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Pharmacokinetic And Pharmacodynamic Interaction Of Terminalia Pallida With Gliclazide In Normal And Diabetic Rats

Satyanarayana Chintanippula[a]* and Bimalendu Chowdhury[a]

[a]Dept. of pharmacology, Roland Institute of Pharmaceutical Sciences, Berhampur,Odisha, India-760010.

Abstract:

The Current study aims to investigate the interaction between traditionally used anti-diabetic agent hydro-alcoholic extract of Terminallia pallida fruits (HATP) and oral hypoglycemic agent gliclazide. Initial dose optimization was performed after administration of 200 mg/kg and 400 mg/kg of extract and determining reduction in serum glucose levels in normal rats. A pharmacokinetic interaction study was performed in both normal and streptozocin induced (55 mg/kg) diabetic rats by administration of gliclazide only or combined with HATP at 400 mg/kg. Single-dose and repeated dose (28 days) pharmacodynamic and pharmacokinetic interaction studies were performed in diabetic rats after co-administartion by measuring serum glucose levels and gliclazide levels respectively. Biphasic pharmacokinetic (serum concentration) and pharmacodynamic(reduction in serum glucose levels) profile was demonstrated by gliclazide. HATP demonstrated higher and dose proportionate serum glucose reduction at 400 mg/kg in normal rats. The reduction in serum glucose levels in normal and diabetic rats was significantly higher in the combined group as compared to only gliclazide group. Repeated co-administartion showed a higher reduction in serum glucose levels as compared to single time co-administartion. There was a significant variation observed in pharmacokinetic parameters with single dose co-administartion in normal, diabetic rats and in repeated dose co-administration in diabetic rats. *HATP showed a significant pharmacodynamic and pharmacokinetic interaction with gliclazide, which necessitates caution and dose adjustment in co-administration of gliclazide with HATP to avoid severe hypoglycemia.*

Keywords: Diabetes, Herb-drug interaction, Gliclazide, Pharmacokinetic interaction, Pharmacodynamic interaction, , Terminalia pallida

1. Introduction:

Diabetes mellitus, a prominent non communicable disease arises from an increase in levels of serum glucose either due to damaged pancreatic beta cells leading to reduced secretion of insulin or desensitization of insulin sensitive tissues to insulin. Diabetes and associated complications are a predisposing factors for the development of obesity, metabolic syndrome and cardiovascular

disorders. Globally there is an increase in diabetic patients by 3.8 times in the past three decades and the global diabetic population might be 700 million by year 2045 [1]. Diabetes has increased premature mortality by 5% in the past two decades and it is the causative factor for mortality of 1.5 million individuals globally in year 2019 [2]. The current antidiabetic treatment regimen includes insulin, its preparations, oral hypoglycemic agents such as metformin, thiazolidinediones, sulphonylureas, alpha glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium/glucose cotransporter 2 inhibitors and other injectables like glucagon-like peptide analogs, gastric inhibitory peptide analogs and glucagon like peptide receptor agonists [3]. Although sulfonylureas are associated with adverse effects such as hypoglycemia, weight gain and cardiovascular effects, they are second to metformin in prescription for diabetes [4]. Sulfonylureas bind to the sulfonylurea receptor located on pancreatic beta cell, blocking ATP sensitive potassium channels thus causing causing the release of insulin.

Herbal preparations are a source of drugs and played a crucial role in the treatment of various disease conditions from ancient times. Even in the current era plants form amajor part of alternative and traditional medicine due to their abundant phytomolecules and their multimode pharmacological activities. As per world health organization records there are 21,000 listed medicinal plants, among which 400 are listed for treatment of diabetes [5]. There is an increase in research and prescription intrest for plant derived products as nutritional supplements and as drugs especially for treatment of metabolic disorders such as diabetes mellitus [6–8].Concominant use of herbal preparations and antidiabetic agents may trigger herb-drug interactions (HDI), which can have impact on safety and efficacy of the drug. HDI may arise due to impact of herbs on pharmacokinetics or pharmacodynamics of the drug. Pharmacodynamic interaction may arise due to enhanced secretion of insulin by various phytomolecules and pharmacokinetic interactions may predominantly arise due to impact of herbs on cytochrome P450metabolic machinery [9,10].

