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# Pharmacokinetic and Pharmacodynamic Interaction of Didymocarpus pedicellata with Gliclazide in Normal and Diabetic Rats

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**ABSTRACT :**

This study evaluated possible interaction between Ayurvedic anti-urolithiac agent hydroalcoholic extract of *Didymocarpus pedicellata* (HADP) leaves and gliclazide. Dose optimization performed by measuring serum glucose levels after 200 and 400 mg/kg HADP administration to normal rats. Pharmacokinetic interaction study in normal rats performed by administration of gliclazide alone and combination with HADP (400 mg/kg). Diabetes was induced by administration of streptozotocin (55 mg/kg) and animals were treated with gliclazide, HADP and combination for 28 days. Pharmacokinetic and dynamic interaction were assessed after single (day 1) and repeated dose (day 28) co-administration by determination of serum gliclazide and glucose levels respectively. Gliclazide showed biphasic concentration time data and glucose reduction with maximum reduction at 2 and 8h post administration. HADP showed dose proportionate hypoglycemic effect in normal rats, hence 400 mg/kg was used for further studies. There was significantly higher decrease in percentage reduction of glucose levels in co-administration group as compared to gliclazide only group in normal, diabetic rats after single and repeated administration. Reduction was higher in repeated administration as compared to single. There was a non significant increase in pharmacokinetic parameters in normal and diabetic rats after single HADP administration. Repeated HADP administration in diabetic rats caused significant increase in all pharmacokinetic parameters. Combination of gliclazide and HADP showed a significant pharmacodynamic and pharmacokinetic interaction with gliclazide. Hence precautions has to be observed in co-administration of gliclazide with HADP and dosage adjustments of gliclazide might be required in a clinical setting to avoid sever hypoglycemia.

**Keywords:** Diabetes, *Didymocarpus pedicellata*, Drug interaction, Gliclazide, Pharmacokinetics, Pharmacodynamics, , Urolithiasis

## Introduction:

Diabetes melitus is a chronic metabolic disorder characterized by high blood glusoe levels arisisng either from reduced insulin secretion or from insulin resistance ininsulin sensitive tissues such as liver, skeletal muscles and adipose tissue. It has serious implications on quality of life and health of the affected individual. Prevalence of diabetes is escalating at avery higher rate across the globe with 108 million individuals affected in 1980 to 412 million individuals in 2014, this escalation is rapid in developing and under developed nations as compared to developed nations (1). Diabetes has directly caused approximatley 1.5 million deaths in 2019 and there was 5% increase in premature mortality caused by diabetes from 2000 to 2016 (1). As per International Diabetes federation report 2019 there are approximately 463 million adults suffering with diabetes and and it may rise to 700 million by 2045 (2). Diabetes is majorly treated with insulin or its analogues, biguanides such as metformin, insulin secretoguages such as sulfonylureas and insulin sensitizers such as thiazolidinediones (3). Sulfonylureas are the antidiabetic agents used as second line drug

after metformin despite of its limitations (4). They act by binding to sulfonylurea receptors located on pancreatic beta cells, which causes blocking of ATP sensitive potassium channel and thereby enhancing secretion of insulin. They are majorly associated with adverse effects such as hyperglycemia, weight gain and cardiovascular risk. Among this class of drugs the newer agents such as gliclazide and glimipride have lower cardiovascular risk as compared to older older drugs such as glibenclamide (5).

Plants are source of numerous phytochemicals with pleotropic actions, there are around 21,000 plants listed by World Health Organization (WHO) for medicinal use, among them 400 are used for diabetes treatment (6). Herbal drugs therapy is considered to be associated with limited adverse effects and currently there is an enhanced intrest in plant derived drugs especially for chronic ailiments such as metabolic disorders (7,8). Due to these advantages there is an increase in use of complimentary and alternative medicine including dietary suppliments and plant derived drugs in the management of diabetes, which accounts approximately to 73% (9).This, in turn, opens up an avenue for herb-drug interactions (HDIs), which can have mild to severe impact on efficacy and safety of the drug. Pharmacological HDIs may arise either from pharmacokinetic interaction or pharmacodynamics interactions. Although pharmacokinetic interactions might be associated with alterations in absorption, distribution, metabolism or renal clearance, among these hepatic metabolic machinerary especially cytochrome P450 (CYP450) enzymes is the predominant causuative factor for HDIs (10). Plants are source of numerous chemicals, which might be responsible for their wide pharmacological effects thus causing pharmacodynamics interaction when co-administered with a drug (11).

