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Hypoglycemic and High Dosage Effects of *Bidens pilosa* in Type-1 Diabetes Mellitus

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Abstract

Ethno-pharmaceutical products have received a lot of international attention in the scientific community in the management of diabetes mellitus (DM). In this study we determined the anti-diabetic and high dosage effects of *Bidens pliosa* in type 1 DM (T1DM). Methodology: Thirty rats were divided into six groups and subgrouped into the extract and non extract treatment groups. The extract treated group was subdivided into three groups which received 200 mg/kg, 400 mg/ kg and 800 mg/kg dosage treatments respectively. The blood glucose levels were monitored using a standard glucometer for one month, and biochemical analysis of the two liver function enzymes; Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were carried out at the Institute of Biomedical Research (IBR-KIU-WC) at the end of week IV. The study revealed that *Bidens pilosa* maintained hypoglycemia for a period of two weeks and this status was lost in subsequent weeks. T1DM rats treated with a dosage of 200 mg/kg showed a better recovery (355.25 - 164.5 mg/dl) of the glucose levels, followed by those that were being treated at 400 mg/kg. The AST and ALT enzymes in blood varied with a mean ± SEM (33.72 ± 32.32 to −7.23 ± 12.61 IU and 22.98 ± 11.12 to 42 ± 38.2 IU, respectively) in both the glibencimide® and in the 800 mg/ kg treatment groups in the study. High dosages of extract were associated (P = 0.049) with increased systemic enzyme leakage. In conclusion, tissue degeneration caused by high levels of the extract was accompanied by leakage of various enzymes (AST and ALT) into the blood, which could be a major etiological factor for the development of secondary systemic pathologies, thus potentially worsening the effects of an existing T1DM prognosis in human patients. The preliminary results indi-

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cate that a dose of *Bidens pilosa* has an anti-diabetic effect for a limited initial duration before starting to cause systemic toxicological effects. It is highly recommended that further investigation into the cellular mechanisms and consequences of any therapy involving *Bidens pilosa* be carried out.

Keywords

Type 1 Diabetes Mellitus, *Bidens pilosa* and Diabetes, Ethno-Pharmaceutical Medicine in Uganda, Sub-Saharan Africa and Diabetes

1. Introduction

Global prevalence of diabetes mellitus (DM) is estimated to be over 10% especially with increasing disease incidence from Sub-Saharan Africa coupled with its low case reporting [1] [2]. The prevalence of DM in association with other metabolic diseases has been reported in Uganda [3] [4]. Gestational diabetes has been reported amongst Sub-Saharan mothers and it has been shown that this can lead to developmental challenges amongst infants [5]. Recent studies in the region have associated the disease in newborns with genetic transmission as a result of the risk possessed by family members in the communities [6]. Risk factors have been shown to exist ranging from lifestyle patterns to nutritional discipline [4] [7]. This has led to the development of herbal management therapies within the communities of Sub-Saharan Africa since clinical treatment therapies are asymptomatic [8] [9]. *Bidens pliosa* is an American native medicinal plant that is widely distributed across the African continent [10] [11]. The development of the herbal industry in tropical Africa has led to the innovation of various therapies for the management of medical cases, whose treatment and management are asymptomatic as well [12] [13]. These herbal therapies often have unfounded mechanism of action, and probably play a crucial role in the development of adverse drug reactions and treatment failure [11] [14].

Analyses of selected enzyme activities in blood serum give valuable diagnostic information for a number of metabolic disease conditions [15]. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are important in the diagnosis of organ (esp. of heart and liver) damage caused by heart attack, drug toxicity, or infection due to the leakage of a variety of enzymes, including these aminotransferases, which leak from the damaged liver or heart cells [16]. ALT catalyzes the transfer of the amino group of alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate, and the reaction is readily reversible. However, during amino acid catabolism, this enzyme (like most aminotransferases) functions in the direction of glutamate synthesis. Thus, glutamate, in effect, acts as a "receiver" of nitrogen from alanine. AST is an exception to the rule that aminotransferases "channel" amino groups to form glutamate. During amino acid catabolism, AST transfers amino groups from glutamate to oxaloacetate, forming aspartate, which is used as a source of nitrogen in the urea cycle and the reaction is also reversible. This study was conducted to determine the effects of *Bidens pilosa* on hyperglycemia and liver enzymes (AST and ALT) as biological markers for the pathological effects of the extract in Wister rats with type 1 DM (T1DM).

2. Materials and Methods

2.1. Study Design

The study involved thirty adult Wister rats (*Norwegian rattus*) that were divided into six groups and monitored for a period of 10 weeks at the Department of Biochemistry and Institute of Biomedical Research (IBR), Kampala International University, Ishaka, Bushenyi, Uganda.