The genus ofTerminaliaharbours around 250 species of the plants, which are highly used used in different traditional systems of medicine. Among these plants T. arjuna,T. chebula and T. pallidaare widely mentioned in Ayurveda, the Indian system of traditional medicine [11]. T. pallida is one among this genus, belongs to Combertaceae family, is abundantly distributed in Tirumal hills of South Eastern ghats[12]. It is known as Hridya in Ayurveda due to its cardiotonic and cardioprotective properties and it is also one of the ingredient in renownened Ayurvedic product Triphala, used for treatment of liver disorders and indigestion [11,13]. Fruits of this plant are traditionally employed for treatment of diabetes mellitus, fruit decoction used to treat diarrhea, peptic ulcers and veneral diseases [11]. The major phytoconstituents of this plant include gallic acid, ellagic acid, gallo-tannic acid, chebulagenic acid, mannitol, etc [13,14]. Pharmacological studies reported antioxidant, antiulcer, cardioprotective, antidiabetic, antiadipogenic, hypolipidemic and hepatoprotective activities in in vitro and in vivo models [11,12,14,15]. As fruits of T. pallida are traditionally used for treatment of diabetes mellitus and due to its cardiotonic properties there might be concominant administration of it with other antidiabetic agents such as gliclazide. This study aimed to Current study is designed to iddetermine and assess pharmacological interaction between hydroalcoholic fruit extract of T. pallida and gliclazide using rat models.

2. Materials and Methods:

2.1. Drugs and Chemicals:

Kits used in this study were obtained from Coral clinical systems (Goa, India). Gliclazidewas obtained as a gift sample from Dr. Reddy's laboratory (Hyderabad, India), Streptozocin was procured from Sisco Research Labs (Mumbai, India). Terminaliapallida fruit extract was obtained as a gift sample from Laila ImpexPvt Ltd., (Vijayawada, India). All other reagents and chemicals were procured from Merck Millipore (Massachusetts, USA) and are of analytical grade.

2.2. Animals:

Adult male Wistar rats of age 8-10 weeks old (220- 250gm) were obtained from Mahaveer enterprises (Hyderabad, India) andacclimatized for a week. They were housed as per CPCSEA standard laboratory guidelines with 12 hours light and 12 hours dark cycle, temperature range of 22±3°C and relative humidity of 50±15%. They were fed with standard pellet diet obtained from Hindustan Lever Ltd., (Bangalore, India) and water ad libitum.

2.3. Experimental Design:

2.3.1. Interaction Study in Normal Rats

This study was designed and executed in IV stages. Gliclazide was administered orally at a dose of 2 mg/kg bw after overnight fasting in stage I. Further animals were subjected to blood collection using retro-orbital plexus puncture under mild isoflurane anesthesia at time points- 0.5, 1, 2, 4, 6, 8, 12 and 24h post gliclazide administration. After phase I same animals were allowed to recover for a washout period of one week and used in further stages. In stage II HATP extract was orally administered at a dose of 200 mg/kg bw and blood was withdrawn at the same time points as of stage I. Further animals were administered with HATP extract at dose of 400 mg/kg bw and blood was collected at above time intervals after a wash out period of 7 days in stage III. In stage IV animals were orally administered with HATP extract at 400 mg/kg bw and gliclazide at 2mg/kg bw with 30 minute time gap after a washout period of week and blood samples were collected. Obtained blood samples were subjected to centrifugation at a speed of 5000 rpm for 5 minutes to collect serum. Serum was further utilized for chromatographic analysis and determination of glucose by glucose oxidase (GOD) peroxidase (POD) method.

2.3.2. Interaction Study in Diabetic Rats

Before induction of diabetes mellitus, animals were deprived with feed for 12 h and provided water ad libitum. Streptozotocin was freshly prepared in citrate buffer (pH 4.5) and intraperitoneally injected at a dose of 55 mg/kg bw. To overcome initial phase of hypoglycemia dextrose solution (20%) was intraperitoneally administered 4-6 h of STZ injection. Furter animals were provided orally with 50% dextrose solution till 24 h. Diabetes induction was verified by serum glucose estimation of animals after 72 h using GOD-POD method. Animals with 250 mg/dl or higher glucose levels wereconsidered to be diabetic and utilized for further experiments. Diabetic animals were divided in to three groups, group I animals were orally administered with only gliclazide, group II were administered orally with only HATP extract and group III animals were co-administered with HATP

extract followed by gliaclazide for 28 days. For estimation of gliclazide and glucose levels serum samples were obtained from aniamals on day 1 and 28 at time points 0.5, 1, 2, 4, 6, 8, 12 and 24 h.