*Didymocarpus pedicellata* is known as shilapushpa in Ayurveda the traditional system of Indian medicine, it belongs to the family *Gesneriaceae*. It was used traditionally/ethnobotanically for the treatment of urolithiasis, micturition, other renal disorders, as diuretic, plaque suppressant and for vasorelaxation (12,13).Research findings indicated its antiurolithic, nephroprotective, spasmolytic, antimicrobial, wound healing effects and it is a major component of commercial formulation cysone used for treatment of urolithiasis (13–15). Major phytochemicals identified in *D. pedicelleta* are didymocarpol, β-sitosterol, pashanone, didymacarpenol, isodidymocarpin, didmyocarpin, pedicin, pediflavone, isopedicin, pedicellin, pedicellic acid and pediflavone (14). As diabetes mellitus especially type 2 diabetes is associated with increased incidence of renal stones (16,17), there is possibility of concominant administration of widely used antiurolithic herb*D. pedicellata* and antidiabetic drugs. Current study is designed to identify and evaluate pharmacokinetic, pharmacodynamic interaction of *D.pedicellata* leaf extract and antidiabetic agent gliclazide using suitable animal models.

**Materials and Methods:**

**Drugs and Chemicals***:*

All kits used in the study were procured from Coral clinical systems (Goa, India).. Gliclazide was obtained as a gift sample from Dr. Reddy's laboratory (Hyderabad, India), Streptozocin was procured from Sisco Research Labs (Mumbai, India),*Didymocarpus pedicellata* leaf extract was obtained as a gift sample from Laila Impex Pvt Ltd., (Vijayawada*,* India). All other reagents and

chemicals used in this study were of analytical grade and were procured from Merck Millipore (Massachusetts, USA)

**Animals:**

Male Wistar rats of 8-10 weeks old (200- 230gm) were procured from Mahaveer enterprises, (Hyderabad, India) andacclimatized for a week. They were maintained under standard laboratory conditions of 22±3°C temperature and 50±15% relative humidity with 12 hours light/12 hours dark cycle. They were provided with a standard pellet diet (Hindustan Lever Ltd., Bangalore, India) and water *ad libitum.*

**Experimental Design:**

Interaction Study in Normal Rats

This experiment was performed in III stages, in stage I animals were fasted overnight, administered with gliaclazide (2 mg/kg body weight) via oral route and blood was withdrawn from all the animals by retroorbital plexus puncture under mild isoflurane anaesthesisa at 0.5, 1, 2, 4, 6, 8, 12 and 24h post administration. After a week of washout and recovery period same animals were used for stage II, where they were administerd with extract (200 mg/kg body weight) and blood samples collected as in stage I. After wash out period for stage III experiments same animals were treated with extract (400 mg/kg body weight) and blood was collected as in stage I. After a week of washout period animals were treated with extract (400 mg/kg body weight) followed by gliaclazide (2 mg/kg body weight) with a time interval of 30 minutes after overnight fasting and blood samples were collected at same intervals as stage I. Serum was collected by centrifugation of blood samples at 5000 rpm for 5 minutes at 4-8°C for determination of glucose levelsby glucose oxidase (GOD) peroxidase (POD) method and chromatographic analysis.

**Interaction Study in Diabetic Rtas :**

Animals were fasted overnightd before the experiment with water *ad libitum.* The rats were injected intraperitoneally with freshly prepared streptozocin in citrate buffer (pH 4.5) solution at a dose of 55 mg/kg body weight. Animals were administered with 20% dextrose solution intraperitoneally after 4-6 h to combat the early phase of hypoglycemia followed by 50% dextrose solution orally up to 24 h. Blood samples were withdrawn after 72 hours of streptozocin administration and serum glucose levels were determinedby GOD-POD method. Animals having blood glucose levels greater than 250 mg/dl were considered to be diabetic and further used for the experiments. Diabetic animals were divided in to three groups, group I animals were treated with only gliaclazide, group II were given only extract and group III animals were treated with extract followed by gliaclazide for 28 days. Blood samples were withdrawn on day 1 and 28 from retro orbital plexus puncture at 0.5, 1, 2, 4, 6, 8, 12 and 24h post treatment, serum samples were collected and utilized for determination of glucose levels and chromatography.

