Global Scientific JOURNALS

GSJ: Volume 8, Issue 8, August 2020, Online: ISSN 2320-9186
www.globalscientificjournal.com

DETERMINATION OF THE ANTIDIABETIC PROPERTY OF THE AQUEOUS EXTRACT OF *BIOPHYTUM SENSITIVUM* ON STREPTOZOTOCIN INDUCED DIABETIC RATS

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Abstract

Diabetes mellitus, a common endocrine disorder of man, is considered one of the major health concerns all over the world. Biophytum sensitivum is used traditionally in the treatment of several diseases including diabetes. This study was aimed at investigating the antidiabetic property of Biophytum sensitivum aqueous extract on streptozotocin induced diabetic rats. Twenty (20) male albino rats weighing 180g – 200g were divided into five groups of four rats each: Group = A- normal control, B- diabetic control, C- diabetic treated with glibenclamide, D- diabetic treated with 200mg/kg of the extract, E- diabetic treated with 400mg/kg of the extract. Diabetes was induced by intraperitoneal injection of streptozotocin at (55mg/kg) in all groups except the normal control groups. The aqueous extract of B. Sensitivum was administered orally for 14 consecutive days. The blood glucose, albumin, total protein, lipid profile, electrolytes and serum enzymes concentrations were investigated after the administration of aqueous extract of B. Sensitivum. From the results, diabetic control group showed significant ($p<0.05$) increase in the levels of blood glucose, total cholesterol, triglycerides, LDL, serum liver marker enzymes, serum kidney marker enzymes, direct bilirubin, potassium ions (K^+) while a significant ($p<0.05$) decrease in albumin, total protein, HDL, total bilirubin, indirect bilirubin, sodium ions (Na^+), chloride ions (Cl^-) and bicarbonate ions (HCO_3^-) when compared to the normal control group. Oral administration of aqueous extract of B. Sensitivum to diabetic rats resulted in a reversal of the above diabetic conditions. However the 400mg/kg was more effective than the 200mg/kg of the extract. Phytochemical screening of the crude extract of B. Sensitivum revealed the presence of Alkaloids, Flavonoids, Tannins, Saponins, Terpens/steroids, Cardiac glycosides, Basan, Carbohydrates, Phenols and Resins. In conclusion, B. Sensitivum

aqueous extract possesses hypoglycaemic, hypolipidemic, renoprotective and hepatoprotective effect, and can therefore be used for the management of diabetes.

Keywords: *Biophytum sensitivum,* Streptozotocin, *glibenclamide*, Diabetes, Phytochemicals.

INTRODUCTION

Medicinal plants have been used in virtually all cultures as sources of medicine, since times immemorial. Herbal medicine is still the mainstay of health care in most developing countries [1]. In spite of the many achievements in health care delivery in the current century, as evidenced by rapid progress and expansion of orthodox medicine, people in Nigeria, and most developing countries, lack regular access to essential/modern medicines primarily because of their high cost [2].

Diabetes mellitus (DM) can be defined as a group of metabolic diseases characterized by chronic hyperglycemia that results from defects in insulin secretion, insulin action, or both, and causes impaired function in carbohydrate, lipid, and protein metabolism [3]. DM is one of the five leading causes of death in the world; serious challenges to the achievement of internationally agreed developmental goals, including the Millennium Development Goals (MDGs). Hyperlipidemia, (associated with generation of oxygen derived free radicals), an attendant effect of DM [4, 5], is a leading cause of both morbidity and mortality in diabetic patients. More than 366 million people suffer from DM and the number is expected to rise to 552 million by 2030 [6]. People with diabetes who depend on life-saving insulin pay the ultimate price when access to affordable insulin is lacking [7].

Long term diabetes is associated with several co-morbidities, such as erectile dysfunction, blindness, poor wound healing, kidney failure, heart disease, etc; as a result of considerable damage, dysfunction, and failure of various organs that develop as the disease progresses [8]. Management of DM is based on oral hypoglycemic agents and insulin, but these clinical approaches either do not succeed in restoring normoglycaemia in most patients or fail after a variable period. Moreover, continuous use of synthetic antidiabetic drugs causes side effects and toxicity [3].

