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Effect of Ethanol Root Extract of *Calliandra Portoricensis* on the Pharmacokinetic fate of Glibenclamide in Rats

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ABSTRACT

Background: Concomitant administration of herbs with conventional drugs may cause pharmacokinetic modification of the drugs, leading to drug toxicity or therapeutic failure. The observed use of *Calliandra portoricensis* (Jacq.) Benth in diabetic patients on glibenclamide has aroused interest and its possible influence on the pharmacokinetics of glibenclamide was investigated.
Methods: The dried root of *Calliandra portoricensis* was pulverized and extracted in 90% ethanol to obtain the crude extract used in this study. After 10 h overnight fast, 30 rats previously acclimatized were given glibencalmide (10 mg/kg) orally. Following a 3-week washout period, the rats were given ethanol root extract of *C. portoricensis* (500 mg/kg) for 5 days followed by glibenclamide (10 mg/kg). In both studies, blood samples were collected from 0 - 48 h post-dosing and assayed for the concentration of glibenclamide using a well-validated HPLC method and the Pharmacokinetic parameters computed.
Results: The C_{max}, $AUC_{0-\infty}$ were significantly lowered ($P<0.05$) in the co-administered group, which resulted in a decrease in bioavailability. The K_{el}, V_d, T_{max} and MCR were higher in the combination group ($P<0.05$). Thus suggests that concomitant use of *C. portoricensis* may have influenced the absorption of glibenclamide thus resulting in decreased AUCan ; also, increase in V_d may have caused increase in the clearance.
Conclusion: The interaction between glibenclamide and *C. portoricensis* may be attributed to the presence of some metal ions in the plant. Thus, caution is advised in the concurrent use of these remedies.

1. Introduction

Plant extracts have been used for a long time as traditional remedies for different ailments in many parts of the world. *Calliandra portoricensis* (Jacq.) Benth (Mimosaceae), a plant originally from West Indies is found in the forest of West Africa expanding from Ivory Coast to Nigeria[1]. *Calliandra portoricensis* locally known as *tude* in Yoruba, *Ogbese* or *Eri Agbo* in Igbo is widely used in Nigeria by traditional herbal practitioners for the treatment of snake bite[2]. The methanol extracts of the roots and leaves of *Calliandra portoricensis* are reported to have antioxidant, analgesic, anticonvulsive, anticancer and anti-inflammatory properties[3-6]. It is also used in the treatment of ulcers, venereal diseases, as an abortifacient, laxative and antisickling agent[7-10].

Glibenclamide (glyburide, Figure 1) is a potent, second-generation oral sulphonylurea antidiabetic agent

widely used to lower blood glucose levels in patients with type II diabetes mellitus as well as gestational diabetes when diet and weight control have proved inadequate[11]. It acts by stimulating the secretion of insulin and enhancing its utilization by appropriate tissues[12]. A number of drug interactions with glibenclamide have been reported. The hypoglycemic activity of glibenclamide is enhanced when administered with captopril, enalapril, chloramphenicol succinate, cefaloridine and cimetidine[13-16]. However, its serum level and hypoglycemic activity are reduced by rifampicin[17], its bioavailability is influenced by antacids1[18, 19]. In 2006, Zaman et al.,[16] demonstrated that glibenclamide formed diamagnetic and nonionic complexes with some metals - magnesium, chromium, cobalt, nickel, zinc and cadmium.

There is increasing awareness on the interactions of herbal medicines with synthetic drugs. These interactions in most instances alter the pharmacokinetic fate of the synthetic drug in patients who are under medical treatment, leading to an increase or decrease in plasma concentrations[20]. The alterations may cause toxicity or lead to therapeutic failure, hence, the need to evaluate possible interaction of such combinations. Increasing prevalence of diabetes in our population[21] and observed use of *Calliandra portoricensis* by traditional medicine practitioners for the treatment of ulcer and arthritis in diabetic patients on glibenclamide has aroused our interest especially in its possible interaction with the antidiabetic drug, which has gained prominence in the management of type II diabetes mellitus.

With the ever-increasing patronage of *Calliandra portoricensis*, there is no scientific literature report of any work on its interaction with glibenclamide whether on a short or long term use. Therefore, this study is aimed at investigating the pharmacokinetic fate of glibenclamide viz-à-viz its possible interaction with *Calliandra portoricensis* when administered concomitantly in order to ascertain the safety and efficacy of such co-administration.