**Chromatography :**

Gliaclazide concentration in serum samples were estimated by high performance liquid chromatograph (Waters, Japan) equipped with variable wavelength programmable UV or photodiode array detector. This reverse phase HPLC system with C8 column (5 µm particle size; 100

mm length x 4.6 mm diameter) was used as stationary phase. Mobile phase used in this study was 60:40 mixture of phosphate buffer and acetonitrile with isocratic method. Mobile phase flow rate was 1.2 ml/min and effluent was monitored at 229 nm wavelength. Metformin was used as internal standard, gliaclazide concentration was determined from ratio of gliaclazide peak area and internal standard peak area. Empower software was used for analysis and interpretation of data (18)**.**

**Sample Preparation &Pharmacokinetic Analysis :**

To 100µl of serum sample (test or standard) 100 µl of internal standard was added and mixed in micro centrifuge tube. To this mixture 200 µl of acetonitrile was added for protein precipitation, resultant mixture was vortexed and centrifuged at 3000 rpm for 5 minutes. Supernatant was collected and filtered through 0.45 µmmembrane filter. Resultant filterate (20 µl) was injected in to HPLC for analysis of gliaclazide. Pharmacokinetic analysis was performed by non compartment analysisusing Kinetica 5.0 software.

**Statistical Analysis :**

All data are represented as mean±SD/SEM, results were analysed by one way or two way analysis of variance (ANOVA) using Graphpad Prism 7.01 software. Results with $p < 0.05$ were considered as statistically significant.

**Results :**

Pharmacodynamic interaction study in normal rats

There was a reduction in serum glucose levels in all the groups of normal rats after treatment at all the time points (Table 1). Hypoglycemic effect was observed with a single dose of gliaclazide in normal rats, which was biphasic with a maximum reduction of 33.60±0.71% at 2h and 26.49±1.27% at 8h post administration. HADP administration to normal rats produced hypoglycemic effect with a maximum reduction of 21.26±0.92% at 200 mg/kg and 28.79±0.71% at 400 mg/kg dose 4h post administration. Combination of HADP high dose with gliaclazide has produced a a significantly higher ($p<0.001$) reduction in serum glucose levels as compared to gliaclazide only treatment with biphasic reduction of 39.73±1.39% at 2h and 32.70±1.00% at 8h post administration (Figure 1).

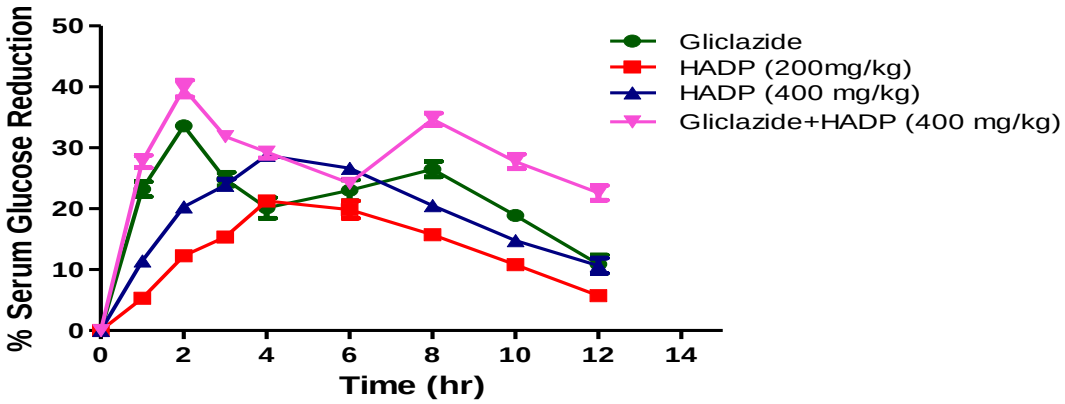
**Table 1 :**

Serum glucose levels in normal rats treated with gliclazide, *Didymocarpus pedicellata* (HADP) 200 and 400 mg/kg and their combination. Data (n=3) was represented as Mean±SEM, analyzed by two way ANOVA and $p < 0.05$ was considered to be significant. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ when compared to gliclazide.