2.2. Plant Collection and Extraction

The leaves were processed using standard protocols [11]. Briefly; fresh plant leaves were collected from Bwegiragye village in Ishaka Bushenyi which is within the university community. The leaves were dried under a shade in the laboratory for 14 days. These were pulverized using an electric blender, and the powdered material

extracted using distilled water on a mechanical shaker (Stuart Scientific Orbital Shaker, UK) for 48 hours. 200 gms of powder were weighed and dissolved in 500 mls of distilled water, and stirred using a stirring rod. The mixture was poured in a 1 litre Beaker and mixed thoroughly on an electric shaker for 48 hours. Mixture was sieved with a clean cloth and filtered using a Watman filter paper (125 mm diameter). Filtrate was kept in a 1000 mlplastic beaker and the weight of the filtrate (380 gm) was weighed, and then concentrated in the oven at about 28˚C - 30˚C for two weeks. The beaker containing the extract was weighed which gave about 25 gm of extract.

2.3. Acute Toxicity Test

Experimental animals were weighed and divided into three groups, 5 animals in each group, animals were weighed and the calculation of volume of extract to be administered to each animal was based on body weight and size. Doses were in the range of low, medium and high; 200 mg/kg, 800 mg/kg, 1000 mg/kg and 2000 mg/kg. Animals were then placed in cages and observed for signs of acute toxicity. The LD_{50} was established at 1000 mg/kg and this was used as foundation for the study dosage groupings and signs observed were basically body shaking which progressed to severe tremors and subsequent death.

2.4. Diabetes Induction

Diabetes was induced by injecting 200 mg/kg of alloxan monohydrate intraperitoneally to overnight-fasted rats (the LD_{50} was determined by an initial induction of the condition until successful results were obtained). 10% glucose solution bottles were kept in the cages for the next 24h to prevent hypoglycemia. After 72 h of injection, fasting blood glucose (FBG) levels were measured. Animals which develop more than 200 mg/dl glucose levels were used for the study.

2.5. Study Groups

Experimental animals were divided into six groups each consisting of a minimum of five adult male rats (n = 5) aged 4 months. Grouping was made according to concentration of extract for treatment. These included: 200 mg, 400 mg, 800 mg extract groups as well as controls which included normal saline group, Glibenclamide® (0.5 mg/kg) group and the sixth group consisting of normal non diabetic rats.Treatments were continued orally for 4 weeks. At the end of the 4th week the rats were fasted for 16 h and blood liver enzymes were determined. Blood was collected and biochemical markers measured. The blood glucose levels were measured using Accu-Chek Active™ Test Meter on blood from the rat's lateral tail vein. The plasma profile of blood was determined from blood collected from retro-orbital venous plexus of the rats under low dosage of ether anesthesia using capillary tubes into Eppendorf tubes containing heparin. The plasma was then separated by centrifugation (5 min, 5000 rpm) and analyzed for specific liver function enzymes AST and ALT using commercial kits and Spectrophotemetericanalysison the fourth week after induction of T1DM. Weights of tissues were taken after one month of administering the extract, using amettle AE260 Delta Range electronic weighing balance.

2.6. Data Analysis

Data was expressed as means from the samples analyzed. The means of fasting blood glucose (FBG) levels for the test and control groups were compared at different times by one-way Analysis of Variance (One-Way ANOVA) using SPSS 16 software. Linear regression was carried out to determine treatment associations and a p value < 0.05 was considered statistically significant.

2.7. Ethical Consideration

No ethical approval was required since the study involved only animal research models. All animals were handled and treated in accordance to the International ethical guidelines on the Care and Management of Laboratory Animals (IUAC).

3. Results

Upon injection with alloxan, hyperglycemia confirmed diabetic model as shown in week 0 of **Table 1**. Hypoglycemia occurred within the first two weeks following treatment with the extract and greatest effect was higher

with increasing dose of the extract. There was an increase in the fasting blood glucose with normal saline above 280 mg/dl of blood for the four weeks of the study. T1DM rats that were being treated with an extract at 200 mg/kg showed a better recovery (355.25 - 164.5 mg/dl of blood) of the blood glucose levels, followed by those that were being treated at 400 mg/kg than those which received normal saline and 800 mg/kg (334 - 175.75 mg/dl of blood) as shown in **Table 1**.

Statistical analysis showed that there existed no relationship between the different dosages administered within the first three weeks ($P > 0.05$) on the blood glucose levels. Further analysis of the variance during week I and II showed no statistical significance ($P = 0.637$) on the blood glucose levels as shown below. Further analysis of glycemic effects between week I and III showed that the 800 mg/kg treatment group had significant results as shown in **Figure 1**.