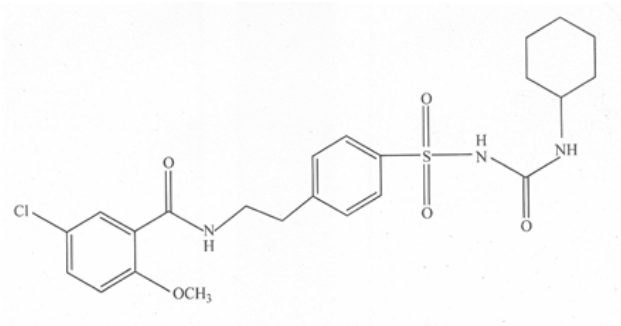

Figure 1: Structure of glibenclamide

2. Materials and methods

2.1 Plant collection, identification and preparation

The root of *Calliandra portoricensis* was harvested in May 2017 from the Botanical Garden of the University of Lagos and authenticated in the Department of Botany, University of Lagos. A specimen of the plant with voucher number (LUH 4598) has been deposited in the Department of Botany Herbarium. The roots were washed, cut into small pieces, oven dried at 40 ºC for two weeks and pulverized in an impact mill. About 854 g of the powdered root was macerated in 2000 mL of 90% ethanol, regularly stirred for 7 days. Filtration was carried out using a Whatman filter paper No 4. The extract was concentrated *in vacuo* and lyophilized to obtain a yield of 274.11 g (32.10% w/w) of the starting dried plant material. The crude extract residue was stored in an airtight bottle and kept in a refrigerator at -20 ºC until used.

2.2 Chemicals and reagents

All chemicals used were of analytical reagent grade. Hydrochloric acid (Riedel- de Haën, Germany), HPLC grade methanol and acetonitrile, glibenclamide reference standard (Sigma-Aldrich), ethanol, ammonia, potassium dihydrogen orthophosphate (BDH Chemicals Limited, Poole England). Olive oil and tablets of glibenclamide were locally purchased. The internal standard, amlodipine was a gift from Swiss Pharma Nigeria.

2.3 Animal study

Thirty Wistar rats used for the study were of both sexes weighing (350 ± 15 g); they were obtained from the Animal Care Centre of the College of Medicine, University of Lagos and acclimatized for 14 days. The animals were kept in a well-ventilated animal house at 25 ± 5 ˚C; 12:12 h (light: dark cycle) and humidity of 55 ± 5%. They were kept in separate plastic cages by gender to avoid conception before and during the study and cared for according to ILAR guidelines, 1996[22]. The animals were fed with standard pellet chow and water *ad libitum*. This study was approved by the Human Research and Ethics Committee (HREC) of the College of Medicine of the University of Lagos, Nigeria with approval number, CMUL/HREC/11/17/304.

2.4 Phytochemical screening

The aqueous ethanol extract of the root of *Calliandra portoricensis* was subjected to preliminary phytochemical screening for the presence of secondary metabolites using standard procedures as described by

Harborne[23] and Talukdar et al.,[24]

2.5 Preparation of standard stock and drug working solutions

Glibenclamide powder, 50 mg and amlodipine (internal standard), 10 mg were separately dissolved in 100 mL distilled water to obtain 500 µg/mL and 100 µg/mL of standard solutions respectively. Glibenclamide stock solution was further diluted to give a working solution of 150 µg/mL from which the calibration curve concentrations were obtained. Amlodipine solution was further diluted to 10 µg/mL. All the solutions were stored at -80 °C.

2.6 Preparation of the root extract of Calliandra portoricensis for administration

The extract of *Calliandra portoricensis,* 5 g was mixed with acacia powder solution, 0.1 g/mL in distilled water. The mixture was further diluted to 10 mL with distilled water.

2.7 Analysis of metals in the root of extract of Calliandra portoricensis

The determination of metals followed a standard procedure as described by Ukpo et al.,[25]. The apparatus were washed and soaked in 10% nitric acid overnight then rinsed with de-ionized water and kept to dry. The powdered root of the plant, 2 g was incinerated in a muffle furnace at 600 °C for 3 h; the ash was dissolved in 5 mL of $HNO_3/HCl/H_2O$ (1:2:3 v/v/v) and heated gently for 30 min until brown fumes disappeared. The ash mixture was filtered and the filtrate made up to 50 mL with de-ionized water. The resultant solution was used for the determination of the presence of copper, zinc, lead, nickel, cadmium, chromium, magnesium, sodium, calcium, potassium and iron using atomic absorption spectrophotometer (Perkin – Elmer model 2380). Calibration curves were prepared for each metal from which the amounts of the metals present in the root extract were obtained as mg metal per 100 g of the plant material.