| **Time (h)** | **Serum Glucose levels (mg/dL)** | | | |
|---|---|---|---|---|
| | **Gliclazide (1mg/kg)** | **HADP (200mg/kg)** | **HADP (400mg/kg)** | **Gliclazide+ HADP (400mg/kg)** |
| 0 | 81.17±1.04 | 81.50±1.85 | 84.50±2.51 | 84.67±2.92 $^{ns}$ |
| 1 | 62.33±0.73 | 77.17±2.12 | 74.83±2.09 | 61.17±2.34 $^{ns}$ |
| 2 | **53.90±0.47** | 71.50±1.78 | 67.33±2.11 | **48.00±2.67** $^{**}$ |

| | | | | |
|---|---|---|---|---|
| 3 | 61.00±0.94 | 69.00±2.00 | 64.33±2.43 | 57.67±1.76** |
| 4 | 64.83±1.28 | **64.17±2.05** | **60.17±2.18** | 59.83±2.00* |
| 6 | 62.50±1.35 | 65.33±2.34 | 62.00±2.10 | 64.16±2.11ns |
| 8 | **59.67±0.92** | 68.67±1.62 | 67.17±2.15 | **55.26±1.37**** |
| 10 | 65.83±0.72 | 72.67±1.64 | 72.00±1.85 | 61.16±1.02** |
| 12 | 72.33±1.29 | 76.83±1.40 | 75.50±1.67 | 65.50±1.28*** |

**Figure 1** Percent Serum glucose reduction in normal rats treated with gliclazide, *Didymocarpus pedicellata* (HADP) 200 and 400 mg/kg and their combination. Data (n=3) was represented as Mean±SEM.




**Chromatography :**

The calibration curve for gliaclazide in rat serum was linear in concentration range of 0.1 to 100 µg/ml (Figure 2). Lower limit of quantification (LLOQ) for gliaclazide was 0.5 µg/ml, chromatogram of gliaclazide with internal standard is provided in Figure 3.

**Figure 2** Calibration curve for gliclazide in rat serum

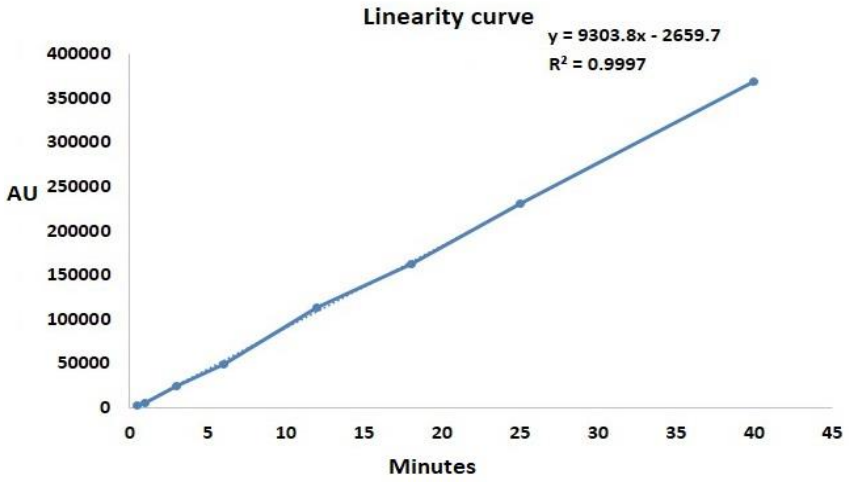
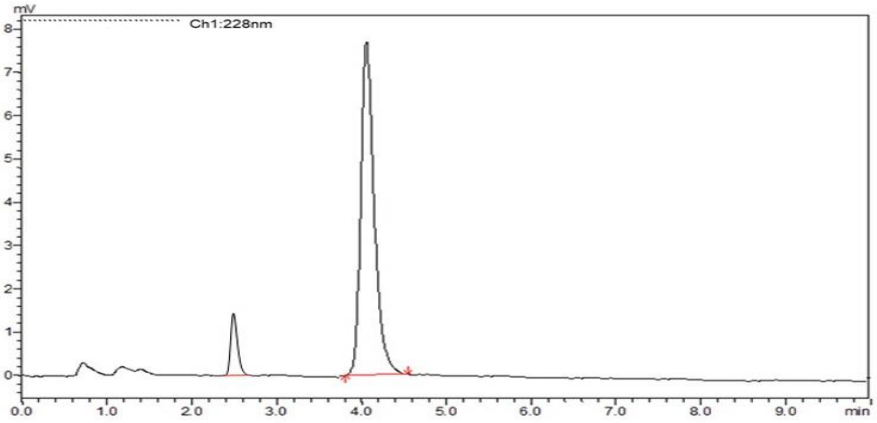


