of analytical grade.

Animal

The male Wistar rats (body weight 250± 10 g) ,were housed in the animal house of the institute. The rats were maintained under standard environmental conditions as per guidelines of CPCSEA, 12 h light and dark cycle and free access to feed and water.

All experimental procedures were carried out in stringent accordance with the guidelines provided by the CPCSEA, and were approved by the Institutional Animal Ethical Committee (IAEC approval No.). DYPIPSR/IAEC/19-20/P-24)

Study design:

The dose of *T.cordifolia*as100 mg/kg of body weight and gliclazide 8.2 mg/kg body of weight was calculated from human oral therapeutic doses based on body surface area for rats.

For oral administration, *T. cordifolia* suspension was prepared by suspending it in 0.5% carboxymethyl cellulose sodium (CMC Na) and gliclazide solution was prepared by dissolving it in distilled water. The study was conducted in two stages as follows:

Stage 1: Evaluation of Pharmacodynamic interaction in normal rats

Stage 2: Evaluation of Pharmacodynamic interaction in Streptozotocin –Nicotinamide (STZ-NIC) diabetic rats

Stage 1: Pharmacodynamic interaction study in normal rats

Wistar rats were divided into four groups, each containing six animals in it. They were treated as follows:

1. Normal Control Group: treated with vehicle 1% CMC (10 ml/kg p.o).
2. Gliclazide Group: treated with Gliclazide at 8.2 mg/kg body weight.
3. *T. cordifolia* Group: treated with *T. cordifolia* 100 mg/kg body weight.
4. Gliclazide + *T. cordifolia* Combination Group: treated with Gliclazide at 8.2 mg/kg + *T. cordifolia ifolia* 100 mg/kg body weight,

The effect of single-dose administration on blood glucose level for 24 hrs was determined by measuring blood glucose levels at 0 min, 30min, 1, 2, 4, 8, 12,24hrs respectively. Then the same animals were further treated mentioned as above for 14days to evaluate the effect of multiple-dose administration.

Stage2: Pharmacodynamic interaction study in STZ- NIC induced diabetic rats

The rats were kept on fasting for 12 hours, water was provided *ad libitum*. Fasting blood glucose was measured by using an Accu-check glucometer by collecting a blood through tail vein puncture. The rats showing optimum blood glucose 80-120mg/dl were selected for the study. Then the rats were injected with Streptozotocin (45mg/kg i.p.) after 15 min of Nicotinamide injection (110mg/kg, i.p.) in all the groups except group I which was normal control (non-diabetic). They were fed with glucose solution (5%) for12 hr. to reduce hypoglycemia and mortality in them. Blood glucose was measured on 24, 48 72 hrs, and rats showing blood glucose ≥250

mg/dl were labeled as diabetic rats and selected for the study.

The rats were divided and treated as follows:

1. Diabetic control group: Diabetic animals treated with 1% CMC (10 ml/kg p.o).
2. Gliclazide Group: Diabetic animals treated with Gliclazide at 8.2 mg/kg body weight.
3. *T. cordifolia* Group: Diabetic animals treated with *T. cordifolia* 100 mg/kg body weight.
4. Gliclazide + *T. cordifolia* Combination Group: Diabetic animals treated withGliclazide at 8.2 mg/kg + *T. cordifolia* 100 mg/kg body weight,

The effect of single-dose administration on blood glucose level for 24 hrs was determined by measuring blood glucose levels at 0 min, 30min, 1, 2, 4, 8, 12,24 hrs respectively. Then the same animals were further treated mentioned as above for 14days to evaluate the effect of multiple-dose administration.

Estimation of biochemical parameters:

At the end of the experiment, the blood was collected by the retro-orbital puncture from each rat. Blood samples were centrifuged at 5000 rpm for 20 min to separate serum and to estimate the serum levels for triglycerides (TG), the estimations were done according to the instructor manual of commercially available kits (Pathozyme enzyme kits).