The rats that were being treated with lower dosage (200 mg/kg) showed the highest rate of adaptability than those that were being treated with higher dosage and normal saline which showed the least adaptation to recovery. By the fourth week, the majority of the rats had died as shown in **Table 2**. Analysis of Variance (ANOVA) showed that there was no statistical significance in the glucose concentrations in the different groups ($P = 0.44$).

Further analysis of the glycemic effects showed that the 800 mg/kg extract had significant hypoglycemic effects slightly comparable to those from the Glibenclamide®. The effects of the extracts (200 mg/kg, 400 mg/kg, and 800 mg/kg) and normal saline on serum AST were measured at week IV. This was shown to be considerably lower at decreased dosage of the extract as shown in **Table 3** and **Table 4**.

Table 1. Mean glycemic changes after administration of extract over four weeks.

Dosage/Time	Time in Weeks				
	0	I	II	III	IV
200 mg/kg	355.3	275.25	164.5	257.3	271.7
400 mg/kg	348.3	284	238.8	283.8	0*
800 mg/kg	334	240	175.75	298.8	0*
Glb 0.5 mg/kg	288.8	77.2	201.5	72.4	0*
Normal saline	375.3	153.3	335	395.7	0*
Non-diabetic	73	59.6	73.2	81.6	0*

Key: Glb = Glibenclamide®; 0* = Time of death of rats.

Table 2. Showing analysis of variance between weeks I & II.

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	3020.69	1	3020.69	0.260	0.64
Residual	46388.64	4	11597.16		

Key: Sig. = significance; df = degrees of freedom.

Table 3. Showing AST (IU) in blood from the various rats under varying treatments.

Group	Dosage/Treatment				
	Glb	200 mg/kg	400 mg/kg	800 mg/kg	Normal Saline
1	7.58	22.17	300.42	−51.33	11.08
2	−8.17	−12.83	2.33	−16.92	−8.17
3	11.67	131.83	0.00	17.50	10.50
4	−4.67	0.00	−2.33	14.58	148.17
5	162.17	0.00	0.00	0	−2.92

The levels of the AST enzyme were shown to be in the mean of 33.72 ± 32.32; −7.23 ± 12.61; 2.22 ± 2.22 in the Glibenclamide®, 800 mg/kg and normal saline treatment diabetic groups. Subsequent analysis of the serum for the ALT levels revealed that the levels of ALT were in the mean of 22.98 ± 11.12; 42 ± 38.2; 199 ± 189 IU of blood for Glibenclamide®, 800 mg/kg and normal saline treatment groups respectively. Linear regression of the extracts from the 400 mg/kg and 800 mg/kg treatments were found to be associated (P = 0.049) with high liver AST as shown in **Table 4**.

The effect of increasing dosage of the extract in the diabetic rats was found not to be significant in relation to the Glibenclamide® (P = 0.24), though a significant effect was shown in relation to the group treated with normal saline on the levels of AST and ALT in the study.

Further analysis revealed that there was no association between the treatment options and the levels of ALT as shown in **Table 5**.

4. Discussion

The study revealed that *Bidens pilosa* maintained hypoglycemia for a period of two weeks, and this status was lost in the subsequent period as shown in **Table 1**. The initial rise in FBG seems to offset the early anti-hyperglycemic effect of the crude extract which is in agreement with previous studies [12]. During the week I and week III, T1DM under the 800mg/kg group showed the greatest therapeutical effect as the blood glucose levels were shown to be closer to the normal as shown in **Figure 1**. There was no statistical significance (P = 0.637) in the hypoglycemic effects towards the end of the study due to the loss of the efficacy of the extract probably as a result of onset of systemic injury, thus cancelling the positive effects observed earlier. This would probably be due to the accumulation of reactive oxygen species due to the oxidative properties of alloxan or the extract. This was followed by an increase in the liver enzymes AST and ALT and subsequent death as described in **Table 3** and **Table 4**. High dosages of the extract were shown to be associated (P = 0.049) with increased systemic damage. The findings in this study agree with previous findings that *Bidens pilosa* mode of action involves modulation of the immune system in rats as it protects the β-cells from the body antibodies [17]. The study revealed that marked toxicities in rats exist that were treated with the extract at high dosage (>200 mg/kg) which is in agreement with previous studies, despite the limited systemic toxicological analysis [18]. These finding are supported by a current study in which the toxicological effects of *Bidens pilosa* have been highlighted [11].

The liver enzymes AST and ALT that where measured in the study are primarily crucial for the indication of the level of systemic damage and as shown they increased with increasing dosage of extract in the different study groups. This could be due to increased systemic overload amidst a pre-existing autoimmune challenge thus accelerating systemic failure and death [19] [20]. Systemic degeneration (especially of the liver) caused by high dosage of the extract was accompanied by leakage of various enzymes from injured tissues into the blood,

Table 4. Showing ALT from the various rats under varying treatments.