Medicinal plants have the ability to produce remarkable chemical structures with diverse biological activities [2] and are widely being used by the traditional medical practitioners for curing various diseases in their day-to-day practice. *Biophytum sensitivum* DC (Oxalidaceae) is a

small, flowering, annual herb with sensitive leaves. It grows throughout tropical Africa and Asia. The medicinal plant is used traditionally in a number of ailments, such as joint pains, inflammations, fever, malaria, wounds, stomach ache, diabetes, gonorrhea, tuberculosis, cough, convulsion, e.t.c [9].

There is, however, a dearth of literature regarding the effects of this plant on diabetes mellitus. Therefore, study aimed at investigating the antidiabetic property of *Biophytum sensitivum* aqueous extract on streptozotocin induced diabetic rats.

MATERIALS AND METHODS

Collection of Plant Material

Biophytum senssitivum (L) DC plant was collected from Tilden Fulani, Toro LGA, Bauchi State. The plant was then identified and verified at the Herbarium Department, Federal College of Forestry Jos, Plateau State, and its voucher number was given as FHJ 230.

Collection of Experimental Animals

Twenty (20) White albino rats (male Wister strain) weighing 150g and above were purchased from the animal house of the University of Jos, Nigeria. The rats were fed with standard feed (purchased from Grand Cereal and Oil Mills Ltd, Jos Nigeria) and water until a weight range of 160g - 205g were obtained.

Chemicals, Drugs and Reagents

Streptozotocin was obtained from Sigma –Aldrich Company, U.S.A. All other reagents and chemicals were of analytical grade, obtained from reputable scientific and chemical companies.

Preparation of the Plant Extract

The plant; *B. sensitivum* was collected, washed to remove the sandy particles on the roots and then air dried at room temperature under shade. When it was completely dried it was pounded to powdery form using local pestle and mortar and sieved to obtain fine powder. The preparation of the decoction was carried out using warm water. 100g of the fine powder was soaked in one (1) litre of distilled water and allowed to stand for 15-30 minutes (to ensure maximum extractions of phytochemicals). The mixture was then filtered using Whatman No. 1 filter paper to remove all

the larger particles. The filtrate was dried in the autoclave at a temperature of 50-60^{o}C for 2 weeks.

PHYTOCHEMICAL SCREENING

Phytochemical screening of aqueous extract of *Biophytum sensitivum* was carried out using standard qualitative procedure [10].

Test for alkaloids (Dragendorff′s reagent test): Procedure: To 2.0 ml of the extract, few drops of the reagent were added and observed for yellow colouration.

Test for flavonoids using lead acetate: Procedure: To 2.0 ml of the extract, add few drops of 10% lead acetate, the formation of cream or light yellow indicate the presence of flavonoids.

Test for saponins: Procedure: To 2.0 ml of the extract, 4 ml of distilled water was added and vigorously shaken for 2 minutes. Frothing which persist on warming was taken as a preliminary evidence for the presence of saponins.

Test for resins: Procedure: To 2.0 ml of the extract, 2.0 ml of acetic anhydride was added followed by the addition of few drops of concentrated H_2SO_4 and the solution was observed for violet coloration to confirm the presence of resin.

+yTest for cardiac glycosides (Salkowsky′s Test): Procedure: 0.5 g of the extract was dissolved in 2.0 ml of chloroform; sulphuric acid was carefully added to form a lower layer. A reddish-brown precipitate at the interphase shows the presence of cardiac glycosides.

Test for steroids and terpenes (Liebermann′s Test): Procedure: To 2.0 ml of the extract, 1 ml of acetic anhydride and concentrated sulphuric acid were carefully added down the side of the test tube and observed for reddish brown color at the interphase, indicating the presence of terpenes and steroids.

EXPERIMENTAL INDUCTION OF DIABETES

Diabetes was induced by intraperitoneal injection of streptozotocin at (55mg/kg) in four (4) groups namely Group B, C, D & E. The animals were left for 48hours after which diabetes was confirmed from the fasting blood glucose using one - touch glucometer. Animals with blood glucose level greater than 120 mg/dl were selected and used for the experiment.