2.8 Administration of Calliandra portoricensis and blood sample collection

After 10 h overnight fast, the animals were given single oral dose of 10 mg/kg b.wt of glibenclamide. Blood samples, 0.1 mL were withdrawn from each rat by a retro-orbital puncture at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 h post-dosing into heparinized Eppendorf tubes and centrifuged immediately at 3000 g for 15 min at room temperature. Plasma was separated using a Pasteur pipette and stored at -80 °C until assayed. In another study, the animals were allowed a washout period of three weeks after which they were fed orally with *Calliandra portoricensis,* 500 mg/kg b.wt daily for 5 days. On the 5th day, at 15 min post-administration, the animals received by oral route 10 mg/kg b.wt glibenclamide; blood samples were collected and treated as in the first study. In both study periods, the animals were not allowed food until 3 h post-dosing. All the samples were assayed within one week of collection.

2.9 Chromatographic conditions and analysis of glibenclamide

The plasma concentration of glibenclamide was determined by a validated high-performance liquid chromatography using the method of Kumar et al.,[26] with some modifications. Basically, the method consisted of spiking the plasma with 1 µg/mL of amlodipine solution (internal standard) and separation of the drugs from the plasma sample by deproteinization using 1 mL acetonitrile. The clear supernatant layer was subjected to HPLC (Agilent 1100 series pump; serial No DE 43630403, Product No G1311A, Hewlett Packard, Germany) analysis using a reverse phase column (C_8 Zorbax Eclipse column, 5 µm particle size, 150 mm x 4.6 mm i.d.) set at ambient temperature with ultraviolet detector (Serial No JP43826101 product No G1314A, Japan) set at a wavelength of 253 nm. An autosampler LC 420 was used as the injector; the flow rate was 0.8 mL/min. The mobile phase consisted of a mixture of acetonitrile and monobasic potassium dihydrogen orthophosphate (40:60 v/v).

2.10 Calibration procedure

Drug-free plasma was spiked with a standard solution of glibenclamide to yield final concentrations of 5 to 80 µg/mL of glibenclamide. To each spiked plasma, 100 µL of 10 µg/mL amlodipine and acetonitrile, 1 mL were added and vortexed. The mixture was centrifuged at 5,000 g for 10 min and 20 µL of the separated supernatant was injected into the HPLC. The peak area ratio of glibenclamide to amlodipine (I.S.) was plotted against its corresponding concentration and the calibration equation obtained from the plot was used to extrapolate for the concentration of glibenclamide in each of the plasma samples.

2.11 Assay validation method

2.11.1 Recovery, precision and accuracy

Comparison of the peak area ratio of glibenclamide in the drug-free plasma with that obtained by direct injection of the same concentration of glibenclamide was

used to determine the extent of the recovery of glibenclamide from the plasma. The intra and inter day assays (n=5) were obtained using four different concentrations of 1, 5, 10, 20 and 40 µg/mL. Working standard drug solutions were prepared fresh on days of assay; relative standard deviation and coefficient of variation were used to assess the precision of the assay method.

2.11.2 Assay stability of glibenclamide

Stability of glibenclamide in distilled water and in spiked plasma was determined within a four-week period following the method of Owolabiet al.,[27]. The drug solution (n = 5, 20 µg/mL) prepared in amber bottle and stored at room temperature was assayed once a week for the period of study. The concentration of glibenclamide in the spiked plasma (n = 5, 20 µg/mL) was determined on the day it was prepared and thereafter stored at – 80 °C. On the day of assay, the plasma was thawed, re-assayed and frozen for the period of the study. The concentrations of glibenclamide were extrapolated from a calibration curve obtained from freshly prepared standard stock solution.

