Antidiabetic Activity of *Physalis angulata* in Streptozotocin Induced Diabetic Wistar Albino Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author CDL designed the study and performed the statistical analysis. Author Okon wrote the protocol and the first draft of the manuscript. Author MKJ managed the analyses. Author CEM managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: *Physalis angulata* have been extensively used for the management of diabetes in folklore medicine, in Nigeria.
Aim: The present study aimed to investigate the antidiabetic effect of aqueous extract of *Physalis angulata* and its potential mechanisms in streptozotocin-induced diabetic rats.
Study Duration: The period of the study was done on 30th September, 2018 at the Department of Biochemistry, Faculty of Basic Medical Sciences, university of Jos, Nigeria.
Methodology: Albino rats of Wistar strain weighing between 200g to 250g were induced with single freshly prepared streptozotocin (55 mg/kg body weight). Diabetes was confirmed after forty eight hours in streptozotocin -induced rats showing fasting blood glucose levels > 10 mmol/l. The rats were randomly divided into four (4) experimental groups (n = 4). A (Control diabetic group fed with normal feed), Group B (Normal control fed with normal feed), Group Group C (Diabetic rats treated with 400 mg/Kg body weight extract of *Physalis angulata* and Group D, (Diabetic rats are treated with 400 mg/Kg body weight of glibenclamide). After 8 days the animals were sacrificed and blood samples were collected for biochemical and hematological analysis. Changes in the animal body weights were also measured within the period.
Results: From the results, it was observed that treatment of rats with extract of *Physalis angulata*

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elevates the reduction of body weight, and caused an increase in the body weight of the treated rats. In the same order, serum glucose significantly decreased (p<0.05) after the 8-day treatment compared to diabetic control. The extent of reversal of hyperglycemia in the *physalis angulata* extract treated animals compared well with the glibenclamide treated group. The results, therefore, showed that *Physalis angulata* extract has a significant (p<0.05) hypoglycemic effect in diabetic rats and the histopathological results of treated groups showed the regenerative/protective effect on *β*-cells of pancreas in diabetic rats.

Conclusion: The current study revealed the antidiabetic potential of *Physalis angulata* being effective in hyperglycemia and it can effectively protect against other metabolic aberrations caused by diabetes in rats, which seems to validate its therapeutic traditional use.

1. INTRODUCTION

Diabetes mellitus describes a metabolic disorder of multiple etiologies. It is characterized by chronic hyperglycemia, with perturbations of carbohydrate, lipid and protein metabolism that result from defect in insulin secretion, insulin action or both [1].

Diabetes mellitus could be seen as heterogeneous group of a complex metabolic disorder associated with high blood glucose concentrations (hyperglycemia) and alterations in the metabolism of major macromolecules resulting from impairments in the secretion of insulin or its action [2]. Diabetes is commonly accompanied with polydipsia, polyuria, microvascular problems involving eyes, kidney and peripheral nerves as well as cardiovascular problems such as hypertension [3]. These complications affect about 50% of diabetic patients and can lead to their death [4] thereby making diabetes a recognized fatal disease in different parts of the world for centuries.

Insulin is a hormone synthesized by the β-cells at the pancreatic islets of Langerhans and its primary role is to tightly control blood glucose levels which usually rise after dietary intake. Thus, insulin is released from the pancreatic β-cells to normalize the glucose level. Therefore, in diabetic patients, anomalies in the production of insulin and/or its utilization cause hyperglycemia. Insulin is also vital to carbohydrates and lipids metabolism because it lowers blood glucose levels by enhancing the glucose uptake by cells and by stimulating glycogenesis as well as inhibiting glycogenolysis. It also retards the breakdown of fats to free fatty acids and ketone bodies [5]. This hormone also encourages the storage of fat into the adipose tissues and reduces gluconeogenesis in liver and kidneys.

At present, diabetes is the fifth major cause of death in the world affecting 366 million individuals globally and this figure is projected to increase to a staggering 552 million by the year 2030 as reported by the International Diabetes Federation [6]. It is also projected that the greatest number of diabetic patients are between 40-59 years of age and about 50% of diabetic cases are still undiagnosed [7]. In 2011 alone, 4.6 million deaths were attributed to diabetes and about USD 465 billion dollars were spent as healthcare expenditures due to diabetes [8]. In Africa, the prevalence rate of diabetes is 4.3% and the region was reported to have the highest mortality rate due to the disease [9]. More specifically, Nigeria population is greatly affected by diabetes because it is the fourth major cause of death in the country [10] affecting all race groups. Also the black community is at risk because of rapid lifestyle and cultural changes [11].