Administration of the Plant Extract: The aqueous extract of *Biophytum sensitivum* was administered through oral route at a dose of 200mg/kg and 400mg/kg body weight daily for 14 consecutive days after the induction of diabetes in the rats.

Administration of standard drug: Standard drug was prepared and administered; 5 mg/kg body weight of Glibenclamide was given orally on a daily basis. This was carried out for 14 consecutive days after the induction of diabetes in the rats.

Experimental grouping: The rats were divided into five groups of four animals each and allowed to acclimatize for three days before the commencement of the experiment. They were kept in wide normal cages. They had free access to feed and water throughout the period of the experiment. The experimental groupings were A, B, C, D and E. Diabetes was induced in groups B, C, D and E by intraperitonial injection of freshly prepared streptozotocin (55 mg/kg body weight /day) while animals in group A were not induced. The groupings and administration of streptozotocin, extract, and standard drug were as follows: The administration was done for 14 consecutive days. Rats in groups A and B served as control while those in groups C, D and E were treated orally with 200 mg/kg body weight and 400 mg/kg body weight of *B. sensitivum* and standard drug respectively.

COLLECTION OF BLOOD SAMPLE

At the end of the experiment, the rats were starved for 24 hours before they were sacrificed by decapitation and the blood was collected through the jugular vein in plane containers for the analysis.

PREPARATION AND ADMINISTRATION OF STREPTOZOTOCIN (STZ)

A 1.0M citrate buffer was prepared for the STZ injection by dissolving 1.4705g sodium citrate solution in 50ml distilled water and the pH maintained with the help of a citric acid at 4.5. The STZ solution of dosage 55mg/kg was administered to the albino rats intraperitorially per body weight.

STATISTICAL ANALYSIS

Result values are expressed as mean± standard deviation. Analysis of variance (ANOVA) was used for comparism. Differences were considered significant when values of $p \leq 0.05$. A Graphpad prism is used to carry out the above analysis.

RESULTS

Table 1: Phytochemical Screening of Crude Aqueous Extract of *Biophytumsensitivum*

Test	Present/Absent
Alkaloids	+
Flavonoids	+
Tannins	+
Saponins	+
Terpens/Steroids	+
Cardiac glycosides	+
Balsan	+
Carbohydrates	+
Phenol	+
Resins	+

+ = present

Table 2: Effect of Aqueous Extract of *B. sensitivum* on Serum Glucose, Total Protein and Albumin in STZ induced Diabetic Rats.

Group	Treatment	Glucose (mmol/L)	Total Protein (g/L)	Albumin (g/L)
A	Normal Control	3.42 ± 0.128	73.00±0.060	37.05±0.084
B	Diabetic Control	17.79 ± 0.-91[a]	57.30±0.155[b]	27.74±0.133[b]
C	Diabetic + Std Drug	4.65 ± 0.157[ab]	67.78±0.428[bc]	32.72±0.115[bc]
D	Diabetic + Extract (200mg)	5.96 ± 0.114[ab]	60.30±0.165[bc]	29.78±0.124[bc]
E	Diabetic + Extract (400mg)	4.91 ± 0.147[ab]	69.94±0.058[bc]	34.32±0.169[bc]

Values are expressed as mean ± SEM, n=4.

[a]Values are significantly different when compared to normal control ($p < 0.05$)

[b]Values are significantly different when compared to diabetic control ($p < 0.05$)

[c]Values significantly increased when compared with diabetic control ($p < 0.05$)

Table 3: Effect of aqueous extract of *B. sensitivum* on total bilirubin, direct bilirubin and indirect bilirubin in STZ induced Diabetic rats.