2.12 Pharmacokinetic analysis of data

The plasma concentration-time data was obtained by non-compartmental analysis. The pharmacokinetic parameters which comprise, the time to achieve peak plasma concentration (T_{max}), the maximum plasma concentration (C_{max}), distribution (V_d), the elimination half-life ($t_{1/2el}$), metabolic clearance (MCR) were estimated by the non-compartmental model using WinNonlin Professional® PK modeling tool version 2.1 Pharmacokinetic software[28]. The area under the curve ($AUC_{o\rightarrow\infty}$) was estimated by the trapezoidal rule method and extrapolated to infinity.

2.13 Statistical analysis

Data were expressed as mean ± SD (standard deviation). The statistical difference in the pharmacokinetic parameters for the groups was accessed by means of an unpaired Student's t- test using Graph pad with the level of statistical significance (P) set at 0.05.

3. Results

3.1 Phytochemical screening and the levels of metal in the ethanol root extract of CP

The ethanol root extract of *Calliandra portoricensis* was found to contain saponins, glycosides, alkaloids and terpenoids with flavonoids being present in abundance. Tannins and anthraquinones were absent. Table 1 shows the metal contents of the root extract of CP. The plant root extract contains metals such as copper (Cu), zinc (Zn), nickel (Ni), chromium (Cr), magnesium (Mg), sodium (Na), calcium (Ca) and potassium (K). The toxic heavy metals, lead (Pb) and cadmium (Cd) were below the detectable level. The levels of essential metals in the extract were found to be higher than those of the nonessential metals. The abundant level of macro-elements, Ca^{2+} and Mg^{2+} were 853.02 ± 48.04 mg/kg and 210.03 ± 11.05 mg/kg respectively. Among the micro-elements, Ni and Cr contents were very low.

Table 1: Mean content of micro and macro elements in the root extract of *Calliandra portoricensis*

Mineral	Mean concentration (mg/kg)
Micro-elements	
Cu^{2+}	31.60 ± 2.03
Zn^{2+}	94.704 ± 4.93
Ni^{2+}	5.33 ± 1.16
Cr^{2+}	1.33 ± 0.58
Macro-elements	
Ca^{2+}	853.02 ± 48.04
Na^{+}	40.73 ± 1.53
K^{+}	35.71 ± 1.53
Mg^{2+}	210.03 ± 11.05

Values are mean ± SD; (n = 5)

Validation Method

Glibenclamide was stable under the conditions of the experiment. The percentage recovery of glibencamide in distilled water or in plasma stored at -80 °C was good throughout the experiment as shown in Table 2. There were no significant changes ($p>0.05$) observed in the concentration of glibenclamide store in distilled water or obtained from repeated freezing and thawing of the plasma. The precision measured as relative standard deviation were less than 6% for all the concentrations studied. The linearity of response was evaluated by plotting the peak area ratio of glibenclamide to amlodipine (I.S.) against its corresponding concentration. The method used gave a good linearity; the regression equation for the result was $Y = 0.112X + 0.0175$ with $R^2 = 0.9995$ (n = 5). The plasma concentrations of glibenclamide (X) were extrapolated from the regression equation. The intra- and inter-day precision, measured as coefficient of variation were less than 5% for all the concentrations studied (Table 3). Accuracy, expressed as percentage bias was not significant ($p>0.05$); the values ranged from -0.45% to -3.00% for intra and inter-day assays. Accuracy as assessed by the

percentage recovery of glibenclamide in the plasma for the intra-day and inter-day assays ranged from 97.11 ± 0.13% to 99.61 ± 0.58% and 97.8 ± 0.21% to 98.6 ± 0.33% respectively (Table 3).

Table 2: Stability of glibenclamide in plasma at room temperature and at -80 °C

Periods (weeks)	Initial Concentration (20 µg/ml)			
	Room Temperature		- 80 °C	
	Final conc. µg/ml	Precision % R. S. D	Final conc. µg/ml	Precision % R. S. D
0	20.1±1.96	3.89	19.9±2.32	5.64
1	20.0±2.14	5.72	20.1±1.89	5.52
2	19.8±2.06	5.67	20.0±1.78	4.94
3	20.1±2.31	4.32	19.7±2.11	2.98
4	19.6±1.83	4.54	19.9±1.38	3.87

Values are mean SD

Table 3: Intra-day and Inter-day precision and accuracy of glibenclamide determination in plasma.