Histopathological examination of pancreas:

Pancreatic tissues from each group were collected and fixed in 10% neutral buffered formalin and submitted to the pathology to Crystal Biological Solutions, Pune.

Statistical analysis:

The experimental data is expressed as mean ± S.E.M. The statistical analysis was carried out by One Way ANOVA followed by Sidak's, multiple comparison tests, and the data blood glucose was also analyzed by Two Way ANOVA followed by multiple comparisons by using GraphPad version 8 for window vista TM BASICS, software, $p<0.05$ considered as statistically significant.

FT-IR Analysis:(4)

As *T. cordifolia* extract contained a complex of phytoconstituents consisting of different functional groups so there might be some overlapping of functional groups between *T. cordifolia* and gliclazide and which might impose some interaction at the receptor level affecting the efficacy of gliclazide. To evaluate the functional groups overlapping between *T. cordifolia* and gliclazide FT-IR analysis was performed.

Procedure :

Dried *Tinospora cordifolia* extrct, pure Gliclazide, and their admixture were subjected to FTIR analysis using the potassium bromide method. Five-milligram powder sample was blended with dried potassium bromide to give a 200 mg weight powder. The powder was compressed using a Sigma potassium bromide press into a tablet, and then placed in the sample compartment of the spectrophotometer and scanned at a range of 4000 - 750 cm-[1][18,19]

RESULT

1.Single-dose study in normal animals and diabetic animals:

In a single-dose study, all the groups did not show significant changes in the blood glucose level in normal animals 24 hours duration. This signifies that the combination of gliclazide and *T. spora* did not produce hypoglycemia therefore safe to be used. Table 1 depicts the effect of treatment on blood glucose level in normoglycemic animals.

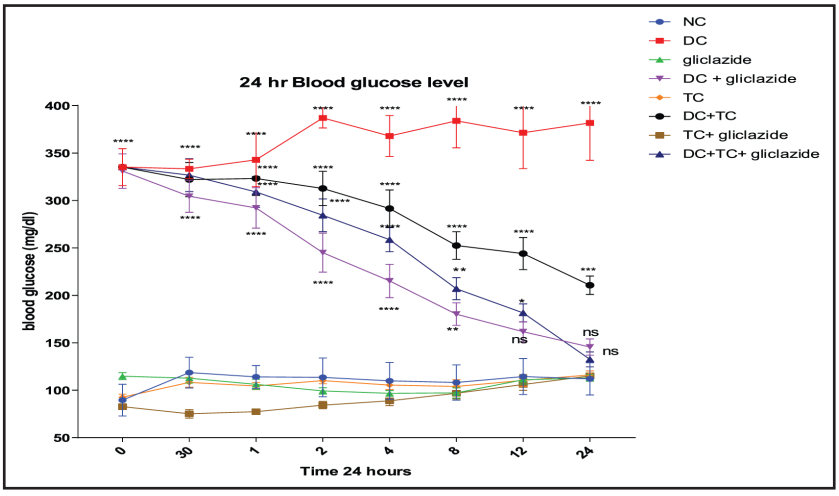


Figure1: Effect of single dose administration on blood glucose level in Normal and diabetic animals for 24 hrs.

All values are expressed as mean ± SEM. n=6
data are subjected to two ways ANOVA followed multiple comparison test
DC is compared with NC.
DC + Gliclazide is compared with normal animal Gliclazide
DC + TCE compared with normal animal TCE
DC+ TCE + Gliclazide compared with normal animal TCE+Gliclazide.
*P<0.05,**p<0.01,***p<0.001,****p<0.0001,NS:Non-significant..