The use of herbal medicine has become increasingly popular worldwide and plant therapy's literature is related to that of humanity, because in most cultures man has always been depended on the curative values of medicinal herb to cure some illness. Efforts are ongoing to evaluate botanical drugs for the management of diabetes mellitus [12].

Physalis angulata is an important genus of the solanaceae family. Most of the species are herbaceous annuals or perennials, native tropical north and south America. Some species have edible fruits and tea make from its roots is considered within popular medicine. It is known by different names. including camapu, cutleaf ground cherry, wild tomato, mullaca, winter cherry, goose berry. In Nigeria especially Yoruba (south west), they are known as koropo, in Igbo it is called Ogwu and Hausa it is called tsaada biri. The medicinal uses of *Physalis angulata* are

numerous; a wide variety of species are used for asthma, urinary problems, rheumatism, and tumors. Their anti-inflammatory and anti-spasmodic properties are also known [13]. Also, some species of *Physalis* are used in local crafts, ornamental and food the most common and most important use is in the preparation of sauces [14].In view of its wide ethnomedicinal values, folklore claims, and reported activities, the plant was validated for its antidiabetic activity.

2. MATERIALS AND METHODS

2.1 Plant Materials and Chemicals

Fresh leaf of *Physalis angulata* was collected from Jos North Local Government Area, Plateau state, Nigeria and was identify and authenticated by Mr. J.J. Azila at the Department of Plant Science and Biotechnology, University of Jos, Nigeria. assigned Voucher specimen No FHJ 291.

Streptozotocin was purchased from Sigma Chemical Co. (St Louis, MO, USA). A one-touch glucometer was purchased from Roche Diagnostics GmbH (Mannheim, Germany) for the analysis of blood glucose (BG). All other chemicals were of analytical grade

2.2 Preparation of Plant Extract

The plant was collected and air dried under shade. The plant was then pounded to powdery form using pestle and mortar. The fine powdery form of the plant was stored in air-tight plastic containers until required for use.

2.2.1 Aqueous extract preparation

Thirty grams of the powdered plant were weighed and dissolved in 250ml of distilled water at room temperature, stirred till well mixed and allowed to stand for 24 hours and filtered using filter paper (Whatman no 1) and subsequently concentrated by using a rotary evaporator at 60°C.

2.3 Experimental Animal

Wistar Strain albino rats weighing 200 g to 250 g used in this study were purchased from the animal house of the University of Jos Plateau state. The animals were housed and maintained under standard laboratory conditions. They were fed with standard rat pellet diet (gotten from Naik

integrated business Nigeria. Km 7, Jos East local Government Area Plateau state.

2.4 Experimental Design

The animals were group as follows: -

Group A: Diabetic control

Group B: Normal control

Group C: Diabetic + leaf extract (400mg/kg)

Group D: Diabetic + standard drugs (Glibenclamide).

2.5 Induction of Diabetes

The animals were left to fast for 14hours but had free access to water. Diabetes mellitus was induced by intra-peritoneal injection of a freshly prepared solution of streptozotocin (STZ) (at 55mg/kg body weight) in 0.1m cold citrate buffer (PH 4.5). The animals were allowed to drink 15% glucose solution overnight. The animals were then left for 72 hours after which the blood glucose levels were measured. Diabetes was confirmed from the fasting blood glucose using one touch select simple Glucometer.

2.5.1 Treatment of experimental animal

Animal Grouping and Feeding

Group C: Diabetes treated rats + crude extract (400mg/kg) + water
Group D: Diabetic treated rats + glibenclamide (standard drug) + water

The standard drug glibenclamide was administered to Group D at 1 mg/kg/day through intragastric tube to compare its efficacy with *physalis angulata* leaf.

