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Research Article

Decreased Serum Sodium and Potassium Ions but Raised Creatinine in Streptozotocin-Induced Diabetic Rats; Reversibility by Methanol and Ethanol Extracts of *Terminalia catappa*

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Abstract

Renal complications in diabetes mellitus is a major concern that stimulates research on various mitigation approaches. This study was investigating the changes in renal parameters in diabetes and comparative effects of methanol and ethanol extracts of *Terminalia catappa*. A total of 30 rats were divided randomly into six groups of five animals per group. Group 1 as control got distilled water, 5ml/kg body weight orally. Group 2 was diabetic group and received distilled water orally, 5ml/kg body weight. Group 3 was administered methanol leaf extract of *T. catappa* at 312.25 mg/Kg body weight orally while group 4 received 362.28 mg/Kg body weight of ethanol extract of *T. catappa* leaves. Groups 5 and 6 were diabetic rats treated with 30 mg/Kg body weight aspirin and subcutaneous administration of insulin, 0.75 IU/Kg body weight respectively. Inducement of diabetes was by use of streptozotocin at 65 mg/Kg body weight. Results showed significant ($p < 0.05$) decrease of Na^+ in diabetic (124.2+1.39 mEq/L), methanol (114.8+1.77 mEq/L) and ethanol (118.2+1.93 mEq/L) extract groups compared with control group value of 140.2+2.31 mEq/L. Also significantly ($p < 0.05$) decreased K^+ was in diabetic (3.42+0.10 mEq/L), methanol (2.96+0.12 mEq/L) and ethanol (3.14+0.06 mEq/L) extract groups compared with control group value of 4.48+0.18 mEq/L. Slight changes in serum creatinine level were observed with increase from control group value of 79.4+1.50 mg/L to 85.2+0.97 mg/L and 81.8+1.28 mg/L in diabetic and ethanol groups respectively but decreased to 71.4+2.06 mg/L in methanol group. Diabetic hyperglycemia related hyponatremia and hypokalemia was not reversed by methanol or ethanol extracts of *Terminalia catappa* leaves but raised serum creatinine was reduced by both extracts and reduction was significant in only methanol extract group. This suggests the inability of the extracts to reverse changes in osmolality in type 1 diabetes mellitus.

Keywords: Sodium Ion; Potassium Ion; *Terminalia catappa*; Bicarbonate; Diabetes Mellitus; Serum Creatinine; Hypokalemia; Hyponatremia

Introduction

Diabetes mellitus is a devastating metabolic disorder characterised by hyperglycemia. Continuous exposure of the body to hypperglycemia as commonly experienced in an uncontrolled diabetes mellitus; type 1 or type 2, often results in damages of various body organs. The body organs commonly affected are retina of the eye, heart, kidney, nerves and blood vessels [1]. Other features of diabetes mellitus are polyphagia, hyper diuresis and polydipsia [2]. Consequent upon these features, destabilization of body fluid homeostasis becomes inevitable. Changes in fluid level of the body is associated with electrolyte balance and kidney functioning [3]. Electrolyte homeostasis is an important physiological mechanism for body fluid maintenance and neuromuscular excitability [4]. Sodium ion abundant in extracellular fluid (ECF) compartment is responsible for maintenance of osmotic equilibrium [5] while potassium ion is abundant in the intracellular fluid (ICF). Potassium ion influences cellular resting membrane potential, cardiovascular electrical activities and haemostasis [4]. There are various mechanisms to ensure restoration of the extracellular and intracellular balance of the electrolyte to maintain electro neutrality and functionality of excitable tissues and other forms of cell signalling [6]. The body design is to conserve more sodium ion and less potassium ion. Disruption of blood concentrations of these ions triggers physiological feedback mechanisms necessary for reset to normal levels. Renal mechanism is paramount in the regulations of body electrolytes. Abnormalities in electrolyte concentrations could be attributed to renal function compromise [7,8]. However, some disorders such as vomiting, diarrhoea and dehydration can also influence the electrolytes balance [9,10]. The activity of Renal disorder such as diabetic kidney disease (DKD) normally occur due to influence of hyperglycemia on osmotic diuresis which result in loss of fluid and electrolytes. The inability to conserve electrolytes associated with diabetes can be handled by dialysis and other forms of medications. Control of blood glucose level with hypoglycemic drugs is not without its attendant effect on the kidney and consequently perturb the renal handling of electrolytes and body fluid [10-12]. Low level of insulin in diabetes affects the activities of Na/K ATPase and this concomitantly compromises Na/K metabolism and plasma membrane transport of Na and K ions with a resultant effect on facilitative transport of monosaccharides across the intestinal epithelium [13,14]. The renal handling of urea and creatinine is also compromised in diabetes mellitus [15]. Protein catabolism, muscle wasting and purines degradation is increased in diabetes mellitus [16]. Any therapeutic approach to enhance renal functioning in diabetes mellitus could provide succour in diabetic related renal complications. Therefore, investigation of Terminalia catappa leaf extract on renal indices was conducted in streptozotocin-induced diabetic rats.