**Figure 3** HPLC chromatogram of gliclazide with internal standard in rat serum




**Pharmacokinetic interaction study in normal rats :**

Pharmacodynamic interaction studies in normal rats demonstrated higher effects with HADP 400 mg/kg dose therefore for further interaction studies this dose was choosen. Gliclazide showed biphasic concentration time data with a $C_{max}$ of 10.78±0.49 µg/ml at 2h and there was an increase in serum concentration at 8h. Co-administration with HADP caused a non significant increase throught all time periods with a $C_{max}$ of 11.46±0.28 µg/ml, which is 5.93% higher than gliclazide only group. Area under curve ($AUC_{0\text{-}inf}$) significantly increased by 5.72% in combined treatment as compared to gliclazide only group ($p<0.05$). Mean resisdence time (MRT) was increased significantly ($p<0.05$) by 1.08%, elimination half life ($T_{1/2}$) increased non significantly by 8.65%, clearance decreased non significantly by 6.31% and volume of distribution (Vd) increased non significantly by 3.13% in combined group as compared to gliclazide only group. Serum gliclazide concentration time profiles of all groups are showed in Figure 4 and determined pharmacokinetic parameters are provided in Table 2.

**Figure 4** Effect of HADP (400 mg/kg) co-administration on serum gliclazide concentration in normal rats. Data (n=3) was represented as Mean±SD