2.6 Collection of Blood Sample

Blood samples were collected from the rats after sacrificed by decapitation. The blood sample was collected into a clean dry centrifuge tubes and was allowed to clot for 40 minutes after which spun at 5000 rpm for 10 minutes. The serum was collected transferred to bijou bottles and kept for serum glucose concentration, total protein, enzymes (AST, ALP, etc), lipid profile, urea, uric acid, electrolytes, albumin and bilirubin.

2.7 Phytochemica Screening of Secondary Metabolites

The phytochemical screening of the leaf of the *Physalis angulata* plant were carried out using standard qualitative procedure [15].

2.8 Biochemical Analysis

2.8.1 Determinatio of serum glucose (Randox kit) principle

Glucose is determined after enzymatic oxidation in the presence of glucose oxidase [16]. The hydrogen peroxide formed reacts under catalysis of peroxidase with phenol and 4-aminophenozone to form a red-violet dye as indicator.

2.8.2 Determination of HDL-cholesterol

High density lipoprotein-cholesterol was determined in serum by the method of Jacobs et al., [17]. The Randox HDL-cholesterol precipitant Kit was used.

2.8.3 Determination of total cholesterol

The levels of cholesterol were determined using Randox kits, a method of enzymatic hydrolysis described by [18]

2.8.4 Determination of triglycerides

This was measure after enzymatic hydrolysis with impasses. The indicator is a quinon-eimine formed from hydrogen eeroxide, 4-aminio phenazone and 4 choloropherol under the catalytic influence of peroxidase.X 200mg/dl

2.8.5 Determination of low density lipoprotein(LDL)

LDL-cholesterol level is generally calculated from the measurements of total cholesterol, HDL-Cholesterol, and triglyceride using fried Ewald's formula, but this calculation method is not sufficient for an accurate determination of LDL-cholesterol the reference method, but the method requires specialized instrumentation and a long measurement time. This makes the reference method difficult to perform in routine laboratory tests, and direct methods are widely used.

2.8.6 Determination of aspartateb aminotransferase (AST)

Aspartate Aminotransferase (AST) like ALT is an intracellular enzyme involved in amino acid and carbohydrate metabolism. It is present in high concentrations in the liver and muscle. It is involved in the transfer of amino group from aspartate to α-Ketoglutarate to form oxaloacetate and glutamate.

2.8.7 Determination of alanine amino transferase (ALT)

Alanine Aminotransferase (AST) is a intracellular enzyme involved in amino acid and carbohydrate metabolism. It is present in high concentration in the liver and muscle. It is involved in the transfer of amino group from alanine to α-Ketoglutarate to form pyruvate and glutamate. The diagnostic implications of this enzyme in the serum include hepatitis and other liver diseases in which the level is often higher than that of AST. Elevated level is also found in metastatic or primary liver neoplasm.

2.8.8 Determination of alkaline phosphatase

The method of King-Armstrong [19] was used in the determination of serum alkaline phosphatase. Phenol released by enzymatic hydrolysis from phenyl phosphate under defined condition of time, temperature and pH is estimate spectrophotometric at 405 nm.

2.8.9 Determination of serum bilirubin

Colormetric method based on that described by[20]Direct (conjugated) bilirubin reacts with diazotized sulphanic acid in allcaline medium to form a blue coloured complex measured at 546 nm.

Total (unconjugated) bilirunin is determined in the presence of caffefine, which release albumin bound bilirubin by the reaction with diazotized sulphanilic acid measured at 578 nm.

2.8.10 Determination of protein

Protein concentratiosns of the various samples were determined by means of the Biuret method as described by Gornal et al., [21] with some modification: potassium iodide was added to the reagent to prevent precipitator of Cu^{2+} ions as cuprous oxide.
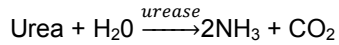
2.8.11 Determination of serum albumin

(Modification of Bartholomeno and Delaney method, [22]

The determination of serum albumin was carried out using colorimetric method.

2.8.12 Determination of serum urea

Urea in serum is hydrolyzed to ammonia in the presence of crease. The ammonia is then measured spectrophotometrically by Berthelots reaction.

$$\text{Urea} + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2$$

NH_3 + hypochlorite + phenol → indophenol (Blue compound)

2.8.13 Determination of serum uric acid (RANDOX KIT)

Uric acid is converted by uricase to allantoin and hydrogen peroxide, which under the catalytic influence of peroxidase oxidizes 3, 5-Dichloro-2hydroxybenzenesulfonic acid and 4-amnophenazone to form a red-violet quinoneimine compound (Fossati et al., 1980).