Materials and Methods

Experimental animals

Adult male Wister rats with body weight between 150-200g were used in this study. They were purchased from the Animal House, Faculty of Basic Medical Sciences, University of Uyo. The rats were kept in cages in the Animal House to acclimatize for two weeks before the start of the experiment. The animals were fed with standard pellets (from Guinea Feeds, Plc Nigeria) and have access to water *ad libitum*.

Collection and Preparation of *Terminalia catappa* leaves

The *Terminalia catappa* leaves collected within the premises of University of Uyo was authenticated at Botany and Ecological Studies Department by a Botanist and was registered with herbarium number UUPH 22(a).

Methanol and ethanol leaf extracts were obtained by macerating 1000g of pulverized leaves in 80 (v/v) methanol and ethanol respectively and were evaporated at 45°C to obtain a pastes. The pastes were stored in refrigerator for use during the experiments.

Induction of experimental diabetes

Induction of diabetes was with streptozotocin (STZ, from Sigma-Aldrich) according to basic protocol in our previous research [17]. Streptozotocin was dissolved in citrate buffer (citric acid and sodium citrate; enzyme grade from Fisher) with pH 4.5 prepared just before administrations. The STZ was administered by intraperitoneal injection, 65 mg/Kg body weight. The animals were provided with 10 % (w/v) sucrose (from Sigma) water for the first 24 hours to avoid severe hypoglycemia. The animals were fasted for about 12 hours. Development of diabetes was assessed after 48 hours. Blood sample from the tail was tested using One Touch glucometer [One Touch Ultra, Life Scan Inc, U.S.A]. Blood glucose ≥200 mg/dL was considered diabetic [17] and the experiment lasted for 14 days

Toxicological study (LD50)

Toxicological study was carried out to determine the toxicity and median lethal dose (LD50) of the leaf extracts of *Terminalia catappa*. This study was carried out in different phases for methanol and ethanol extracts.

Methanol leaf extract of *Terminalia catappa*

The toxicity study was carried out following Lorke's method [18]. The result was calculated with mathematical formula. The maximum dose producing 0% mortality was 3000 mg/Kg and minimum dose producing 100% mortality was 3250 mg/Kg. Thus, the square root of the product of these two values was 3122.50 mg/Kg. Based on this result, 10%, 20% and 30% of the LD_{50} were calculated for the research work as low dose, middle dose and high dose respectively. The values are; Low dose (LD); 10% of LD_{50} = 312.25 mg/kg, Medium dose (MD; 20 % of LD_{50} = 624.50 mg/kg and High dose (LD) 30% of LD_{50} = 936.75 mg/kg.

Ethanol leaf extract of *Terminalia catappa*

The toxicity study was carried out following Lorke's method [18]. The result was calculated with mathematical formula. The maximum dose producing 0% mortality was 3500 mg/Kg and minimum dose producing 100% mortality was 3750 mg/Kg. Thus, the square root of the product of these two values was 3622.84 mg/Kg. Based on this result, 10%, 20% and 30% of the LD_{50} were calculated for the research work as low dose, middle dose and high dose respectively. The values are; Low dose (LD) 10% of LD_{50} = 362.28 mg/kg, Medium dose (MD) 20 % of LD_{50} = 724.56mg/kg and High dose (LD) 30% of LD_{50} = 1086.84 mg/kg.