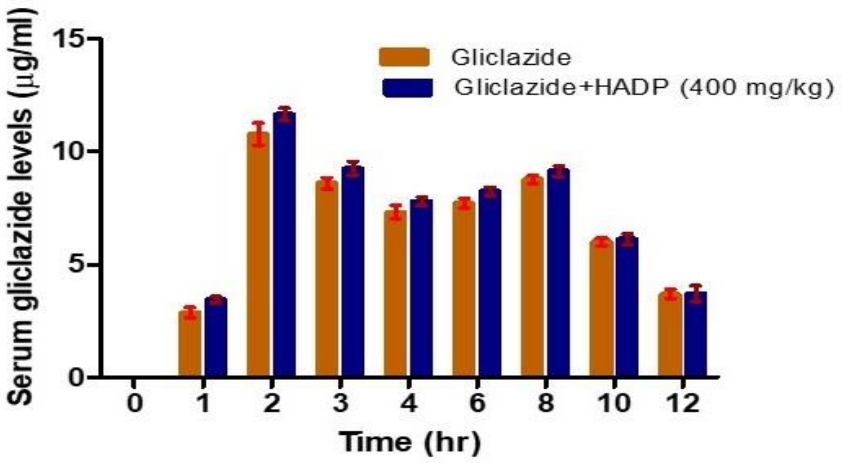


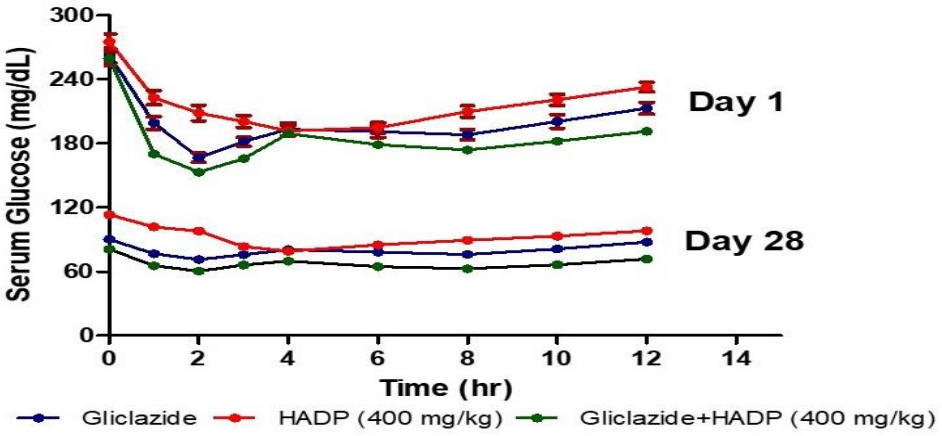
**Table 2** Effect of HADP (400 mg/kg) co-administration on pharmacokinetic parameters of gliclazide in normal rats. Data (n=3) was represented as Mean±SD, analyzed by two way ANOVA and $p < 0.05$ was considered to be significant. $^{*}p<0.05$, $^{***}p<0.001$ when compared to gliclazide.

| PK Parameter | Gliclazide | Gliclazide + HADP (400mg/kg) |
|---|---|---|
| **$AUC_{0-t}$** (µg/ml/h) | 81.91±0.89 | 86.13±1.05*** |
| **$AUC_{total}$** (µg/ml/h) | 98.73±2.30 | 104.97±1.01*** |
| **$T_{1/2}$** (h) | 3.18±0.13 | 3.50±0.17 |
| **Clearance** (L/h/kg) | 0.071±0.00 | 0.064±0.00 |
| **$V_d$** (ml/kg) | 0.084±0.00 | 0.089±0.00 |
| **MRT** (h) | 7.80±0.22 | 8.89±0.40* |
| **$C_{max}$ (**µg/ml) | 10.78±0.49 | 11.46±0.25 |
| **$T_{max}$** (h) | 2.00±0.00 | 2.00±0.00 |

**Pharmacodynamic interaction study in diabetic rats :**

Administration of STZ has caused severe hyperglycemia in the animals indicating induction of diabetes. Administration of gliclazide has caused significant reduction in blood glucose level in comparison to basal level and even it is found to be biphasic with higher reduction at 2h followed by 8h. Maximum reduction in blood glucose level observed was 36.46±0.58% at 2h. Single dose administration of HADP also caused a reduction in blood glucose levels with maximum reduction of 24.29±0.90% at 4h. Simultaneous administration of HADP and gliclazide has caused significantly higher reduction in blood glucose levels as compared to gliclazide only group with a maximum reduction of 44.59±0.79% at 2h post administration. Repeated administration of HADP for 28 days has caused a significant reduction in the blood glucose levels of animals as compared to day1. Simultaneous administration of HADP and gliclazide to diabetic animals has caused higher reduction in blood glucose levels as compared to gliclazide only group (Figure 5).

**Figure 5** Effect of gliclazide, HADP 400 and their combination on serum glucose levels in diabetic rats on day 1 and day 28



**Pharmacokinetic interaction study in diabetic rats :**

Diabetic rats also showed biphasic concentration-time data for gliclazide similar to normal rats. Single dose administration of HADP caused a non significant increase of 6.93% and repeated dose administration of HADP for 28 days caused a significant ($p<0.001$) increase of 26.40% in Cmax. There was a significant variation observed in all major pharmacokinetic parameters with single and repeated administration of HADP with gliclazide. AUCtotal increased by 12.91%, T1/2 by 15.84%, Vd by 3.43%, MRT by 5.76% and clearance decreased by 15.02% with single dose administration. Whereas with repaetad dose administration AUCtotal increased by 54.11%, T1/2 by 74.26%, Vd by 35.94%, MRT by 5.76% and clearance decreased by 35.02%. Serum gliclazide concentration time profiles of all groups are showed in Figure 6 and determined pharmacokinetic parameters are provided in Table 3.