2.8.14 Determination of sodium (Na^+) and potassium (K^+) in serum

2.8.14.1 Flame photometer

Using compressed air diluted serum is sprayed as fine droplets into a non luminous gas flame which becomes coloured by the characteristic emission of sodium or potassium metallic ions in the sample. Using a light fitter or prism system, the light of wavelength corresponding to the metal being estimated is selected. The amount of light emitted depend on the concentration of metallic ions presence in the sample.

3. RESULTS

The Table 1 shows detail results of the phytochemical analysis and serum glucose concentration, total protein, enzymes (AST, ALP, etc.), lipid profile, urea, uric acid, electrolytes, albumin and bilirubin.

Table 1. Result of the phytochemical screening of crude aqueous extract

Phytochemicals	Crude aqueous
Alkaloids	+
Flavanoids	+
Tannins	+
Saponins	+
Cardiac-Glycosides	-
Balsam	+
Carbohydrate	+
Phenol	X
Resins	X

Key: + = present - = absent

4. DISCUSSION

Diabetes is complex metabolic disorder characterized by hyperglycemia together with the biochemical alterations of glucose metabolism. Terpenes/steroid are chemical compounds that occur naturally and have protective or disease preventive properties.

Table 2. Result of effect of aqueous extract of the leaf of *Physalis angulata* on serum glucose, protein and albumin levels in streptozotocin-induced diabetic rats

Treatment	Glucose(mmol)	Proteins(g/l)	Albumin
Normal control	7.88±3.343	77.85±0.50	38.81±0.50
Diabetic control	17.64±0.293[a]	59.46±0.67[a]	28.88±0.14[9]
Diabetic + STD drug	4.47±0.247[ab]	72.08±0.58[ab]	36.11±0.18[ab]
Diabetic+ leaf extract (400 mg/kg)	5.38±0.614[ab]	72.22±0.58[ab]	38.12±0.97[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 3. Result of the Effect of aqueous extract of the leaf of *Physalis angulata* on total bilirubin, direct bilirubin and indirect bilirubin levels in streptozotocin-induced diabetic rats

Treatment	Total bilirubin	Direct bilirubin (DB)	Indirect bilirubin (IB)
Normal control	9.33±0.214	3.71±0.127	5.62±0.087
Diabetic control	37.58±0.348[a]	20.43±0.296[a]	17.15±0.052[a]
Diabetic + STD drug	14.55±0.247[ab]	4.74±0.248[ab]	9.81±0.001[ab]
Diabetic+ leaf extract (400 mg/kg)	16.49±0.289[ab]	5.05±0.138[ab]	11.44±0.151[ab]

DB = Direct bilirubin, TB = Total 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. Results of the effects of leaf extract of *Physalis angulata* on total cholesterol, triglyceride, HDL and LDL level in streptozotocin-induced diabetic rats

Treatment	Total cholesterol (mmol/L)	Triglyceride (mmol/L)	HDL (mmol/L)	LDL(mmol/L)
Normal control	4.24±0.439	1.03±0.078	1.67±0.058	1.54±0.303
Diabetic control	5.11±0.094[a]	2.42±0.218[a]	0.37±0.049[a]	2.32±0.173[a]
Diabetic + STD drug	4.33±0.245[a]	1.12±0.063[a]	0.99±0.111[ab]	2.22±0.071[ab]
Diabetic + extract (400 mg/kg)	4.78±0.086[a]	1.44±0.060[a]	0.82±0.119[ab]	2.52±0.093[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. Result of effect of the leave extract of *Physalis angulata* on Alanine Amino transferase (ALT), Aspartate Amino transferase (AST) and Alkaline Phosphatase (ALP)

Group	ALT (U/L)	AST(U/L)	ALP (U/L)
Normal control	11.51±10.234	15.69±0.131	133.90±0.554
Diabetic control	59.70±0352[a]	82.92±0.534[a]	419.95±0.451[a]
Diabetic +STD drug	15.09±0.147[ab]	17.49±0.500[ab]	149.47±0.279[ab]
Diabetic+ extract (400 mg/kg)	17.74±0.134[ab]	21.04±0.343[ab]	234.74±0.474[ab]