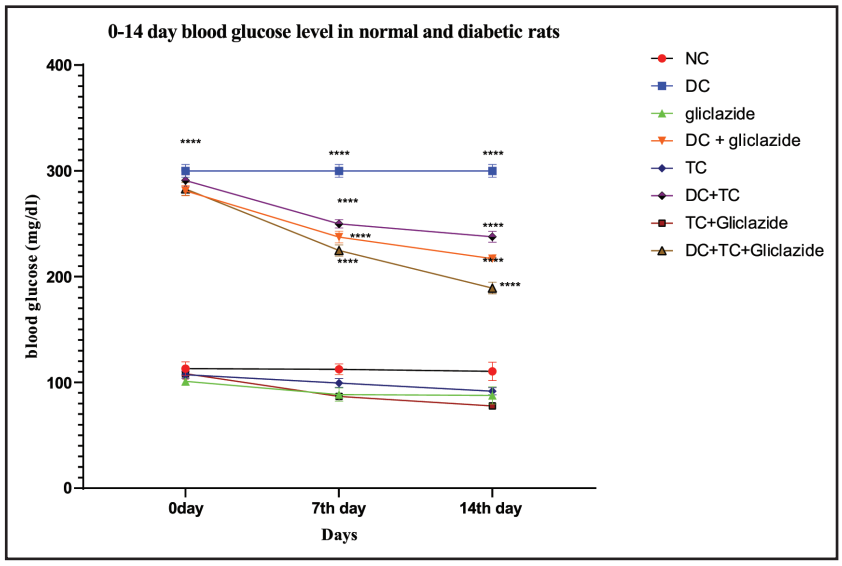
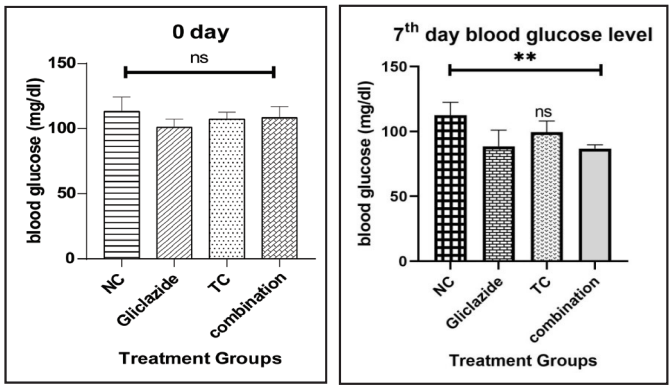
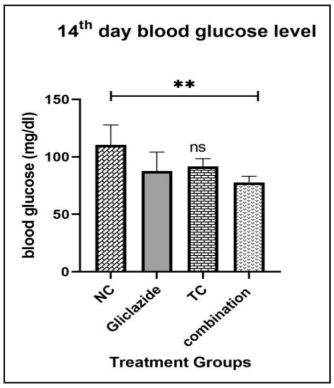


Figure 2: Effect of multiple dose administration of test substances for 14 days on blood glucose level in Normal and diabetic animals.

All values are expressed as mean ± SEM. n=6
All data are subjected to Two-Way ANOVA followed by multiple comparison.
DC is compared with NC.
DC + Gliclazide is compared with normal animal Gliclazide
DC + TCE compared with normal animal TCE
DC+ TCE + Gliclazide compared with normal animal TCE+Gliclazide.
*P<0.05,**p<0.01,***p<0.001,****p<0.0001,NS:Non-significant.



(a) 0 day (b) 7th day



(c) 14th day

Figure 3: Effect of multiple dose administration of test substances for (a) 0 day (b) 7th day and (c) 14th day on blood glucose level in Normal animals.