Design of the experiment

The experimental animals were randomly distributed into six (6) groups of five (n = 5) rats per group as follows:

- **Group 1:** Control group administered with only distilled water orally at a dose of 5 ml/kg body weight.
- **Group 2:** Diabetic group administered with only distilled water orally at a dose of 5 ml/Kg body weight.
- **Group 3:** Diabetic group with methanol extract of *Terminalia Catappa* at a dose of 312.25 mg/kg body weight administered orally.
- **Group 4:** Diabetic group treated with ethanol extract of *Terminalia catappa* leaf at a dose of 362.28 mg/Kg body weight by oral administration.
- **Group 5:** Diabetic group administered with aspirin orally at a dose of 30 mg/Kg body weight.
- **Group 6:** Diabetic group treated with insulin at a dose of 0.75IU/Kg body weight by oral administration.

Determination of renal indices parameters

Serum Creatinine and Serum urea were determined by spectrometry using in Randox biochemical kit.

Determination of electrolytes parameters

Sodium, potassium, calcium, and bicarbonate concentrations were determined spectrophotometrically as outlined in Randox biochemical kit.

Determination of serum protein

Serum total protein and albumin levels in the serum were measured with kits using an automated chemistry analyzer (Easy RA Medical, USA) according to manufacturer`s instructions.

Determination of fasting blood glucose

The blood glucose was determined using glucometer (One Touch Glucometer, USA). Blood from tip of the rat tail was dropped into Glucose strip and the readings were recorded.

Statistical analysis

The results are presented as mean ± Standard Error of Mean (SEM). Difference between values of the groups were evaluated using analysis of variance (ANOVA). The statistical analysis was by Microsoft Excel and GraphPad Prism (Graph Pad Inc., USA) version 7.0. Multiple comparison was carried by Post-hoc test using Turkey's Post-hoc test. The probability level of $p < 0.05$ was considered as level of significance

Results

Serum level of sodium ion

The results analysis for sodium ion (Na^+) as seen in figure 1 shows that Na^+ was 124.2 ± 1.39 mEq/L in the diabetic group and was reduced significantly ($p < 0.05$) when compared with 140.2 ± 2.31 mEq/L in control group. The diabetic groups treated with

methanol and ethanol extracts were 114.8 ± 1.77 mEq/L and 118.2 ± 1.93 mEq/L respectively with significant ($p < 0.05$) reduction compared with control group. The Na^+ level for aspirin treated group was 136.8 ± 2.78 mEq/L, slightly lower than control group value but significantly ($p < 0.05$) higher than the values for diabetic, methanol extract and ethanol extract groups. Insulin treated diabetic animals had Na+ reduced to 121.8 ± 3.28 mEq/L which was equally significantly ($p < 0.05$) lower than control and aspirin treated groups values.

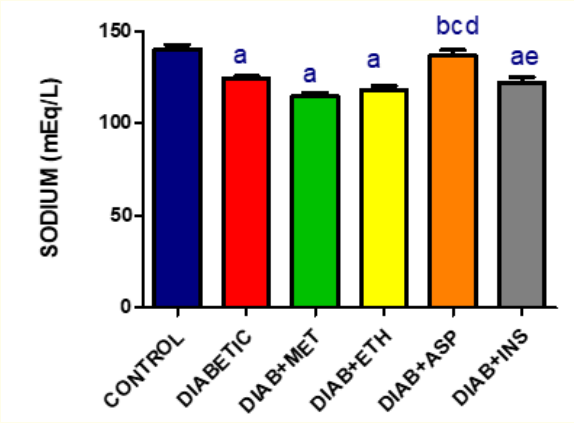

Figure 1: Serum Sodium level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$. a = test compared with control, b = test compared with diabetic group, c = test compared with diabetic+methanol extract group, d = test compared with diabetes+ethanol extract group, e = test compared with diabeties+aspirin group.