Nominal concentration (µg/ml)	Concentration found [a] (µg/ml)	R.S.D. (%) [b]	Accuracy [c] (%)	Recovery [a] %
Intra-day (n = 5)				
1	0.91 ± 0.11	2.45	-3.00	97.11 ± 0.13
5	4.93 ± 0.16	0.76	-1.40	98.65 ± 0.43
10	9 78 ± 0.09	0.54	-2.20	97.82 ± 0.28
20	19.60 ± 0.37	0.39	-2.20	97.80 ± 0.66
40	39.80 ± 0.47	0.57	-0.45	99.61 ± 0.58
Inter-day (n = 5)				
1	0.98 ± 0.23	3.97	-2.00	98.1 ± 0.35
5	4.89 ± 0.36	3.83	-2.20	97.8 ± 0.21
10	9 85 ± 0.17	2.78	-1.50	98.5 ± 0.16
20	19.70 ± 0.45	4.21	-1.45	98.6 ± 0.33
40	39.11 ± 0.68	2.93	-2.20	97.8 ± 0.49

[a]Values are mean SD

[b]coefficinet of variation

[c]% bias = (conc. found – nominal conc.)/nominal conc. X 100

3.3 Pharmacokinetic analysis of data

A representative chromatogram of the standard solution of glibenclamide and the internal standard, amlodipine presented in Fig. 2 is as obtained from a fully validated HPLC method, while Figs. 3a and 3b present representative chromatograms of the plasma concentration of glibenclamide with or without the ethanol root extract of *Calliandra portoricensis* respectively. The mean plasma concentration-time curve of glibenclamide with or without simultaneous administration of *Calliandra portoricensis* is shown in Figure 4. The pharmacokinetics parameters of glibenclamide following treatment with or without the ethanol root extract of *Calliandra portoricensis* are presented in Table 4. Glibenclamide was rapidly absorbed after administration; its concomitant administration with the ethanol root extract of *Calliandra portoricensis* resulted in a significant ($p<0.05$) decrease in the absorption of glibenclamide by 37.14% with decreases in C_{max} and T_{max} by 33.73% and 8.99% respectively. The ethanol root extract of *Calliandra portoricensis* caused a 69% increase in the volume of distribution (V_d). However, there was a significant decrease ($p<0.05$) in AUC_{0-48} when glibenclamide was co-administered with *Calliandra portoricensis* root extract.

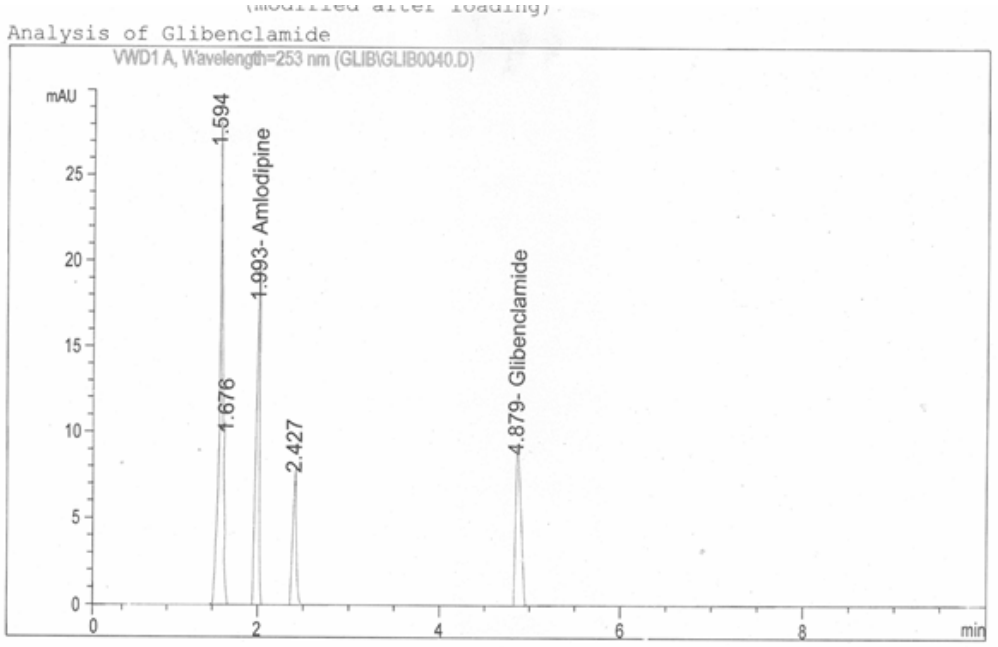

Figure 2 A representative chromatogram of glibenclamide and amlodipine (IS)