In STZ- NIC induced diabetic animals significant persistent hyperglycemia was found in the control group while groups treated with gliclazide and T. spora alone showed a reduction in the blood glucose level after 30 min of oral dose administration. The group treated with a combination of gliclazide and T. spora showed more reduction in the blood glucose level as compared to the groups treated with the single drugs as observed in Table 2

2. Multiple-dose study

2.1Effect of combination on blood glucose level in Normal and STZ-NA induced diabetic rats (Multiple dose study):

The multiple-dose study was conducted in normal and diabetic rats. The fasting blood glucose (FBG) levels in the DC group were found to be significantly elevated as compared to NC ($P < 0.001$). Oral administration of TCE (100 mg/kg), Gliclazide (8.2mg/kg)in normal and diabetic rats significantly reduced the FBG levels to 91.75, 87.75mg/dl, and 237.75, 217 mg/dl respectively. However, the combination treatment provided more glycemic control than either of the Gliclazide and the TCE alone in both normal and diabetic rats suggesting synergy between them. The concomitant treatment with TCE+ Gliclazide in both treatment groups (normal and diabetic rats) for 14 days reduced the FBG levels to 77.75, 189.25mg/dl, respectively. Moreover, none of these combinations led to any incidence of hypoglycemia, which may occur as an adverse event in case of an overdose of the antidiabetic drug combination. Table 3 and Table 4 depicts the blood glucose level on 0, 7 and 14 days in normal and diabetic animals

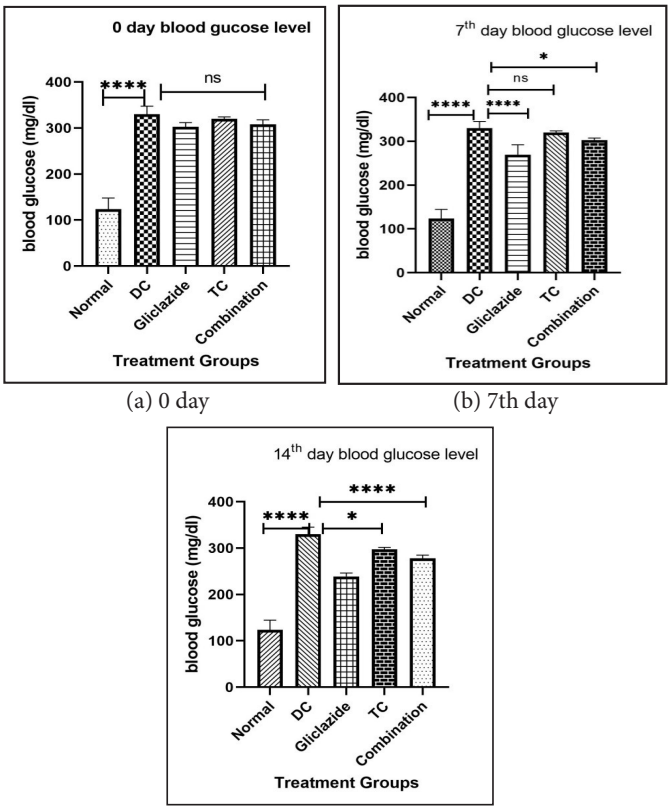
2.2. Effect of combination on Triglycerides in STZ-NA induced diabetic rats (Multiple dose study).

At the end of the 14 – day treatment with test substances, the triglyceride level of Normal control group was 49.86 ±5.32 mg/dl, in diabetic control group it was found to be increased at 87.34 ±2.45 mg/dl. In treatment groups the triglycerides levels in gliclazide, TCE and Combination group was found to 61.12±2.67, 66.06±3.40, 72.44±4.05 mg/dl respectively.

2.3. Histopathology

Effect of combination (Gliclazide 8.2 mg/kg +TCE 100mg/kg) on histopathology pancreas.

As per the result obtained from laboratory the test substances treated group did not showed significant pathological changes in pancreatic tissue.



(a) 0 day (b) 7th day

(c) 14th day

Figure 4: Effect of multiple dose administration of test substances for (a) 0 day (b) 7th day and (c) 14th day on blood glucose level in diabetic animals.