Group	Treatment	TB(µmol/L)	DB(µmol/L)	IDB(µmol/L)
A	Normal Control	9.52 ± 0.199	3.82 ± 0.082	5.70±0.117
B	Diabetic Control	0.19 ± 0.095[a]	20.90 ± 0.186[a]	-20.71±0.091[a]
C	D + Std Drug	14.79 ± 0.107[ab]	4.94 ± 0.131[ab]	9.85±0.024[ab]
D	D + Extract (200mg)	18.86 ± 0.090[ab]	5.88 ± 0.146[ab]	12.98±0.056[ab]
E	D + Extract (400mg)	15.05 ± 0.097[ab]	5.05 ± 0.089[ab]	10.00±0.008[ab]

D= Diabetic, DB= Direct bilirubin, TB= Total bilirubin, IDB= Indirect Bilirubin

Values are expressed as mean ± SEM, n=4.

[a]Values are significantly different when compared to normal control ($p < 0.05$)

[b]Values are significantly different when compared to diabetic control ($p < 0.05$)

Table 4: Effect of aqueous extract of *B. sensitivum* on lipid profile in STZ induced Diabetic rats.

Group	Treatment	Total Cholesterol (mmol/L)	Triglyceride (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
A	Normal Control	3.24 ± 0.143	0.90 ± 0.134	1.71 ± 0.043	0.98±0.026
B	Diabetic Control	5.10 ± 0.047[a]	2.13 ± 0.074[a]	0.35 ± 0.040[a]	3.96±0.032[a]
C	D + Std Drug	4.05 ± 0.098[ab]	1.18 ± 0.123[ab]	1.24 ± 0.076[ab]	2.38±0.069[ab]
D	D + Extract (200mg)	4.78 ± 0.107[ab]	1.71 ± 0.129[ab]	1.02 ± 0.093[ab]	2.95±0.040[ab]
E	D + Extract (400mg)	4.32 ± 0.114[ab]	1.24 ± 0.114[ab]	1.02 ± 0.080[ab]	2.64±0.141[ab]

Values are expressed as mean ± SEM, n=4.
[a]Values are significantly different when compared to normal control ($p < 0.05$)
[b]Values are significantly different when compared to diabetic control ($p < 0.05$)

Table 5: Effect of aqueous extract of *B. sensitivum* on some serum biomarkers in STZ induced Diabetic rats

Group	Treatment	ALT(U/L)	AST (U/L)	ALP(U/L)
A	Normal Control	11.20 ± 0.125	15.34 ± 0.225	134.38 ± 0.274
B	Diabetic Control	59.73 ± 0.109[a]	83.46 ± 0.257[a]	419.71 ± 0.238[a]
C	D + Std Drug	15.21 ± 0.245[ab]	17.52 ± 0.252[ab]	149.75 ± 0.262[ab]
D	D + Extract (200mg)	16.02 ± 0.114[ab]	18.68 ± 0.124[ab]	174.45 ± 0.239[ab]
E	D + Extract (400mg)	15.05 ± 0.136[ab]	17.75 ± 0.158[ab]	152.79 ± 0.109[ab]

Values are expressed as mean ± SEM, n=4.
[a]Values are significantly different when compared to normal control ($p < 0.05$)
[b]Values are significantly different when compared to diabetic control ($p < 0.05$)

Table 6: Effect of aqueous extract of *B. sensitivum* on urea, creatinine and uric acid concentrations in STZ induced Diabetic rats.

Group	Treatment	Urea (mmol/L)	Creatinine (µmol/L)	Uric Acid (µmol/L)
A	Normal Control	3.86 ± 0.103	69.50 ± 0.242	139.17 ± 0.123
B	Diabetic Control	29.78 ± 0.100[a]	470.73 ± 0.181[a]	523.64 ± 0.221[a]
C	D + Std Drug	5.55 ± 0.212[ab]	78.35 ± 0.261[ab]	143.90 ± 0.069[ab]
D	D + Extract (200mg)	6.22 ± 0.140[ab]	109.56 ± 0.247[ab]	156.41 ± 0.204[ab]
E	D + Extract (400mg)	5.88 ± 0.065[ab]	89.57 ± 0.253[ab]	139.57 ± 0.344[ab]

Values are expressed as mean ± SEM, n=4.
[a]Values are significantly different when compared to normal control ($p < 0.05$)
[b]Values are significantly different when compared to diabetic control ($p < 0.05$)

Table 7: Effect of aqueous extract of *B. sensitivum* on serum electrolytes Concentrations in STZ induced Diabetic rats.