± 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 the leaf extract of *Physalis angulata* on uric acid, urea and creatinine in streptozotocin induced diabetic rats

Group	Uric Acid (umol/L)	Urea (mmol/R)	Creatinine (mmol/L)
Normal control	138.36±0891	3.64±0.236	69.95±0.755
Diabetic control	522.81±0.617[a]	29.94±0.212[a]	470.63±0.441[a]
Diabetic +STD drug	142.93±0.577[a]	5.81±0.314[ab]	78.50±0.356[ab]
Diabetic + extract (400mg/kg)	241.05±0.351[a]	6.82±0.434[ab]	130.99±0.469[ab]

Values are expressed as means ± 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 the leaf of *physalis angulata* on some serum electrolytes in streptozotocin-induced diabetic rats

Group	Sodium (Na$^+$) (mmol/L)	Potassium (mmol/L)	Chloride (Cl$^-$) (mmol/L)	Bicarbonate (HC0$_3^-$) (mmol/L)
Normal control	144.15±0.124	3.36±0.164	114.03±0.066	26.98±0.064
Diabetic control	134.09±0.051[a]	6.13±0.051[a]	95.95±0.124[a]	13.98±0.047[a]
Diabetic+ STD drug	139.40±0.227[ab]	4.25±0.047[ab]	108.10±0.160[ab]	24.94±0.099[ab]
Diabetic + extract (400mg/kg)	138.15±0.122[ab]	5.00±0.105[ab]	105.19±0.223[ab]	23.05±0.098[ab]

Values are expressed as means ± 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)

Many kinds of natural products, such as terpenoids, alkaloids, flavonoids, phenolic, and some others, have shown antidiabetic potential [23]. The presence of tannins may also be responsible for antidiabetic properties [24].

Many flavonoids have demonstrated to act on biological targets involved in type 2 Daibetic mellitus such as: α-glycosidase, glucose cotransporter or aldose reductase. Flavonoids in Diabetes usually reduces aldose reductase, enhances insulin release, increases calcium ions uptake and reservation of pancreatic cells. Saponins have hypocholesterolemic effect, anti-carcinogenic, anti-oxidative, anti-tumor, anti-virus, anti-hepatic, anti-diabetic and

hepatoprotective properties. Terpenes are useful for the prevention and/or treatment of diabetes type 2, obesity and neuropathy.

Plants with hypoglycemic activities are known to contain one or more phytochemicals. Thus the significant antidiabetic effect of extracts of *Physalis angulata* could be due to the presence of these phytochemicals.

Table 2. Shows the serum glucose level of the diabetic rats treated with 400mg/kg of *Physalis angulata* significantly (P<0.05) reduced when compared to the diabetic control rats.

This proves that the plant *Physalis angulata* (leaf) has a dose dependent anti-diabetic property and it is capable of lowering blood glucose levels in streptozotocin-induced-diabetic rats.

The maintenance of normal glucose homeostasis requires a complex, highly integrated interaction among the liver, muscle, adipocytes, pancreas and neuroendocrine system. Recent studies have shown that the kidneys also play a central role in glucose homeostasis by reabsorbing all the filtered glucose, an adaptive mechanism that ensures sufficient energy is available during fasting periods. This mechanism becomes maladaptive in diabetes, however, as hyperglycemia augments the expression and activity of the sodium-glucose co-transporter (SGLT) 2 in the proximal tubule of the kidney. As a result, glucose reabsorption may be increased by as much as 20% in individuals with poorly controlled Diabetes. SGLT2 is a low affinity, high-capacity glucose transport protein that reabsorbs 90% filtered glucose, while the high-affinity, low-capacity SGLTI transport reabsorbs the remaining 10%. SGLT2 represents a novel target for the treatment of Diabetes. In animal studies, SGLT2 inhibition reduces plasma glucose levels, resulting in improved β-cell function and enhanced insulin sensitivity in liver and muscle. Defronzo et al. [25].