Serum level of potassium ion

In figure 2, the Potassium level (K^+) of control group was 4.48 ± 0.10 mEq/L while diabetic group level was reduced significantly ($p < 0.05$) to 3.42 ± 0.10 comparing it with control group. Diabetic group administered with methanol and ethanol extracts showed further reductions to 2.96 ± 0.12 mEq/L and 3.14 ± 0.06 mEq/L respectively. These reductions were significant ($p < 0.05$) compared with control group. Also diabetic group treated with aspirin and insulin were 3.92 ± 0.10 mEq/L and 4.06 ± 0.13 mEq/L respectively. The value of aspirin treated group was significantly ($p < 0.05$) lower than control group but higher than methanol and ethanol extract treated groups. But insulin treated group showed significant ($p > 0.05$) increase compared with other groups except control and aspirin treated group.

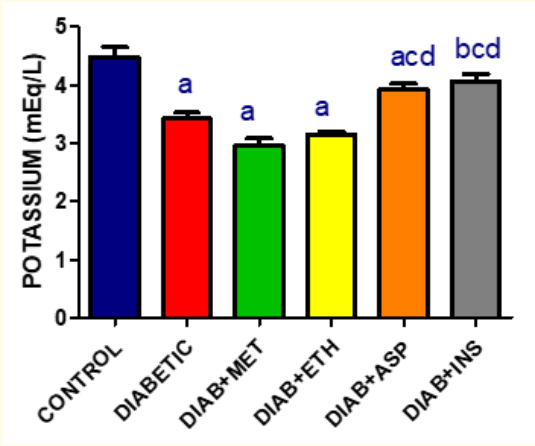

Figure 2: Serum Potassium level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$. a = test compared with control, b = test compared with diabetic group, c = test compared with diabetic+methanol extract group, d = test compared with diabetes+ethanol extract group.

Serum level of bicarbonate ion

The results of Bicarbonate ion (HCO_3) is represented in figure 3. The results show that HCO_3 was 24.0 ± 1.23 mEq/L in the control group and 28.0 ± 0.71 mEq/L in diabetic group. The methanol extract treated group was 24.4 ± 1.08 mEq/L and ethanol extracts group was 24.8 ± 0.92 mEq/L. Aspirin and insulin treated groups were 24.6 ± 1.6 mEq/L and 25.2 ± 1.72 mEq/L respectively. The observed changes were not significant compared to control or other groups.

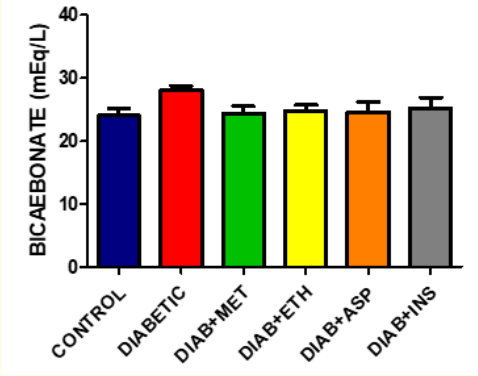

Figure 3: Serum Bicarbonate level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$.

Serum level of creatinine

The serum creatinine level (figure 4) showed 79.4 ± 1.50 mg/dL, 85.2 ± 0.97 mg/dL, 71.4 ± 2.06 mg/dL, 81.8 ± 1.28 mg/dL for control, diabetic, diabetic + methanol and diabetic + ethanol treated groups respectively. Comparing these values, there was significant reduction in methanol treated group compared with diabetic group and a significant increase in ethanol treated group compared with methanol treated group but there was no significant difference with control group. The result of aspirin treated diabetic group was 92.0 ± 2.10 mg/dL, significantly ($p < 0.05$) higher than control, methanol and ethanol groups while insulin treated diabetic group had value of 78.8 ± 2.65 mg/dL and was only different significantly ($p < 0.05$) with aspirin treated group.

