



## Exploring the ameliorating potentials of *Phyllanthus fraternus* methanolic leaf extract on hepatic and renal dysfunctions in diabetic rats

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### Abstract

Uncontrolled hyperglycaemia gives rise to dysfunctions of the liver and kidney among other complications. Regulating the levels of sugar with available conventional substances often produce undesirable effects, therefore, search from medicinal plants for alternative anti-diabetic treatment cannot be overburdening. The study was undertaken to explore the potential(s) of *Phyllanthus fraternus* methanolic leaf extract in ameliorating kidney and liver dysfunctions in diabetic rats. Twenty-four diabetic and six normal rats were used for the study. The rats were grouped into five (5) of six rats each (Group I-V) and the treatment lasted for 28 days; group I was normal control, II was diabetic control, III was metformin treated 5 mg/kg b.w, IV and V were diabetic treated with the extracts at 200 and 300 mg/kg b.w respectively. The diabetic rats treated with the extracts and metformin were found to have significantly ( $p < 0.05$ ) lower concentrations of the enzyme markers of hepatic damage (AST, ALT and ALP). Furthermore, the levels of non-enzyme markers of hepatic damage were significantly ( $p < 0.05$ ) improved while the levels of creatinine and urea in the serum decreases which implies improved renal functions. Therefore, the plant can be an alternative source of a novel oral bioactive agent against uncontrolled diabetes mellitus.

**Keywords:** Diabetes, Hepatic function, *Phyllanthus fraternus*, Renal function, Streptozotocin

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## 1. Introduction

Diabetes mellitus has remained a major concern to the global public well-being particularly among developing nations, which are confronted by the escalation in its prevalence (Jamaludin et al., 2016). More than 463 million people have been affected by diabetes mellitus globally (Nair et al., 2020) and this number is likely to surge up to 693 million by the year 2045 (Cole and Florez, 2020).

Diabetes mellitus as described by the World Health Organization (WHO) is a group of metabolic diseases marked by hyperglycaemia over an extended period (WHO, 2014). This prolonged abnormal hyperglycaemia

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usually arises due to either inadequate secretion of insulin, insulin resistance or even both (Mirzaei et al., 2020). Patients with marked hyperglycaemia (high blood sugar level) are usually confronted with frequent urination (polyuria), incessant thirst (polydipsia) and constant hunger (polyphagia) when not given the treatment, diabetes can result in numerous complications (WHO, 2013). Diabetic ketoacidosis and nonketotic hyperosmolar coma are some acute complications of diabetes (Kitabchi et al., 2009). Prolonged and improperly managed diabetes can lead to complications such as renal failure, stroke, cardiovascular disorders, retinopathy among others (WHO, 2013). Complications from diabetes mellitus are among the most important causes of mortality (Mirzaei et al., 2020).

Diabetes mellitus has been reported by Pickup and Williams (2003) to cause derangement in the metabolism of carbohydrates, lipids and protein. It has also been reported that a good metabolic control can be very helpful in halting or at least slowing the development of diabetic-related complications (Floretto et al., 1998; and Renu et al., 2004).

Various plants with medicinal properties have been utilized in the treatment of numerous health challenges throughout the history of mankind. Plants possess the inherent ability to produce wide-ranging active compounds that are useful for self-defense against predators (insects, fungi and herbivorous mammals) and others exert important biological functions in humans (Lai and Roy, 2004; and Tapsell et al., 2006). Chemical substances from plants tend to exert their activity on the human body via similar processes to those of conventional drugs; therefore, herbal medicines have a similar mode of action to that of conventional drugs (Lai and Roy, 2004; and Tapsell et al., 2006).

The utilization of herbs in managing diseases is very common among non-industrialized countries because it is relatively cheaper than conventional drugs. This underscores the need to explore the potentials of the enormous diversity of herbs that Africa, especially Nigeria is gifted with by nature. *Phyllanthus fraternus* is one of the plants that have been reported to possess a lot of pharmacological activities including antidiabetic properties. Therefore, this study is designed to assess the activity of the plant against some diabetic conditions such as renal and liver dysfunctions in streptozotocin-induced diabetic rats.

## 2. Materials and methods

### 2.1. Materials

#### 2.1.1. Collection of study plant material

The fresh leaves of the plants (*Phyllanthus fraternus*) were collected in the morning at Hayin gada in Girei Local Government area of Adamawa state, Nigeria. The plant was then ascertained as *Phyllanthus fraternus* by a botanist in the Department of Biological Sciences, Modibbo Adama University of Technology, Yola, Adamawa state.