2.4. Chromatography

High performance liquid chromatograph (Waters, Japan) with UV or photodiode array detector was used for estimation of serum gliclazide levels. Stationary phase used in the study was C8 column with 5 µm particle size; 100 mm length x 4.6 mm diameter whereas phosphate buffer and acetonitrile cocktail (60:40) was used as mobile phase 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 [16].

2.5. Sample Preparation & Pharmacokinetic Analysis

Test or standard serum sample (100µl) was added to internal standard (100µl), vortex mixed and acetonitrile (200 µl) was added for protein precipitation. Further mixture was vortexed, centrifuged at 3000 rpm for 5 minutes and collected supernatant was filtered through 0.45 µm membrane filter. Filterate (20 µl) was injected in to HPLC for gliclazide analysis and Kinetica 5.0 software was used for analysis of pharmacokinetic data.

2.6. 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.

3. Results

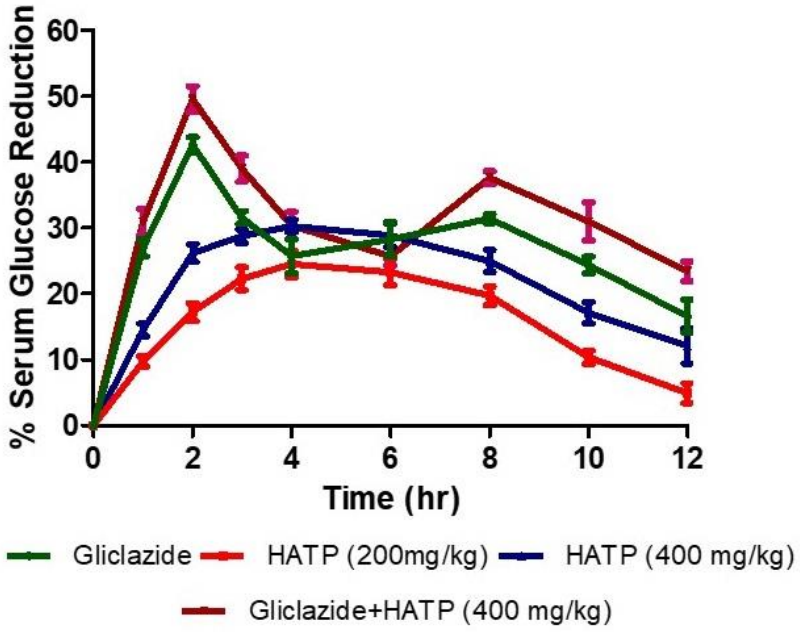
3.1. Pharmacodynamic interaction study in normal rats

Treatment with gliclazide and HATP at 200 & 400 mg/kg bw caused serum glucose level reduction till 12 h (Table 1). Biphasic serum glucose reduction was observed with gliclazide administration. Maximum reduction of 42.62±1.18% and 31.44±0.65% observed at 2h and 8h post administration respectively. Treatment with HATP caused a maximum reduction of 24.54±2.03% and 30.29±0.92% respectively with 200 mg/kg and 400 mg/kg bw at 4h. Co-administartion of gliclazide with HATP 400 mg/kg bw caused significantly higher ($p<0.001$) reduction in serum glucose levels as compared to gliaclazide only treatment with biphasic reduction of 49.57±1.97% at 2h and 37.620±0.99% at 8h (Figure 1).

Table 1 Serum glucose levels in normal rats treated with gliclazide, Terminalia pallida fruit hydroalcoholic extract (HATP) at 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)	HATP (200mg/kg)	HATP (400mg/kg)	Gliclazide+ HATP (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±2.11 ^{ns}
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, Terminalia pallida fruit hydroalcoholic extract (HATP) 200 and 400 mg/kgand their combination. Data (n=3) was represented as Mean±SEM



3.2. Chromatography

Linear calibration curve in concentration range of 0.1 to 100 µg/ml was obtained for gliclazide (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