Group	Treatment	Na^+ (mmol/L)	K^+(mmol/L)	Cl^-(mmol/L)	HCO_3(mmol/L)
A	Normal Control	144.23 ± 0.168	3.67 ± 0.88	113.98 ± 0.159	27.40 ± 0.225
B	Diabetic Control	134.30 ± 0.179[a]	6.19 ± 0.073[a]	96.38 ± 0.236[a]	14.01 ± 0.043[a]
C	D + Std Drug	139.27 ± 0.203[ab]	4.05 ± 0.058[ab]	108.32 ± 0.253[ab]	25.37 ± 0.228[ab]
D	D + Extract (200mg)	140.12 ± 0.121[ab]	5.04 ± 0.072[ab]	110.95 ± 0.095[ab]	23.95 ± 0.333[ab]
E	D + Extract (400mg)	141.16 ± 0.143[ab]	4.65 ± 0.158[ab]	112.14 ± 0.158[ab]	26.38 ± 0.224[ab]

Values are expressed as mean ± SEM, n=4.
[a]Values are significantly different when compared to normal control ($p < 0.05$)
[b]Values are significantly different when compared to diabetic control ($p < 0.05$)

DISCUSSION

The study evaluated the antidiabetic properties of the aqueous extract of *Biophytum sensitivum* on STZ induced diabetic rats. Diabetes is characterized by hyperlipidemia due to uninhibited actions of lipolytic enzymes and near absence of insulin [11]. Prolonged hyperlipidemia ends with severe complications which generate more oxidative stress. Free radicals react with lipids and cause lipidperoxidation [4]. The increase level of oxidative stress will increase the hyperlipidemia in animals. The abnormal high concentration of serum lipids in diabetes is mainly due to the increase in the mobilization of fatty acids from the peripheral tissues, since insulin inhibits the hormone sensitive lipase [12]. Diabetes mellitus lead to impaired carbohydrate metabolism and increased lipolysis causing accumulation of acetyl-coA. Increased availability of acetyl-coA leads to the synthesis of cholesterol which causes hyperlipidemia. Insulin deficiency causes hypercholesterolemia due to metabolic abnormalities [4].

In this study, the results of phytochemical screening (table 1) showed that *B. sensitivum* extract contains alkaloids, flavonoids, saponins, resins, cardiac glycosides, phenols, terpenes and steroids. The determination of blood glucose concentration among others is a useful quantitative parameter for diabetes. The treatment of STZ induced diabetic rats with 200 and 400mg/kg b. Wt of *B. sensitivum* showed a significant ($p < 0.05$) decrease in the concentration of glucose when compared to the diabetic group (table 2). The decrease was almost equal to that of the normal control and was as effective as that of the Glibenclamide (Glb) treated diabetic group [13]. This could mean that the extract of *B. sensitivum* acts through increasing insulin secretion which enhance the uptake of glucose by adipose or muscle tissues and inhibiting intestinal absorption of glucose [14, 15].

Table 2 shows that there was a significant decrease in the concentration of albumin and total serum protein of the STZ induced diabetic rats when compared with the normal control and the treated groups. This observation may be attributed to numerous effects of hyperglycemia in STZ induced diabetes. Hyperglycemia increases gluconeogenesis and as such, leads to excess protein breakdown as well as excess loss of nitrogen, resulting in negative nitrogen balance. The concentration of total protein in the normal control differs significantly when compared to diabetic control. Treatment with the extract of *B. sensitivum* increased the concentration of total protein and it differs significantly from the normal and diabetic controls ($p < 0.05$).

Glibenclamide treatment group also increased the concentration of total protein and it differs significantly when compared with normal and diabetic control ($p< 0.05$). Concentration of albumin in the treatment group was increased. This may have resulted from either enhanced synthesis or decreased catabolism of albumin [16 - 20].

From table 3, the concentration of bilirubin in normal control group differs significantly ($p < 0.05$) when compared to diabetic control group. Treatment with the aqueous extract of *B. sensitivum* (both 200 and 400mg/kg b. Wt) increased the concentrations of total bilirubin (TB) and indirect bilirubin (IDB) but decreased the concentration of direct bilirubin (DB), so also treatment with Glibenclamide [21 -23].