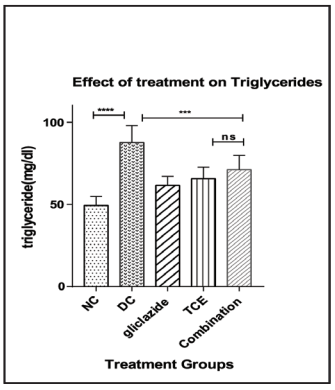


Figure 5: Effect of treatment on triglyceride level in diabetic animals

All value are expressed as mean ± SEM .n=6. Vertical lines represent SEM.
All data are subjected to One way ANOVA followed by Brown Forsythe, Multiple comparison test.
Group I (Gliclazide),Group II (TCE),Group III(combination) is compare with NC.
****p<0.01,**p<0.001,***p<0.001,NS:Non-significant.

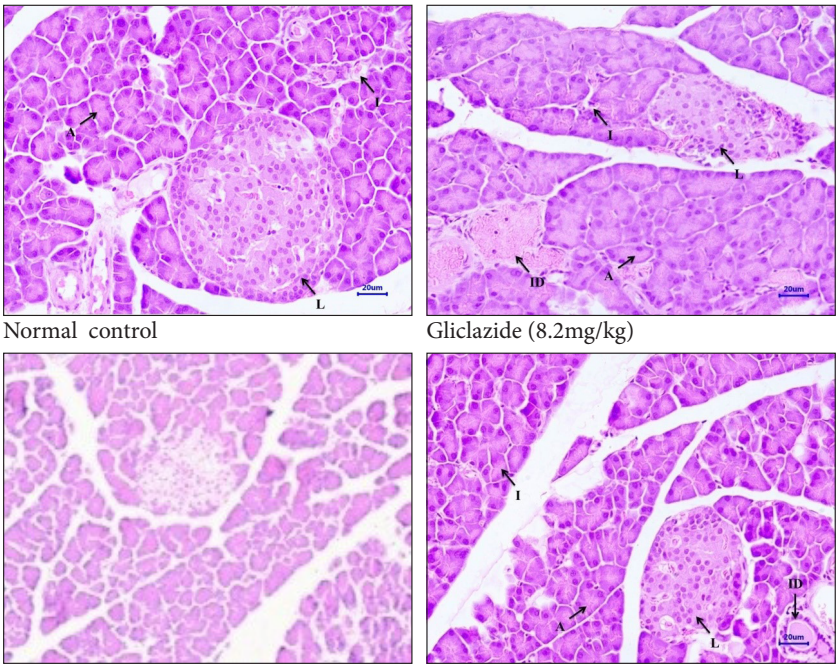
3. FTIRAnalysis (Fourier-transform infrared spectroscopy)

DISCUSSION

Diabetes mellitus is a chronic illness associated with an increase in blood glucose level (hyperglycemia) altered metabolism of lipids, carbohydrates, and proteins, and an increased risk of complications from vascular disease. The global burden of diabetes is continuously increasingyear by year.Various therapeutic approaches for the management of diabetes, such as the Pharmacological drug approach, Non-pharmacological approach, herbal remedies apart from Gene therapy, Trans-differentiation, Stem cells, Enhancing self-replication of β-cells are also used for the management of diabetes. Manytimes use of two or more approaches together is followed by the patients and practitioner that may significantly affect one another.

According to the WHO, nearly 70% of the world population still depends upon herbal medicine as a medium of complementary and alternative medicine. Complementary and alternative therapies as well as traditional herbal home remedies are booming because they are perceived to be free of side effects and generally recognized as safe due to their natural origin. Due to high prices and potential side effects of synthetic drugs, people rely more on herbal drugs and this trend is growing, not only in developing countries but in developed countries too. Millions of people use herbs either as food or in the form of medicine along with prescription and nonprescription medications. Which ultimately results in the herb-drug interaction.HDIis described as those undesirable reactions which occur as a result of concomitant administration of herbal medicines and conventional drugs.HDI gives adverse effects or treatment failure of the conventional drug. Various pharmacokinetic and pharmacodynamic parameters are affected due to herb-drug interaction(HDI).The use of alternative therapy is mostly not supervised by practitioners resulting in increased harm to patients, especially if they are using herbal and prescription medications that have latent interactions.For the management of diabetes, various oral hypoglycemic agentsare used. One of the widely used drugs is Gliclazide. Gliclazide is second generation Sulphonylureas that acts by stimulating insulin secretion through the β Sulphonylureas receptor and possibly through a direct effect on intracellular calcium transport. Apart from that various people consume herbs and herbal products in their daily routine like Aloe Vera, Bilberry extract, Bitter melon, Cinnamon, Fenugreek, Ginger, Okra,Tinospora cordifolia, and many more. In that most of the marketed preparation as antidiabetic contained Tinospora cordifolia. The various study reported that berberine is an active constituent of Tinospora cordifolia which shows antidiabetic properties. Tinospora cordifolia is has caught attention as a promising therapeutic agent for the treatment