#### 2.1.2. Experimental animals used for the study

Thirty (30) male albino rats of about six weeks ranging between 100-130 g in weight were purchased from the Institute of Veterinary Research in VOM, Plateau state. They were given pelletized grower diet (Vital feeds, UACN) and water *ad libitum* with normal 12 h dark/light cycle.

### 2.2. Equipment

The equipment used in this study include; Electronic balance (Golden mettle-2G2-USA), ACCU-CHEK Glucometer and ACCU-CHEK Test Strips (GC-Roche Diagnostic-Germany), Centrifuge (Techmel, USA), Spectrophotometer (Vis spectrophotometer 721- PEC Medical USA), Water bath (HH-2 B-Scientific),

### 2.3. Chemicals

The following chemicals/reagents were used; Streptozotocin (Tocris Bioscience London), Methanol (Sigma-Aldrich Chemie GmbH, Germany), Metformin, chloroform, (Sigma Aldrich-Germany), Alanine Transaminase (ALT), Aspartate Transaminase (AST), Total Protein, Albumin, Creatinine, Urea, Direct Bilirubin, Total Bilirubin, Assay kits (Randox laboratory, London).

## 2.4. Methods

### 2.4.1. Plant material

The fresh leaves of the plant collected were carefully washed and dried under shade. It was pulverized using mortar and pestle and the powder obtained was used for the extraction.

### 2.4.2. Extraction

Extraction was carried out by soaking 200 g of the pulverized plant material in 2 L of methanol for a period of 24 h with intermittent shaking, it was thereafter filtered using a methylene clothe and concentrated on a water bath at 55°C (Ugwu et al., 2011).

### 2.4.3. Diabetization of the rats

Diabetes was induced in an overnight fasted rats by a single administration of streptozotocin intraperitoneally at 60 mg/kg body weight (Al-Hariri et al., 2011; and Mohammed, 2012). The rats were given 5% glucose solution water for the first 24 h in order to prevent lethal hypoglycaemia that may arise as a result of immense release of insulin from the pancreas (Barry et al., 1997).

The fasting blood glucose was tested at the third day (72 h) and rats with blood glucose level of more than 300 mg/dl were considered diabetic and hence used for the study (Akbarazadeh et al., 2007; and Parthasarthy and Ilavarasan, 2009).

## 2.5. Experimental design

The 24 diabetics rats were randomly grouped into four, while the six healthy rats were used as normal control. The rats were treated once daily for 28 days using intragastric tube. The treatment given to each group is shown below;

Group	Treatment
Group I (Normal control)	Normal + no treatment
Group II (Negative control)	Diabetic + no treatment
Group III (Positive control)	Diabetic + Metformin 5 mg/kg b.w
Group IV	Diabetic + ME 200 mg/kg b.w
Group V	Diabetic + ME 300 mg/kg b. w

Food and water were provided to all the groups *ad libitum*.

## 2.6. Collection of blood sample

Blood samples were collected through cardiac puncture in plain bottles after the four weeks treatment by anaesthetizing the rats using chloroform-soaked cotton wool in a sealed jar. Serums were obtained by centrifuging the samples for five minutes at 3,000 revolutions per minute (rpm).

## 2.7. Determination of biochemical markers of hepatic and renal functions

Biochemical markers such as the alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), albumin, urea, and creatinine were measured by spectrophotometric method using Randox kit (Milajerdi et al., 2017).

## 3. Results

### 3.1. Effect of the treatments on levels (IU/L) of enzyme markers of hepatic damage

Enzyme markers of liver damage (AST, ALT and ALP) have been shown by this study (Table 1) to have been increased in diabetic control far above the values obtained in normal rats. Nevertheless, the treatments administered have lowered significantly ( $p < 0.05$ ) the levels of these enzymes in the treated groups when compared against the diabetic untreated group.

### 3.2. Effect of the treatments on levels of non-enzyme markers of hepatic damage

The result (Table 2) showed that, conjugated bilirubin (CB) and total bilirubin (TB) levels have increased significantly ( $p < 0.05$ ) in diabetic untreated group (control) when compared against the normal control. On the other hand, the levels of albumin (ALB) and total protein have markedly decreased in the diabetic untreated group (control) when compared against the healthy untreated rats (normal control). However, the treatments administered have significantly ( $p < 0.05$ ) increased their serum levels in relation to the diabetic untreated group. All the treated groups in relation to the normal control showed no significant difference ( $p < 0.05$ ) in the levels of the TB except the 200 mg/kg b.w that is significantly higher.