Group	Dosage/Treatment				
	Glb	200 mg	400 mg	800 mg	Normal saline
1	20.42	−5.25	9.33	9.33	819.58
2	−7.58	−8.17	−11.08	12.25	449.17
3	61.83	−7.00	−8.75	−5.83	−196.58
4	18.08	0	−35.58	194.25	−35.00
5	22.17	0	0	0	−37.92

Table 5. Showing Analysis of Variance (ANOVA) between weeks I & II.

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	208.67	3	69.56	0.031	0.99
Residual	2265.79	1	2265.79		

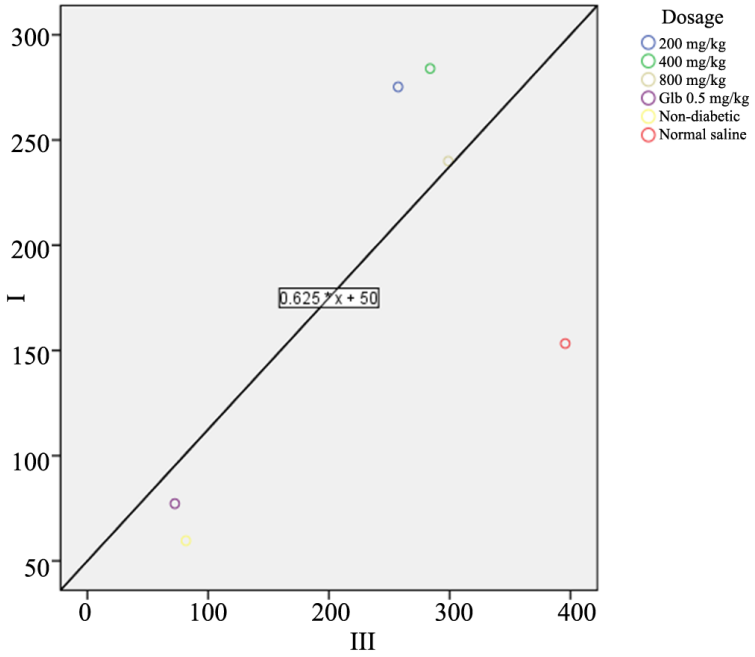

Figure 1. Showing changes in plasma glucose levels under different treatments for the period of week I and III.

which has been shown to be associated with development of secondary systemic pathologies [19]. In human patients, concurrent T1DM followed by generalized systemic challenges would make diagnosis of the disease more difficult as a result of the development of systemic failure probably due to high dosage of the extract. The toxicological effects have been shown to be due to increased plasma levels of enzymes (AST/ALT) due to liver injury in conjunction with other tissues leading to poor and delayed cellular recovery from injury. This probably is responsible for the increased mortalities exhibited in the study after week II, which is in agreement with recent findings [21].

Despite its use as an ingredient in food for human consumption, studies on systemic toxicity of *Bidens pilosa* in humans and animals are still inadequate and insufficient [10] [22]. This study evaluated the therapeutical and toxicological effects of *Bidens pilosa*, which showed that development of sub-chronic toxicities is a major challenge worth to be investigated further for the promotion of alternative medicine especially for Sub-Saharan Africa. Limitations to this study included limited organ systemic toxicological analysis as well as the limited biological markers measured for cellular injury due to severe financial constraints.

5. Conclusion and Recommendations

This study shows that *Bidens pilosa* has hypoglycemic effects on diabetes, but the toxicological effects associated with this plant, which occurs naturally within Sub-Saharan Africa including Uganda, are a major concern following high doses of the extract as shown in the study. The findings highlight the need for further toxicological studies regarding most of the herbal therapies in the region for improved development of community livelihoods and above all, for the protection of the general public against unnecessary development of drug reactions and resistance. The continuous usage of herbal therapies in rural communities of Sub-Saharan Africa should be used with caution and not indiscriminately as it has been throughout the ages.

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Competing Interests

The authors declare there are no conflicting interests associated with this work.

Authors Contributions

All authors contributed equally, reviewed and approved the final manuscript.
M.O.A., N.M., M.T., N.E.: Designed the study, wrote the protocol and participated in data collection.
M.O.A., E.N., J.P., K.I.K.: Carried out literature search, analysis, writing and manuscript preparation.

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Abbreviations and Their Meanings

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
FBG	Fasting blood glucose
Glb	Glibenclamide®
IBR	Institute of Biomedical Research
IU	International units
KIU-WC	Kampala International University Western Campus
LD_{50}	Lethal dose
SEM	Square error mean