The administration of 200 and 400mg/kg bd. Wt of *B. sensitivvum* in STZ induced diabetic rats significantly ($p < 0.05$) reduced the serum total cholesterol (TC). This may be due to gut intra-luminal interactive effect of saponins [24]. The same results were observed in Glibenclamide treated diabetic rats.

The result showed an increase in HDL levels, table 4. The increased HDL (cardioprotective lipid) level by *B. sensitivum* aqueous extract was comparable to the control rats. This result is indicative that *B. sensitivum* is cardioprotective since it raises the HDL levels and reduces the LDL levels [25, 26].

Triglycerides are neutral fats, major energy reserve for the body stored in adipose tissues. It is made by the body from sugar, alcohol or other food sources. Diabetic condition increases the lipolysis and produces more free fatty acids. The release of fatty acids increases the production of ketone bodies and triglycerides synthesis [11]. Hypertriglyceridemia is one of the most common lipid abnormalities in diabetes. In this study, the triglycerides are increased significantly in the STZ induced diabetic rats as shown in table 4. However the aqueous extract of *B. sensitivum* reduced the TG level as such of normal rats in the STZ induced diabetic rats.

The serum levels of Alanine amino tranferase (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) were reduced significantly ($p < 0.05$) in both the 200 and 400mg/kg b. Wt of *B. sensitivum* treated group as shown in table 5, when compared to the diabetic control group. Similarly, decreased levels of ALT, AST and ALP were observed in Glibenclamide treated diabetic rats. The increase release of these enzymes into the serum is an indication of hepatotoxic effect of STZ [9, 27]. Therefore, since *B. sensitivum* aqueous extract significantly reduces the levels of ALT, AST and ALP in serum, it is hepatoprotective.

The effect of *B. sensitivum* aqueous extract on the kidney function was assessed by the determination of the serum Urea, Creatinine and Uric acid. The concentration of urea, creatinine and uric acid were significantly ($p< 0.05$) higher in diabetic rats when compared to the normal rats. This is an indication that STZ induces renal dysfunction in diabetic rats. The treatment of STZ diabetic rats with 200 and 400mg/kg b. Wt of *B. sensitivum* aqueous extract significantly ($p < 0.05$) reduced the levels of urea, Creatinine and Uric acid when compared with the diabetic control (table 6), thus indicating that *B. sensitivum* has renal protective property.

Routinely measured electrolytes are Na^+, K^+, Cl^- and HCO_3^-. These four ions in plasma exert the greatest influence on water balance and acid-base relationship [28]. The increased volume and metabolites excretion via the kidneys, usually in excess of normal thresholds give rise to imbalance in homeostasis with respect to electrolytes [17]. There was a significant ($p < 0.05$) decrease in the serum Na^+, Cl^- and HCO_3^- of the diabetic control group (table 7), when compared to the normal control. Treatment with 200 and 400mg/kg b. Wt of *B. sensitivum* aqueous extract increases the Na^+, Cl^- and HCO_3^- to almost the values of the normal control. It is imperative that the increased electrolytes and water levels usually observed in diabetes could lead to the depletion of extracellular fluid electrolytes and thus lead to the excretion of electrolytes by parietal and non parietal cells, which may account for the observed significant decrease in the serum Na^+, Cl^- and HCO_3^- [17]. Also there was a slight decrease in the concentration of K^+ in the *B. sensitivum* diabetic treatment groups to almost the levels of the normal control when compared to the diabetic group. The Glibenclamide treatment group also showed this trend of increased Na^+, Cl^- and $HCO_3^-$and decreased K^+ when compared to the normal control. It has been reported that a significant total body deficit of K^+, initial serum K^+ is typically normal or elevated because of the extracellular migration of K^+ in response to acidosis. K^+ levels generally fall further during treatment as insulin therapy drives K^+ into cells [29].

In conclusion, the results of this study showed that both the 200 and 400mg/kg were very effective but the 400mg/kg was much better when compared to the normal control.

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