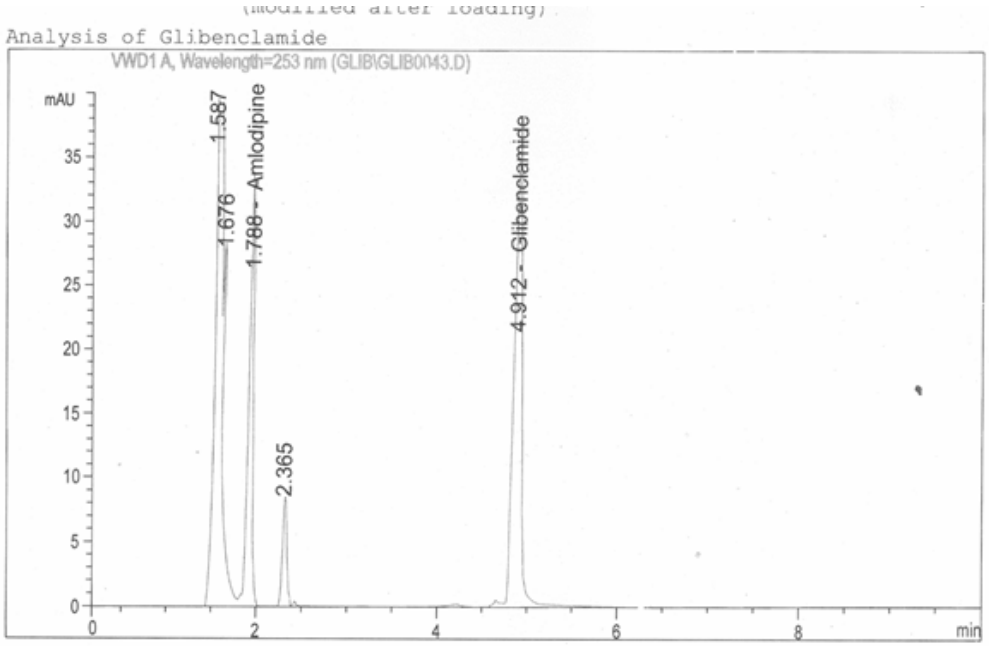

Figure 3a. A representative chromatogram of the plasma concentration of glibenclamide with the ethanol root extract of *Calliandra portoricensis.*

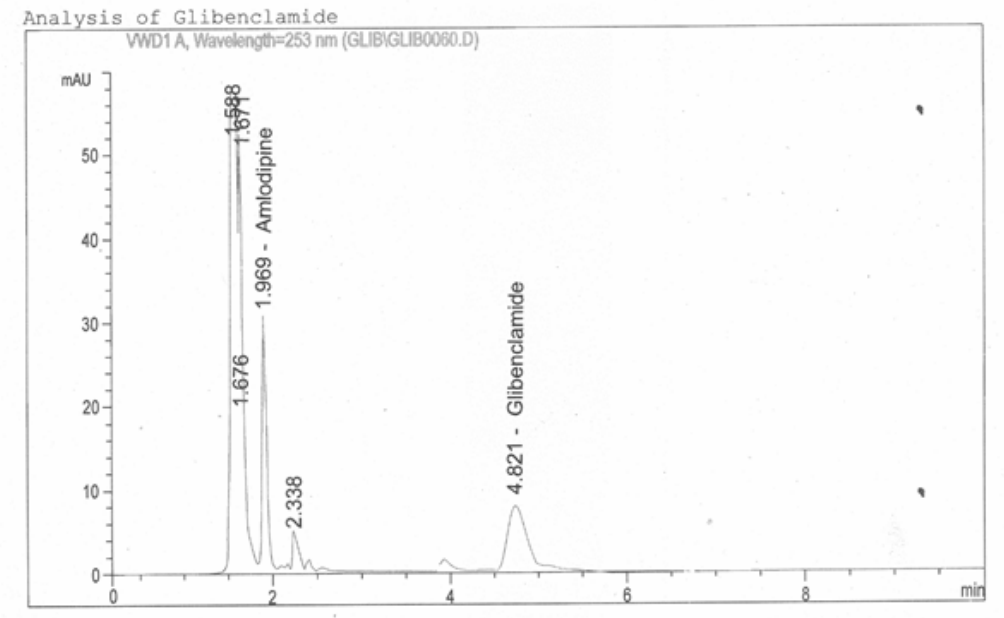

Figure 3b. A representative chromatogram of the plasma concentration of glibenclamide without the ethanol root extract of *Calliandra portoricensis*.