Diabetes mellitus has been known to be associated with lipid disorders and cardiovascular complications. Diabetic state appears to be associated with increased synthesis of cholesterol. Table 4 shows an increase in cholesterol levels in diabetic control and a significant (p<0.05) reduction was observed in rats fed with 400mg/kg extract of P*hysalis angulata* aqueous extract. In Diabetes mellitus, glucose is not utilized by the body cells.

The body sources for glucose from lipid and protein, as a result more lipids and proteins are broken down to yield acetyl CoA, which is channels to form cholesterol thereby increasing cholesterol. This significant reduction in serum cholesterol and triglyceride levels may also be due to reduction to inactivation of the multienzyme complex of fatty acid synthesis HMG-CoA reductase.

High levels of cholesterol in the blood have been linked to damage to arteries and cardiovascular disease. Monounsaturated and polyunsaturated fats increase HDL-cholesterol and saturated fats increased LDL-cholesterol.

The increase in serum LDL and triglycerides may be due to the action of hormone sensitive lipase, which promotes lipolysis and subsequently increases the level of plasma free fatty acids and triglycerides. These free fatty acids are catabolized to acetyl Co A which is further channeled to cholesterol synthesis thus, increasing blood cholesterol level.

Increased and/or decreased concentration of serum enzymes are used as indices of cellular damage. The heart, liver, and skeletal muscles are the main sites for the synthesis of Aspartate transaminase (AST) and Alanine transaminase (ALT). ALT and AST are transaminase enzymes. Alkaline phosphatase (ALP), a hydrolase enzyme is present in a number of tissues including liver, bone, intestine, and placenta. An ALP test is used to detect liver diseases or bone disorder. ALT catalyzes the reversible transamination between L-alanine and α-ketoglutarate to form pyruvate and L-glutamate as such having an important role in gluconeogenesis and amino acid metabolism. The reaction is reversible, but the equilibrium of the ALT reaction favors the formation of L-alanine. Another explanation might be up-regulation of ALT enzyme activity. Among the amino acids, Alanine is the most effective precursor for gluconeogenesis. Gluconeogenesis is increased in subjects with Type 2 Diabetes Mellitus due to increased substrate delivery (e.g. alanine) and an increased conversion of alanine to glucose. ALT might thus be up-regulated as a compensatory response to the impaired hepatic insulin signaling or, alternatively, may leak more easily out of the hepatocytes as a consequence of fatty infiltration and subsequent damage [26].

Table 5 show elevated AST level in streptozotocin-induced diabetic rats. These finding is consistent with the results obtained

from several other studies done by various researches. According to Goldberg et al., [27]. It was identified that the prevalence of AST enzyme activity in diabetic patients was (101 patients) 15% diabetic patients. AST function normally to transfer the amino group from an amino acid, Aspartate in the case of AST to a keto acid, producing pyruvate and oxaloacetate, respectively. It is located in the cytoplasm of the hepatocyte; an alternative form of AST is also located in the hepatocyte mitochondria. Although, both transaminase enzymes are widely distributed in order tissue of the body, the activities of AST outside the liver are low and, therefore, this enzyme is considered more specific for hepatocellular damage [28].

ALP is a hydrolytic enzyme serine protease acting optimally at pH 10. It has been reported in few earlier studies that many diabetics may also exhibit elevated ALP [29] Type 2 Diabetes Mellitus being a metabolic syndrome in which the fat metabolism is dysregulated, there is consequent elevation of Free Fatty Acids leading to subsequent fatty liver. ALP in the liver is found to be associated with cell membrane which adjoins the biliary canaliculus, and so high plasma concentration of liver isoenzyme indicates cholestasis rather than simply damage to the liver cells. According to [30] it was estimated that the liver enzymes AST. ALT, and ALP were significantly higher in diabetic patients as compared to non-diabetic control. [31]. A survey of our result Table 5 reveals that aqueous extract of 400mg/kg of *physalis angulata* significantly (p<0.05) reduced the serum enzyme levels of ALP, AST and ALT.