Figure 6: Effect of treatment on Histopathology of pancreas.



Normal control

Gliclazide (8.2mg/kg)

T.cordifolia(100mg/kg)

combination (*T.cordifolia* + gliclazide)

of different diseases. If the diabetic patient on Gliclazide therapy consumesTinospora cordifolia some interaction might be possible to occur.

In the present study, the pharmacodynamic interaction between *Tinospora cordifolia* and Gliclazide was evaluated in normal as well as STZ-NIC induced diabetic rats. The study was conducted in two phases: one is in normal animals and another is in STZ-NIC induced diabetic Wistar rats. In Both phases, the two types of studies were conducted.

The first study was the evaluation of single-dose administration of combination (Gliclazide + TSE) i.e. acute study. The second was an evaluation of the effect of multiple-dose administration of combination (Gliclazide + TSE) i.e. sub-acute study.

In normal rats,a consistent decrease in blood glucose was observed in animals treated with Gliclazide, TCE, anda combination of both till 24 hrs of administration. At 30min after administration of the combination of Gliclazide and TCE, more decrease in blood glucose level was observed as compared to individually treated groups. The time of 30min can be considered as onset of action of

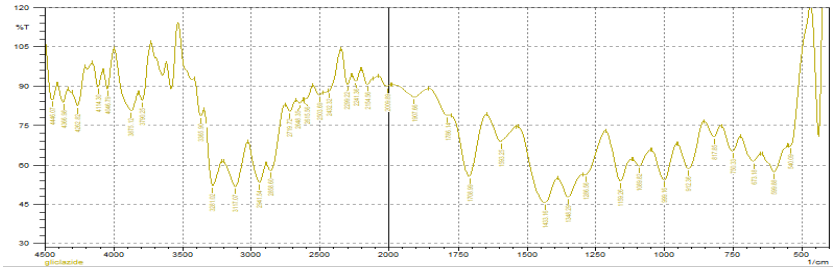
Table 1: Effect of single dose of administration of test substances on blood glucose level in normoglycemic animals for 24 hrs.

Sr. No	Treatment group	Blood glucose level (mg/dl)							
		0min	30min	1hr	2hr	4hr	8hr	12hr	24hr
1	Normal Control	89.57± 16.77	118.57± 16.19	114± 11.99	113.57± 20.38	109.85± 19.50	108.14± 18.54	114.42± 18.90	112.14± 39.28
2	Gliclazide	114.83± 3.67 ^{ns}	112.66± 5.04 ^{ns}	106.16± 5.30 ^{ns}	99.33± 3.33 ^{ns}	96.66± 3.03 ^{ns}	97.16± 5.38 ^{ns}	111± 4.62 ^{ns}	113± 3.51 ^{ns}
3	TCE	92.66± 3.17 ^{ns}	108.33± 5.21 ^{ns}	104.5± 3.80 ^{ns}	110.16± 3.33 ^{ns}	105.5± 4.82 ^{ns}	104 ± 7.08 ^{ns}	110.33 ±6.26 ^{ns}	116.16± 4.21 ^{ns}
4	TCE+gliclazide	82.66± 3.12 ^{ns}	75.16± 4.53 ^{ns}	77.33± 2.86 ^{ns}	84.33± 3.93 ^{ns}	88.83± 5.10 ^{ns}	96.8± 5.88 ^{ns}	106± 6.13 ^{ns}	115± 3.16 ^{ns}