**Figure 6** Effect of HADP (400 mg/kg) co-administration on serum gliclazide levels in diabetic rats on day 1 and day 28

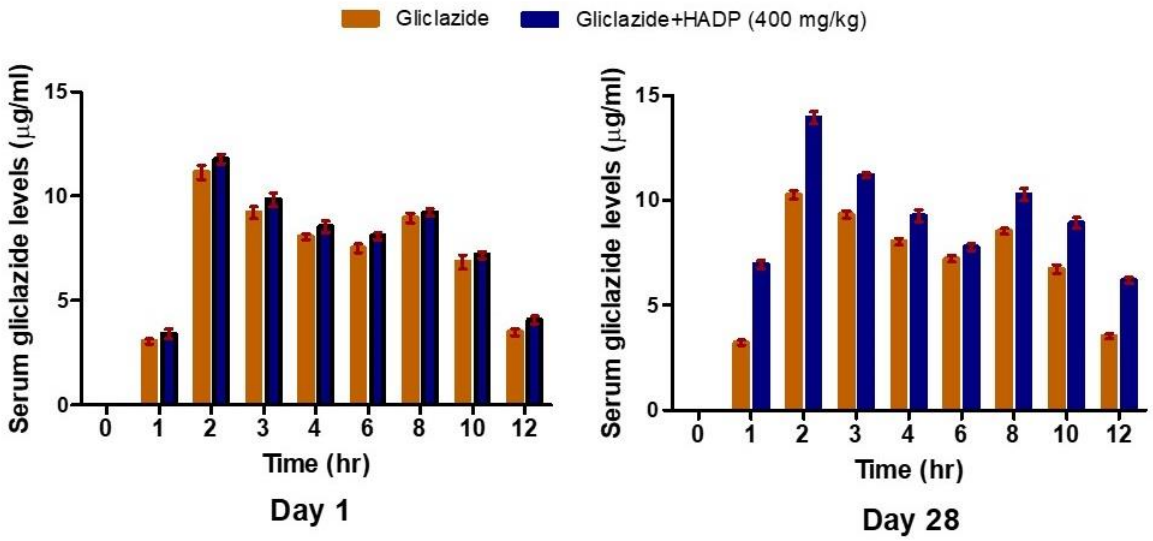



**Table 3** Effect of HADP (400 mg/kg) co-administration on pharmacokinetic parameters of gliclazide in diabetic rats on day 1 and day 28. Data (n=3) was represented as Mean±SD, analyzed by two way ANOVA and $p < 0.05$ was considered to be significant. $^{*}p<0.05$, $^{***}p<0.001$ when compared to gliclazide.

| PK Parameters | Day 1 | | Day 28 | |
|---|---|---|---|---|
| | Gliclazide | Gliclazide + HADP (400mg/kg) | Gliclazide | Gliclazide +HADP (400mg/kg) |
| $AUC_{0-t}$ (µg/ml/h) | 85.57±0.18 | 94.25±0.23*** | 83.61±0.10 | 106.1±0.12*** |
| $AUC_{total}$ (µg/ml/h) | 100.28±1.23 | 112.14±1.92*** | 99.54±1.23 | 154.91±1.12*** |

| | | | | |
|---|---|---|---|---|
| **$T_{1/2}$** (h) | 2.99±0.18 | 3.48±0.14 | 3.13±0.17 | 5.47±0.27*** |
| **Clearance** (L/h/kg) | 0.070±0.00 | 0.066±0.00 | 0.070±0.00 | 0.043±0.00** |
| **$V_d$** (ml/kg) | 0.079±0.00 | 0.088±0.00 | 0.081±0.00 | 0.102±0.00** |
| **MRT** (h) | 7.50±0.10 | 8.24±0.09* | 7.67±0.07 | 10.361±0.04*** |
| **$C_{max}$ (**µg/ml) | 11.14±0.29 | 11.97±0.13 | 10.62±0.01 | 13.94±0.06*** |
| **$T_{max}$** (h) | 2±0$^{ns}$ | 2±0$^{ns}$ | 2±0$^{ns}$ | 2±0 $^{ns}$ |