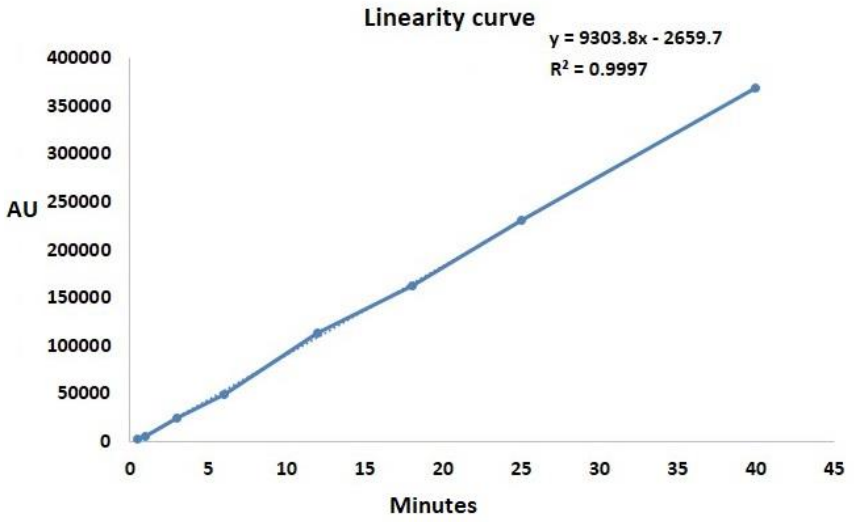
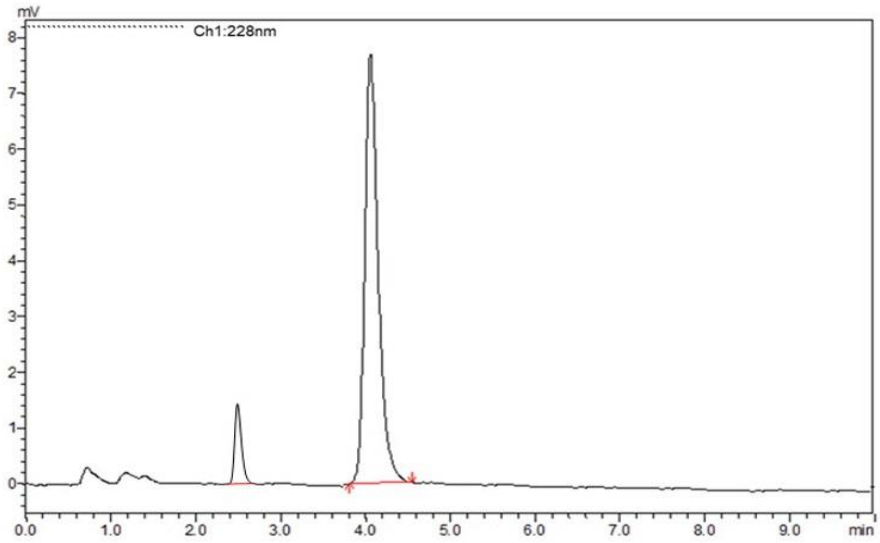


Figure 3 HPLC chromatogram of gliclazide with internal standard in rat serum



3.3. Pharmacokinetic interaction study in normal rats

As pharmacodynamic studies in normal rats demonstrated dose dependent reduction in serum glucose levels, for further studies HATP at 400 mg/kg bw was used. Biphasic conncentartion time data was observed with gliclazid and C_{max} was 11.04±0.31 µg/ml at 2h and second spike of 9.05±0.39 µg/ml observed at 8h. Co-administration of gliclazide with HATP caused significant increase ($p<0.05$) in gliclazide concentration throug all time intervals as compared with only gliclazide treated group and C_{max} was 14.19±0.61 µg/ml. Pharmacokinetic parameters were significantly ($p<0.001$) increased; Area under curve ($AUC_{0\text{-}inf}$) increased by 1.17 times, Mean resisdence time (MRT) by 1.18 times, elimination half life ($T_{1/2}$) by 1.22 times whereas volume of distribution (Vd) increased non significantly by 1.07 times in combined treatment as compared to gliclazide only

treatment. Clearance decreased ($p<0.001$) significantly by 1.30 times in combined group as compared to gliclazide only group.Serum gliclazide concentration time profiles of all groups are depicted in Figure 4 and determined pharmacokinetic parameters are provided in Table 2.