Treatments	AST	ALT	ALP
Normal control	12.33 ± 2.33	13.33 ± 5.04	25.00 ± 10.58
Diabetic control	63.00 ± 3.46	42.66 ± 4.37	217.66 ± 3.52
Standard control (Met.5 mg/kg-b.w.)	26.33 ± 8.2 <sup>a</sup>	18.33 ± 2.66 <sup>a</sup>	76.66 ± 2.36 <sup>a</sup>
ME 200 mg/kg b.w.	37.66 ± 1.20 <sup>ab</sup>	24.00 ± 4.04 <sup>a</sup>	115.33 ± 7.12 <sup>a b</sup>
ME 300 mg/kg b.w.	30.33 ± 0.88 <sup>a</sup>	21.33 ± 0.33 <sup>a</sup>	110.33 ± 7.21 <sup>a b</sup>

**Note:** Values expressed are mean ± SEM; n = 6. Dissimilar superscript letters across same column implies a statistically significant difference at  $p < 0.05$ , AST=Aspartate aminotransferases, ALT = Alanine aminotransferases, ALP = Alkaline phosphatase, ME = Methanolic extract, Met. = Metformin and b.w. = body weight;  
Key: a = lower significantly in relation to diabetic untreated control, b = higher significantly in relation to metformin treated control.

Treatments	CB (mg/dl)	TB (mg/dl)	ALB (g/l)	TP (g/l)
Normal Control	0.33 ± 0.57 <sup>b</sup>	0.78 ± 1.15 <sup>b</sup>	38.33 ± 0.88 <sup>b</sup>	69.00 ± 2.88 <sup>b</sup>
Diabetic Control	0.91 ± 0.33 <sup>a c</sup>	1.57 ± 1.45 <sup>a</sup>	16.00 ± 1.15 <sup>a</sup>	45.33 ± 0.88 <sup>a</sup>
Standard Control (Met.5 mg/kg-b.w.)	0.50 ± 0.57 <sup>ab</sup>	1.02 ± 1.45 <sup>b</sup>	34.66 ± 1.76 <sup>b</sup>	70.33 ± 1.85 <sup>b</sup>
ME 200 mg/kg b.w.	0.59 ± 0.33 <sup>ab</sup>	1.11 ± 0.57 <sup>ab</sup>	38.66 ± 1.76 <sup>b</sup>	67.66 ± .66 <sup>b</sup>
ME 300 mg/kg b.w.	0.56 ± 0.57 <sup>ab</sup>	1.00 ± 0.57 <sup>b</sup>	35.00 ± 0.58 <sup>b</sup>	69.67 ± .45 <sup>b</sup>

**Note:** Values expressed are mean ± SEM; n = 6. Dissimilar superscript letters across same column implies a statistically significant difference at  $p < 0.05$ , CB= conjugated bilirubin, TB = total bilirubin, ALB = albumin, TP = total protein, ME = Methanolic extract, Met. = Metformin and b.w. = body weight.  
Key: a = lower significantly in relation to diabetic untreated control, b = higher significantly in relation to metformin treated control, and c = higher significantly in relation to the metformin treated (standard) control.

### 3.3. Effects of treatments administered on serum markers of kidney function in diabetic rats

The result obtained shows an increase in the levels of urea and creatinine in the serum of the diabetic untreated groups in relation to the healthy untreated rats (Table 3). Treatment with MEPF had a decreasing effect on serum urea, with maximum effect exhibited by the standard drug (metformin). MEPF 200 mg/kg b.w. showed the least effect in reducing serum urea. Similarly, treatment with MEPF and metformin have also been shown to decrease significantly  $p < 0.05$  the level of serum creatinine when compared to the diabetic control. Maximum effect was observed in the metformin-treated group.

**Table 3: Effects of treatment administered on biochemical markers of kidney function in streptozotocin-induced diabetic rats**

Treatment	Urea (mg/dl)	Creatinine (mg/dl)
Normal Control	26.33 ± 0.12 <sup>b</sup>	0.88 ± 1.20 <sup>b</sup>
Diabetic Control	59.13 ± 0.12 <sup>a</sup>	2.25 ± 1.76 <sup>a</sup>
Standard Control (Met.5 mg/kg-b.w.)	27.33 ± 0.17 <sup>b</sup>	0.90 ± 1.15 <sup>ab</sup>
ME 200 mg/kg b.w.	30.36 ± 0.22 <sup>b</sup>	1.16 ± 1.15 <sup>ab</sup>
ME 300 mg/kg b.w.	28.60 ± 0.23 <sup>b</sup>	0.96 ± 0.57 <sup>b</sup>

**Note:** Values expressed are mean ± SEM; n = 6. Dissimilar superscript letters across same column implies a statistically significant difference at  $p < 0.05$ , AST =Aspartate aminotransferases, ALT = Alanine aminotransferases, ALP = Alkaline phosphatase, ME = Methanolic extract, Met. = Metformin and b.w. = body weight;  
Key: a = lower significantly in relation to diabetic untreated control, b = higher significantly in relation to metformin treated control.