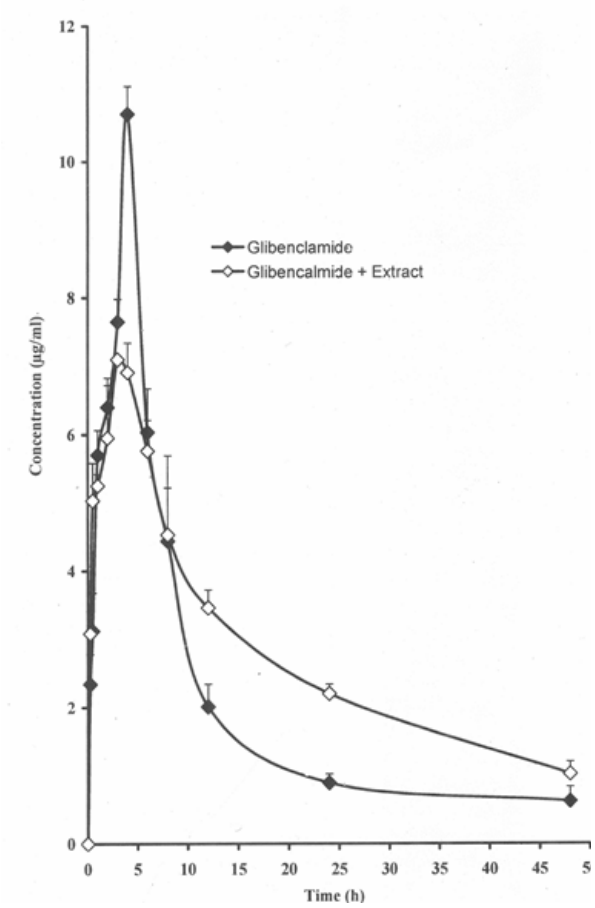

Figure 4. Mean plasma concentration-time curve of glibenclamide with (◊) and without (♦) co-administration of C*alliandra portoricensis*.

Figure 3b. A representative chromatogram of the plasma concentration of glibenclamide without the ethanol root extract of *Calliandra portoricensis*.

Pharmacokinetic Parameters	Glibenclamide	Glibenclamide + *Calliandra portoricensis*
$T_{½ab}$ (h)	2.33 ± 0.52	1.93 ± 0.66
$T_{½el}$ (h)	4.13 ± 1.09	3.67 ± 0.48
K_{ab} (h^{-1})	0.33 ± 0.08	0.45 ± 0.14
K_{el} (h^{-1})	0.17 ± 0.07	0.20 ± 0.02
C_{max} (µg/mL)	14.5 ± 3.62 [a]	9.71 ± 4.14[a]
T_{max} (hr)	3.67 ± 0.33 [a]	4.00 ± 2.00[a]
V_d (mL/Kg)	17.4 ± 8.17[a]	29.4 ± 11.5[a]
MCR (mL/Kg.h)	2.95 ± 0.89	5.56 ± 2.18
F	0.55 ± 0.15[b]	0.51 ± 0.11[b]
$[AUC]_{0-48}$ (µg.h/mL)	115 ± 20.7	89.4 ± 40.6
$[AUC]_{0-\infty}$ (µg.h/mL)	121 ± 17.4	97.4 ± 40.3

Values are mean±SD; [a]$p<0.05$; [b]$p>0.05$

$T_{½ab}$, absorption half-life; $T_{½}$el, elimination half-life; K_{ab}, absorption rate constant; K_{el}, elimination rate constant; C_{max}, maximum concentration; T_{max}, time to maximum concentration; V_d, volume of distribution; MCR, metabolic clearance; F, bioavailability; AUC, area under concentration.

4. Discussion

A number of drug interactions with glibenclamide have been reported, many of which are potentially hazardous. The bioavailability of glibenclamide has been reported to be influenced by antacids[16,29] which are known to contain divalent metals. Thus the possibility of glibenclamide interacting with metal-containing products when co-administered is evident. Therefore this study sought to investigate the possible pharmacokinetic interaction of glibenclamide after concomitant administration with *Calliandra portoricensis*, a medicinal plant used in the treatment of arthritis and which is suspected to contain some metals.