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

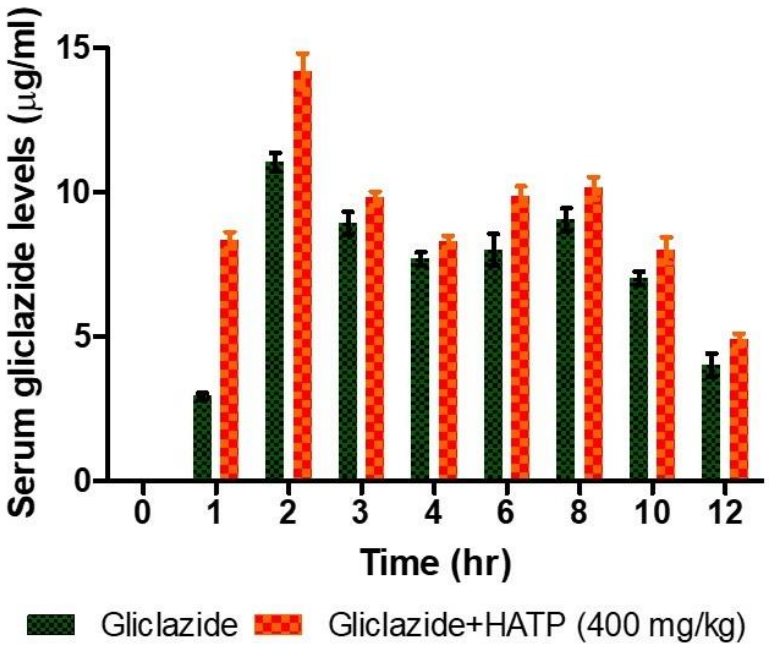


Table 2. Effect of HATP (400 mg/kg) co-administration on pharmacokinetic parameters of gliclazide in normal rats.Data (n=3) was represented as Mean±SD, analyzed by two way ANOVA and $p < 0.05$ was considered to be significant. $^{*}p<0.05$, $^{***}p<0.001$ when compared to gliclazide.

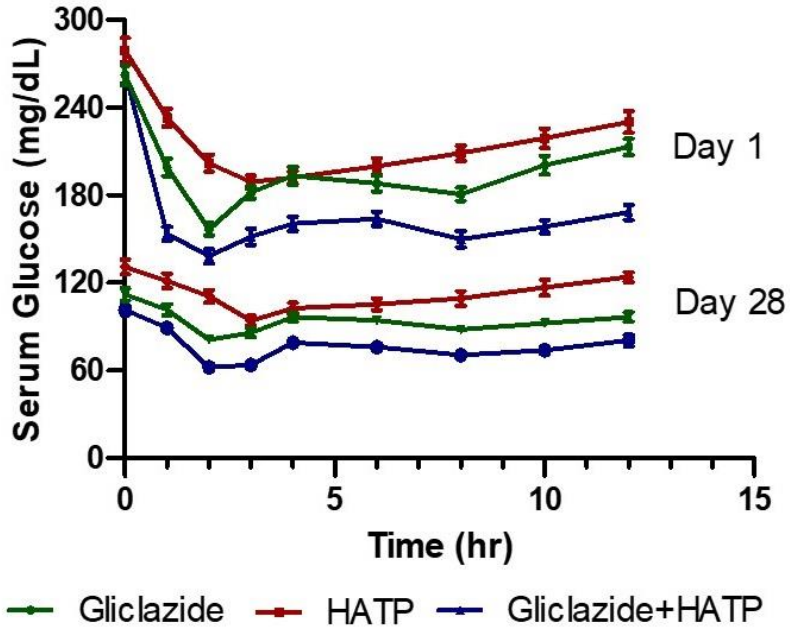
PK Parameter	Gliclazide	Gliclazide + HATP (400mg/kg)
AUC_{0-t}(µg/ml/h)	85.86±1.08	96.99±1.23***
AUC_{total}(µg/ml/h)	101.32±1.92	118.12±2.06***
$T_{1/2}$(h)	2.99±0.14	3.65±0.10
Clearance (L/h/kg)	0.074±0.00	0.057±0.00***
V_d(ml/kg)	0.082±0.00	0.088±0.00
MRT (h)	7.63±0.29	8.97±0.31***
C_{max} (µg/ml)	11.04±0.16	12.10±0.10 **
T_{max}(h)	2.00±0.00	2.00±0.00