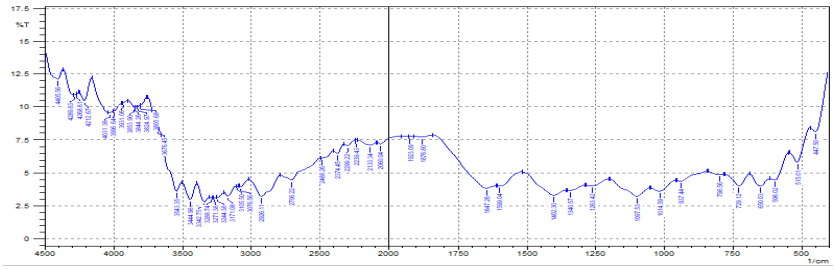
Table 2: Effect of single dose of administration of test substances on blood glucose level in STZ-NIC induced diabetic animals for 24 hrs.

Sr. No	Treatment group	Blood glucose level (mg/dl)							
		0min	30min	1hr	2hr	4hr	8hr	12hr	24hr
1	Diabetic Control	335.16± 19.51****	333.33± 10.09****	342.83± 28.22****	387.00± 10.58****	368.00± 21.57****	384.00± 28.50****	371.33± 37.69****	381.66± 39.28****
2	Diabetic Gliclazide	331.00± 18.16****	304.50± 16.90****	292.16± 21.31****	245.00± 20.54****	215.16± 17.58****	180.16± 11.86*	161.6± 10.55^{ns}	145.5± 8.54^{ns}
3	Diabetic TCE	335.16± 19.51****	322± 17.96****	323± 17.91****	312.66± 18.11****	291.50± 19.54****	252.50± 14.51****	244.00± 16.86****	210.66± 9.70***
4	STZ+ TCE+ Gliclazide	335.16± 19.51****	326.66± 17.34****	309± 16.25****	284.33± 17.24****	258.66± 12.64****	207± 11.60**	181.50± 9.49*	132.5± 7.86^{ns}

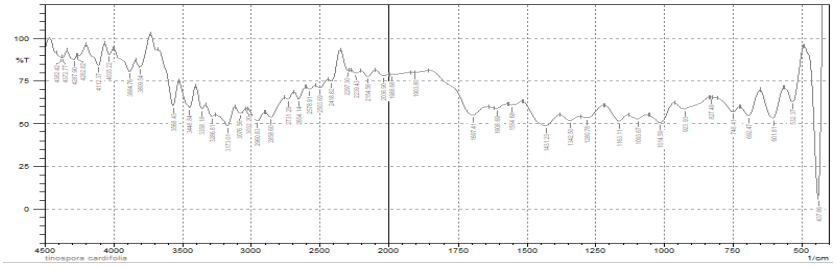
Figure 7: FTIR spectra of (a) Gliclazide (b) TCE alone (c) Admixture of Gliclazide and TCE



(a) FTIR spectra of Gliclazide alone



(b)FTIR spectra of *T. cordifolia* alone



(c) Admixture of Gliclazide + *T. cordifolia*

Function group	Gliclazide	Tinospora cordifolia	Gliclazide + TC
C = O/Amine	1697.41 cm^{-1}	1647.26 cm^{-1}	1708.99 cm^{-1}

Table 3: Effect of multiple dose administration of test substancesfor 14 days on blood glucose level in normoglycemic animals.