**Discussion:**

Increased therapeutic usage of medicines from alternative systems is one of the major contributory factor for drug interactions. (19) As diabetes mellitus is one of the predisposing factor for urolithiasis there is propability for co-administration of agents to reduce urolithiasis along with anti-diabetic medication. Present study evaluated herb drug interaction between antidiabetic agent gliclazide and leaves of *Didymocarpus pedicellata,* which is used in Ayurveda for treatment of urolithiasis. Results of the study demonstrated biphasic concentration time data and blood glucose reduction in normal and diabetic animals with gliclazide, which is similar to earlier reports and this might be due to its enterohepatic recycling and biliary excretion(20). To evaluate effect of HADP on blood glucose levels and to optimizatie dose of HADP for further interaction studies normal rats were treated once with 200 and 400 mg/kg doses. Results of the study exhibited reduction in blood glucose levels in normal rats at 200 and 400 mg/kg doses demonstrating hypoglycemic potential of HADP. As the reduction in blood glucose level was dose proportionate 400 mg/kg dose of HADP was used for further interaction studies. Single and repeated dose co-administration of HADP with gliclazide has significantly enhanced hypoglycemic effect of gliaclazide in normal and diabetic rats, which might be due to pharmacodynamics/pharmacokinetic interaction. As HADP demonstrated hypoglycemic effect, the drug interaction might be due to pharmacodynamics interaction between gliclazide and HADP.

As pharmacokinetic interactions are the predominant causative factor for interactions arising from co-administration of herbs and drugs, role of pharmacokinetic interaction in this study was assessed by determination of serum gliclazide after co-administartion of gliclazide and HADP. There was non significant increase in serum concentrations of gliclazide at all the time points and significant variation in major pharmacokinetic parameters such as area under curve, half life, clarance and volume of distribution in single dose co-administered group as compared to gliclazide group. Similar results were observed even in diabetic animals with single dose of HADP co-administration. Repeated dose administration of HADP caused higher variation in the concentrations of gliclazide and its pharmacokinetic parameters as compared to single dose administration. These results depict involvement of pharmacokinetic interaction along with pharamcodynamic interaction upon co-administration of HADP and gliclazide. Pharmacokinetic interaction may arise from variations in absorption/distribution/ metabolism/excretion. As gliclazide has wide and rapid oral absorption without involvement of any transporters, increase in serum levels after co-administration with HADP might not be due to effect on absorption (21). Gliclazide is extensively metabolized in to inactive metabolites by CYP2C9 and 2C19, induction or inhibition of these enzymes will have

significant impact on its serum levels and pharmacokinetics (22). Herbal medicines have many components, which might have impact on CYP metabolic machinary thus causing pharmacokinetic interactions and drug herb interactions (19). β-sitosterol one of the major component of *D.pedicellata* has inhibitory potential on various metabolic enzymes individually and there are also reports of CYP inhibitory potential of plants containing it as major phytoconstituent (23,24). These data suggest its CYP inhibitory property of β-sitosterol, which might be blocking metabolism of gliclazide thus responsible for its increased serum levels when co-administered along with HADP.

**Conclusion:**

Results of our study indicate hypoglycemic potential of HADP and increased reduction of glucose levels in normal and diabetic rats after single and repeated administration along with gliclazide. Study also showed increased serum levels of gliclazide after co-administration with HADP in single/multiple doses in both normal and diabetic animals. Pharmacokinetic interaction might be arising due to metabolic CYP2C9 inhibition by β-sitosterol. From our results it can be concluded that HADP has pharmacokinetic and pharmacodynamics interaction with gliclazide thus causing hypoglycemia with co-administration. So, precautions has to be taken and dose adjustments has to be performed when *D.pedicellata* is used for treatment of urolithiasis in diabetic patient undergoing treatment with gliclazide.

**Ethical Approval :**

The experiments were approved by Institutional Animal Ethical Committee, Roland Institute of Pharmaceutical Sciences, Berhampur (926/PO/Re/S/06/CPCSEA) and conducted as per Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

**Conflict of Interest :**

Authors declare that they have no conflict of interest

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