3.4. Pharmacodynamic interaction study in diabetic rats

Induction of diabetes mellitus by STZ has caused significant increase in serum glucose levels of the animals. Gliclazide treatment has significantly reduced serum glucose levels as compared to base

levels. In diabetic animals also there was biphasic serum glucose reduction with maximum reduction at 2h followed by 8h. Maximum reduction in blood glucose level observed was 1.67 times at 2h. Single dose administration of HATP also caused a reduction in blood glucose levels with maximum reduction of 1.48 times at 3h. Simultaneous administration of HATP and gliclazide has caused significantly higher reduction in blood glucose levels as compared to gliclazide only group with a maximum reduction of 1.91 times at 2h post administration. Repeated administration of HATP for 28 days has caused a significant reduction in the blood glucose levels of animals as compared to day 1. Simultaneous administration of HATP 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, HATP 400 and their combination on serum glucose levels in diabetic rats on day 1 and day 28



3.5. Pharmacokinetic interaction study in diabetic rats

Similar to normal animal concentration-time data, there was biphasic concentration-time profile observed for gliclazide in diabetic rats. Single dose administration of HATP caused a significant ($p<0.01$) increase of 1.16 times and repeated dose administration of HATP for 28 days caused a significant ($p<0.001$) increase of 1.50 times in C_{max}. There was a significant ($p<0.001$) variation observed in all major pharmacokinetic parameters with single and repeated administration of HATP with gliclazide. AUC_{total} increased by 1.30 times, $T_{1/2}$ by 1.50 times,V_d by 1.19 times, MRT by 1.19 times and clearance decreased by 1.24 times with single dose administration. Whereas with repaetad dose administration AUC_{total} increased by 1.67 times, $T_{1/2}$ by 1.72 times,V_d by 1.43 times, MRT by 1.40 times and clearance decreased by 2.00 times. 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 HATP (400 mg/kg) co-administration on serum gliclazide levels in diabetic rats on day 1 and day 28

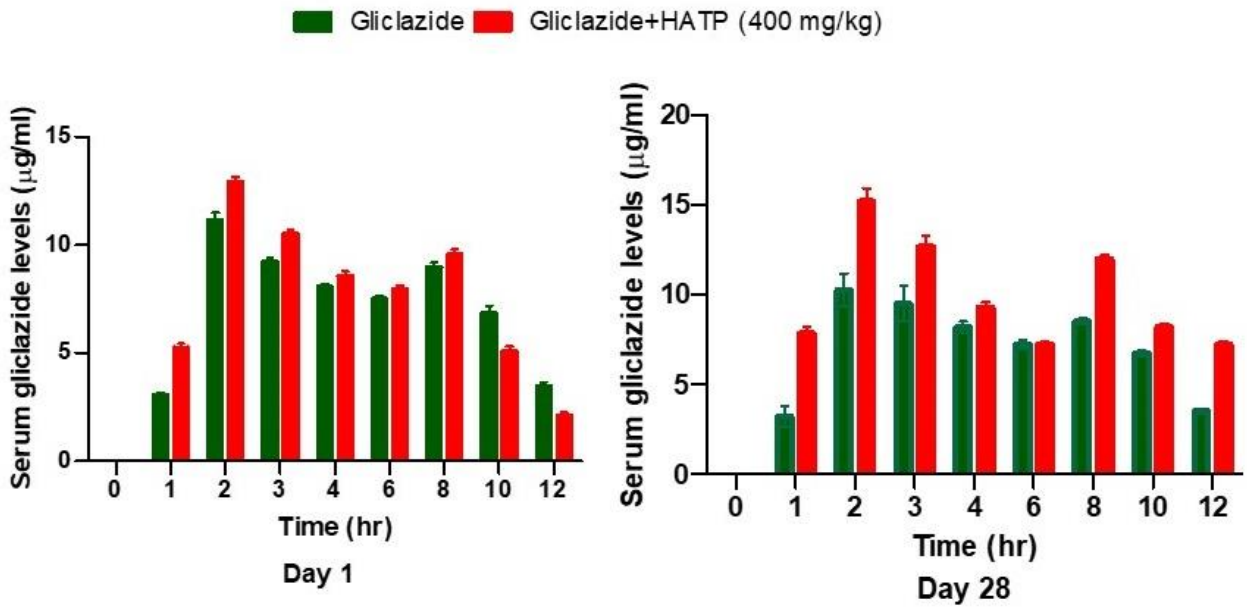


Table 3 Effect of HATP (400 mg/kg) co-administration on pharmacokinetic parameters of gliclazide in diabetic rats on day 1 and day 28. Data (n=3) was represented as Mean±SD, analyzed by two way ANOVA and $p < 0.05$ was considered to be significant. $^{*}p<0.05$, $^{***}p<0.001$ when compared to gliclazide.