#### 4. Discussion

The regulation of glucose level is one of the major hepatic functions in both pathological and physiological states like diabetes mellitus. Hepatic impairment is among the life-threatening complications in diabetic patients (Jamaludin et al., 2016). The prolonged treatment of streptozotocin induced diabetic rats with methanolic extract of *Phyllanthus fraternus* (MEPF) has been shown to control the high blood glucose concentration which when left untreated causes life-threatening complications that include hepatic and renal failures (Nadro and Elkanah, 2017).

The baseline and important markers of assessing the extent of injury to the liver are the measurement of the levels of the enzyme markers of hepatic damage (alkaline phosphatase ALP), aspartate transaminase (AST) and alanine transaminase (ALT), (Nannipieri et al., 2005; and Longo et al., 2011). Increased levels of these enzyme (AST, ALT, ALP) in the blood are associated with diabetes mellitus or other pathological conditions.

The treatment with methanolic extract of *Phyllanthus fraternus* (MEPF) has significantly lowered the levels of these enzyme markers in serum, which remains higher in the diabetic-untreated group. The high serum levels of these hepatic enzyme indicators in the untreated diabetic control might be due to leakage from the hepatic tissues and their consequent accumulation in the bloodstream (Chaudary et al., 1993; and Zarei et al., 2015).

The study also shows significant improvement in the levels of non-enzymatic indicators of hepatic damage, particularly the decreased serum levels of albumin and total protein seen in the diabetic-untreated group which might be due to decreased protein synthesis or increased renal loss (Al-Aboudi and Afifi, 2011) has significantly ( $p < 0.05$ ) increased in all the treated groups. This finding agrees with an earlier submission by (Zarei et al., 2015) where he affirmed that the decreased serum levels of albumin and protein in diabetic rats are results of the increase in the catabolism of proteins which in turn causes direct damage to the synthesis and secretion of albumin. Renal loss is the leading cause of the decrease in serum level of albumin, pathological conditions that cause damage to the membrane of the glomerular usually leads to an increase in permeability of all proteins, but that of albumin is specifically affected by the neutralization of the negatively charged groups on the surface of the membrane. This seems to be the major mechanism for albuminuria often associated with diabetic nephropathy (American Society for Clinical Pathology, 2014).

It has also been established that chronic renal and hepatic diseases as well as unstable angina have direct effect on the composition of the human serum albumin (Friedman and Fadem, 2010; Wong, 2007; and Ju et al., 2008).

The high serum levels of both conjugated and total bilirubin recorded in the diabetic untreated control group might be owing to impaired uptake of bilirubin, its overproduction, conjugation, excretion or backward leakages from damaged bile ducts or liver cells (Yoshinari and Igarashi, 2010).

Urea and creatinine are normal waste products that are excreted by the kidney. Urea and creatinine are metabolic by-products of protein and creatine respectively. The diabetic untreated control group is characterized by increase in serum levels of urea and creatinine, this is as a result of impairment in the excretion of these substances by the kidney as in the case of diabetic nephropathy consequently leading to the accumulation of these substances (urea and creatinine) in the blood. Treatments with MEPF lowered the serum level of urea and creatinine significantly. This finding has agreed with results from earlier studies using different plants (Alderson et al., 2004; and Leonard et al., 2006). This improvement in renal biochemical functions following treatment with MEPF could be due to its ability to correct the metabolic disorders in animals by the ability of the kidney tubules to regenerate (Kissane, 1985).

## 5. Conclusion

Hepatic and renal damages are part of the complications of diabetes mellitus. The study showed significant reductions in the levels of ALP, ALT, AST and bilirubin in the serum which suggests improvement in hepatic function, with the marked increase in the levels of albumin and total protein. Also, there is a significant improvement in renal function when the treatment groups were compared against diabetic control. Hence, the methanolic extract of *Phyllanthus fraternus* is an effective anti-diabetic plant with the ability to halt and reverse this life-threatening disease and its complications.

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