Sr. No	Treatment group	Blood glucose level		
		0 day	7th day	14th day
1	Normal Control	113.00 ± 6.54	112.5 ± 5.85 ns	110.5 ± 5.33 ns
2	Gliclazide	101.00 ± 3.74 ns	88.50 ± 1.50 ns	87.75 ± 0.75 ns
3	TCE	107.25 ± 3.17 ns	99.50 ± 0.96 ns	91.75 ± 1.93 ns
4	TCE + gliclazide	108.00 ± 5.11 ns	86.7 ± 1.03 ns	80.75 ± 0.48 ns

combination however consistent decrease in blood glucose was observed till the end of 24hrs.

In diabetic rats alsoa consistent decrease in blood glucose level in animals treated with Gliclazide, TCE, and a combination of both for 24 hrs after administration. At 30 min Gliclazide group showed more reduction in blood glucose level which continued till 12hrs but in the combination group, it more decrease in blood glucose level observed at 1hrs that continued till 24hrs. So we can conclude that the onset of hypoglycemic action for the combination group is 30min while the duration of action is till 24 hours in single-dose administration studies both in normal as well as diabetic rats.

A multiple-dose study was also conducted in normal as well as STZ-NIC induced diabetic rats. In normal rats,a consistent decrease in blood glucose level was observed in the group treated with the combination of Gliclazide and TCE till 28thdays of administration while on 14th days significant reduction in blood glucose level was observed as compared to groups treated with individual drugs. In STZ-NIC induced diabetic rats a consistent decrease in blood glucose level was observed in the group treated with the combination of gliclazide and TCE till the 14th day. Since 14th-day combination-treated groups showed similar degrees of reduction in blood glucose level as compared to Gliclazide treated group. This might be due to a physiological shift due to the hyperglycemic paradigm in diabetes-induced rats.

In FTIR analysis was found that a combination of TCE and gliclazide did not show any overlapping of functional groups indicating no physical or functional group interaction at the receptor level.

The literature revealed that both drugs used in combination here produce antidiabetic activity by a different mechanism of action i.e gliclazide shows its antidiabetic action through β Sulphonylureas receptor and TCE is reported to be antidiabetic by increasing insulin secretion.

From the results, it can be concluded that a combination of gliclazide and TCE produces some pharmacodynamic interaction which might be utilized correctly to adjust the dose and dosage regimen of gliclazide to improve the efficacy and safety of OHAs and thereby benefit the patients. The combination also can be explored to control diabetic complications after a well-planned study.

CONCLUSION

The present study involved the evaluation of pharmacodynamic interaction between gliclazide and *T. cordifolia* in normal as well as STZ-NIC induced diabetic rats indicated that combination of gliclazide and *T.cordifolia* group showed a more significant decrease in blood glucose, increase

Table 4: Effect of multiple dose administration of test substances for 14 days on blood glucose level in STZ-NIC induced diabetic animals:

Sr. No	Treatment group	Blood glucose level		
		0 day	7th day	14th day
1	Diabetic Control	300.00± 5.93	320.00± 5.93****	310.00± 5.93 ****
2	Diabetic Gliclazide	281.25± 4.66****	237.50± 5.56****	217.00± 6.12****
3	Diabetic TCE	291.00± 5.28****	250.00± 3.89****	237.00± 5.17****
4	STZ+ TCE+ Gliclazide	283.00± 6.18****	224.75± 5.25****	189.25± 5.54****

in insulin level with and also reduced onset of action and increased duration of hypoglycemic effect of gliclazide as compared to a single drug. The groups treated with a combination of these two showed significantly better effects compared with individual herb/drug treatments. Further, the combination of *T.cordifolia*with gliclazide in normal animals showed more hypoglycemia as compared to diabetic rats. Concomitant administration of *T. cordifolia* with Gliclazide should be done with consultation and under the supervision of physicians. It is essential to increase the level of awareness among diabetic patients and health care providers regarding the possibility of drug-herb interactions to avoid either ineffectiveness and /or reduce the adverse effects of the therapy used.

Future prospective:

Further detailed mechanistic and pharmacokinetic study to explore the exact molecular mechanism of this interaction and pharmacokinetics of OHA needs to be conducted to confirm this interaction

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