The use of *Calliandra portoricensis* in the treatment of hypertension could be due the abundant presence of the macro-elements, Ca^{2+} (853.02 ± 48.04 mg/kg) and Mg^{2+} (210.03 ± 11.05 mg/kg) in the plant root extract. The very low levels and non-detectable level of some toxic heavy metals might be an indication that the soil in the plantation sites of C*alliandra portoricensis* was not contaminated. There are reports that glibenclamide forms complexes with essential and trace metals. The high concentration of Ca^{2+} in the root extract of *Calliandra portoricensis*, supports the report that calcium carbonate retards the availability of glibenclamide[30]. The study of Zaman *et al.,*[16] reported the complex formation of magnesium, zinc, chromium and nickel with glibenclamide. Thus the presence of these metals in the root extract of *Calliandra portoricensis* may have a significant effect on the absorption of glibenclamide

as it may hinder the permeability of the drug through the gut wall. With this, the result of our pharmacokinetic study of glibenclamide was not unexpected.

Glibenclamide either in distilled water or plasma stored at -80°C was stable throughout the experiment. According to Eurachem guide[31], an analytical response is linear over certain concentration ranges if the regression (R^2) value obtained is higher than 0.995. Therefore the regression value of R^2 = 0.9995 obtained in this study indicates good linearity. That the intra- and inter-day precision was less than 5% for all the concentration studied indicates that 10% of the results obtained were equal to the mean. The accuracy, expressed as percentage bias was not significant, evident from the fact that there is no obvious difference between the mean concentration and nominal concentration of the glibenclamide.

The pharmacokinetic results of glibenclamide showed a rapid absorption after administration with increased maximum plasma concentration, C_{max}. However, concomitant administration of glibenclamide and the root extract of *Calliandra portoricensis* showed a significant ($p<0.05$) decrease in C_{max} by 33 % and an increase in T_{max} by 8.99 %. The faster a drug is absorbed, the greater the peak plasma concentration, C_{max} and the shorter the time to peak plasma concentration, T_{max}[32,27]. The result of this study may imply that the decrease in C_{max} of glibenclamide is due to the interference of *Calliandra portoricensis* with the extent of absorption of glibenclamide. The reduction in the absorption of glibencalmde may be due to the chelation of the drug by metal of the root extract of *Calliandra portoricensis*. The decrease in the extent of absorption of glibenclamide in this study is evident by a similar decrease observed in the AUC_{0-48} when co-administered with *Calliandra portoricensis*. It is known that a drug with a short elimination half-life will be eliminated from the body quicker than a drug with a longer elimination half-life[33]. The result of our study is therefore consistent with increased drug elimination, which is evident by large drug clearance in the group that was administered with glibenclamide and *Calliandra portoricensis*. However, the bioavailability of the drug in the two study models showed a very slight significant difference.

The volume of distribution, V_d is an important pharmacokinetic property of a drug. It is a major determinant of the half-life and dosing frequency of a drug[34]. The extract of the root of *Calliandra portoricensis* caused a 69% increase in the V_d. A drug with a high V_d will have a higher affinity for tissues thus the propensity to leave the plasma into the tissue, while a drug with low V_d will remain in the plasma, thus available for its therapeutic action[33,34]. *Calliandra portoricensis* may probably increase the lipophilicity of glibenclamide thus influencing its binding ability to plasma proteins and affecting the availability of the drug in the plasma. This shows that *Calliandra portoricensis* caused a reduction in the amount of glibenclamide entering the systemic circulation thereby reducing the therapeutic efficacy of glibenclamide. The increase in V_d when concomitantly administered with *C. portoricensis* may also be the reason for the increase in clearance in this group.

5. Conclusion

The root extract of *Calliandra portoricensis* reduced the absorption of glibenclamide and increased the clearance of the drug. These effects resulted in significantly reduced bioavailability. The interaction of *Calliandra portoricensis* on glibenclamide may be attributed to the presence of some metal ions in the plant which may probably chelate glibenclamide, reducing its lipophilicity and absorption. Therefore, care should be taken in the co-administration of these agents as is common among the locals.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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