Creatinine is a waste product produced by the muscles and excreted through the kidneys. It is the best routine blood test used to measure how well the kidneys are functioning. Serum creatinine level is one of the sensitive monitors of nephropathy while serum urea is a reliable index of end stage renal failure. Urea is produced from the oxidative deamination of amino acids in which ammonia is generated, transported to the liver for the formation of urea through the urea cycle. Uric acid is the product of breakdown of purines. The blood levels of uric acid are a function of the balance between the breakdown of purines and the rate of uric acid excretion. Hyperuricemia is an underlying risk factor for type 2 diabetes mellitus, as it causes pro-inflammation endocrine imbalance in vascular smooth muscle cells and adipose tissue which lead to cell surface morphological changes and

insulin resistance [32]. As shown in Table 6 evidence of hyperuricemia, hypercreatinaemia and ureamia in diabetic control rats. The treatment of diabetic rats with 400mg/kg *Physalis angulata* aqueous extracts reduced the observed serum increase in the levels of uric acid, creatinine and urea. This suggests that the aqueous extract of *Physalis angulata* ameliorated the renal dysfunction observed in non-treated diabetic rats. This assertion is supported by both the calculated urea and creatinine clearances.

Elevated serum uric acid (SUA) levels (i.e. hyperuricemia) have been associated with metabolic syndrome and cardiovascular diseases, morbidity and mortality. Elevated SUA predict onset of type 2 Diabetes mellitus. SUA levels are increased during the early stages of impaired glucose metabolism.

Bilirubin is an excretory product formed by the catabolism of heme which is excreted by the liver. Bilirubin has been recognized as a substance with potent antioxidant properties. The first report on the antioxidant effects of bilirubin was published as early as 1954 Bilirubin attached to sugar is called 'direct' or 'conjugated' bilirubin, and bilirubin without sugar is called 'indirect' or 'unconjugated' bilirubin. All the bilirubin in the blood together is called 'total' bilirubin. Elevated serum bilirubin may indicate impairment of the excretory function of the liver, excessive hemolysis or obstruction of the biliary tract.

Direct and total bilirubin levels increased significantly in steptozotocin induced diabetic rats, suggesting that Diabetes affects bilirubin excretion. Diabetic rats fed with 400mg/kg extract of *physalis angulata* had significant reduction in bilirubin levels indicating that extracts of *physalis angulata* enhanced the excretion of bilirubin and reduced oxidation.

Electrolytes such as sodium (Na^+), Potassium (K^+) Chloride (CL^{-1}) and bicarbonate (HCO_3^-) are involved in the maintenance of osmotic pressure of the heart and other muscles, electron transfer reactions and in the catalysis and cofactors for enzymes.

A fall in plasma sodium arising due to a rise in blood glucose is a result of the syndrome of hyperosmolar non-kenotic state. The significant increase in Na^+ to suggest that, enhances Na^+ ion balance prevent hyperosmolar non-kenotic state. The most common cause of genuinely high

potassium (hyperkalemia) is related to the kidneys such as acute kidney failure.

Plasma chloride levels vary and to a greater extent depend on the plasma concentration of Na^+ and HCO_3^-. Plasma HCO_3^- levels usually provide a useful guide to acid-base status. Decrease in serum Cl^- and HCO_3^- are indications of renal tubular acidosis, acute renal failure or metabolic acidosis.

The increase in serum Cl^- and HCO_3^- in *physalis angulata* (leaf) extract treated diabetic rats observed in this study would suggest that the extract enhances rehydration and/or prevent against metabolic acidosis.

The kidney has been described as the major regulator of calcium balance on a daily basis in normal health. In this study it may be possible that the decrease in serum sodium in diabetic control rats may be due to impaired sodium hemeostatis. The increase in sodium level in diabetic rats on physalis angulata (leaf) extract may have enhanced the mobilized of sodium.

5. CONCLUSION

The plant *physalis angulata* (leaf) has been shown from this study to exhibit therapeutic effect on Diabetes mellitus as claimed by some Nigerian herbalists. It was demonstrated to have hypoglycemic, hypolipidemic and hypocholesterolemic properties. It lowers elevated activities of serum enzymes in diabetic rats. The plant enhances protection against renal dysfunction as was shown by reduced creatinine level. It possesses phytochemicals responsible for its hypoglycemic and hypolipidemic effects.

These properties provide some biochemical basis for the use of *physalis angulata* (leaf) for management of Diabetes mellitus and confirms its role as a traditional anti-diabetic remedy.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The experimental design was conducted in accordance with the guidelines approved by the institutional animal ethical committee of University of Jos, Nigeria.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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