PK Parameters	Day 1		Day 28	
	Gliclazide	Gliclazide + HATP (400mg/kg)	Gliclazide	Gliclazide +HATP (400mg/kg)
AUC_{0-t}(µg/ml/h)	84.31±1.10	95.68±0.99***	85.19±1.27	111.65±2.08***
AUC_{total}(µg/ml/h)	98.79±1.47	128.20±2.03***	101.27±2.39	169.08±3.86***
$T_{1/2}$(h)	2.94±0.37	4.42±0.23	3.19±0.19	5.50±0.31***
Clearance (L/h/kg)	0.073±0.00	0.059±0.00	0.070±0.00	0.035±0.00***
V_d(ml/kg)	0.072±0.00	0.086±0.00	0.076±0.00	0.109±0.00***
MRT (h)	7.62±0.23	9.06±0.49*	7.60±0.09	10.68±0.07***
C_{max} (µg/ml)	11.28±0.48	12.93±0.61	10.75±0.1	15.72±0.15***
T_{max}(h)	2±0^{ns}	2±0^{ns}	2±0^{ns}	2±0^{ns}

4. Discussion:

Concominant usage of medicines from traditional systems of medicine is predominant factor for drug interactions as they will be used without consulting with physicians [17]. As drugs from traditional medicine are considered safe they will be used without prescription and especially in case of chronic metabolic disorderes there is more possibility of co-administration of medicines from other systems along with antidiabetic drugs. In this study we evaluated hern drug interaction of gliclazide and fruits of Terminalia pallida, which is traditionally used for treatment of diabetes. Study results depicted biphasic pharmacokinetic and pharmacodynamic profile of gliclazide in both diabetic and normal animals due to enterohepatic recirculation and biliary excretion as observed in literature [18]. Intially HATP was administered at 200 and 400 mg/kg bw doses for dose optimization and test efficacy in normal rats. Results of the demonstrated dose dependent hypoglycemic potential of HATP and from this data 400 mg/kg dose was used for further experiments. There was a significant increase in blood glucose reduction effect of gliclazide observed in single and repeated dose co-administration of HATP in normal and diabetic rats, which might be due to pharmacodynamics and or pharmacokinetic interaction. HATP only administration showed reduction in blood glucose levels indicationg pharmacodynamic drug-herb interaction between gliclazide and HATP.

Role of pharmacokinetic interaction was further studied by determining pharmacokinetic parameters in normal and diabetic animals after co-administartion. There was 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 HATP co-administration. Repeated dose administration of HATP depicted higher variation in the serum gliclazide levels and pharmacokinetic parameters as compared to single dose administration. These results suggest involvement of both pharmacokinetic and pharmacodynamic herb-drug interaction between HATP and gliclazide. Pharmacokinetic interaction may not involve absorption phase for gliclazide as it has rapid oral absorption [19]. 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 [20]. Plant based treatments might have possible effect on CYP450 metabolic machinery due to their ubiquitous components, which might cause pharmacokinetic interactions and drug herb interactions [17]. Gallic acid one of the major phytoconstituents has inhibitory effect on CYP3A4 metabolic machinery and several studies reported metabolic inhibitory potential of Terminalia arjuna, another plant from same genus [21,22]. These data suggest a possible metabolic machinery inhibition by HATP, which might be causing pharmacokinetic herb-drug interaction.

5. Conclusion:

Current study results demonstrate hypoglycemic potential of HATP and enhanced hypoglycemic effect of gliclazide when co-administered once or repeatedly with HATP in normal and diabetic rats. Our Study also demonstrated significant rise in gliclazide serum levels in normal and diabetic rats

after HATP co-administration in single or multiple doses. Inhibition of CYP based metabolic machinery by gallic acid and other components of HATP might be responsible for increase in serum gliclazide levels, thus causing pharmacokinetic interaction. Study results conclude that HATP 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 by patients when HATP is used in alternative systems of medicine in diabetic patient undergoing treatment with gliclazide.

6. 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.

7. Conflict of Interest

Authors declare that they have no conflict of interest

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