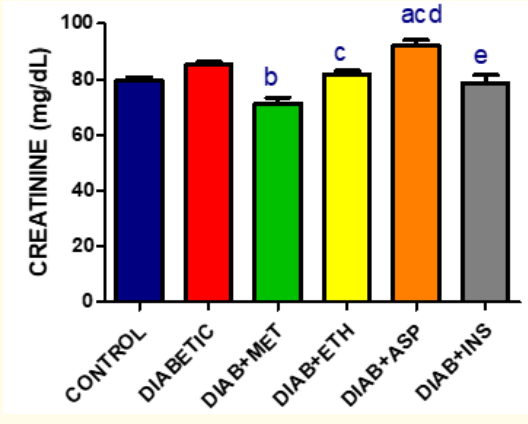

Figure 4: Serum creatinine level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$. a = test compared with control, b = test compared with diabetes group, c = test compared with diabetes+methanol extract group, d = test compared with diabetes+ethanol extract group, e = test compared with diabetes+aspirin group.

Serum level of urea

The serum level of urea in diabetic group was 4.10 ± 0.21 mg/dL showing slight increase compared with results of control group which was 3.9 ± 0.4 mg/dL but methanol and ethanol treated group with 3.48 ± 0.11 mg/dL and 3.86 ± 0.33 mg/dL respectively showed marginal reduction compared to control and diabetic groups. The mean values for aspirin and insulin groups were 4.1 ± 0.12 mg/dL and 3.72 ± 0.23 mg/dL respectively and the changes observed were only marginal.

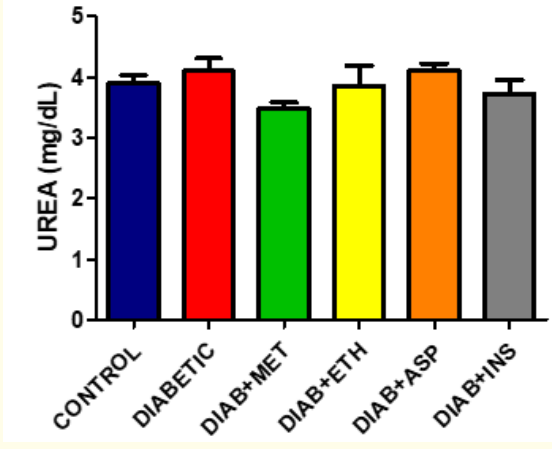

Figure 5: Serum Urea level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$.

Serum level of uric acid

The Uric acid level results are in figure 6. The results show that uric acid was 228.0 ± 6.78 g/dL in control group. The value was increased significantly ($p < 0.05$) to 294.0 ± 4.80 g/dL in diabetic group. The diabetic methanol treated group uric acid value decrease to 255.6 ± 3.67 g/dL which was significantly ($p < 0.05$) lower than diabetic group but marginally higher than control group. The ethanol extract treated group which was 188.6+9.18 g/dL was significantly ($p < 0.05$) reduced compared with control, diabetic and diabetic methanol treated groups. The aspirin treated group with 234.8 ± 9.17 g/dL and insulin treated group with 247.2 ± 8.79 g/dL were significantly ($p < 0.05$) lower than diabetic but higher than diabetic ethanol groups and no significant changes compared to control group and methanol treated group.

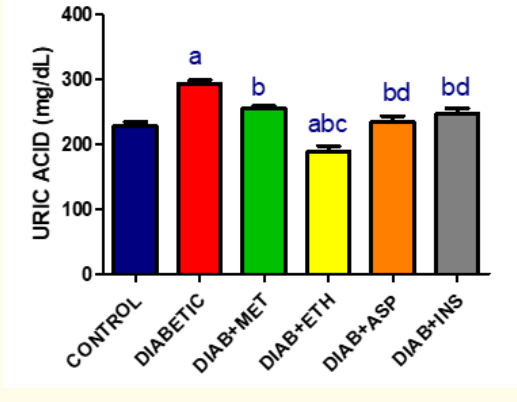

Figure 6: Serum Uric acid level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$. a = test compared with control, b = test compared with diabetic group, c = test compared with diabetic+methanol extract group, d = test compared with diabetes+ethanol extract group.

Blood level of glucose

Table 1 represent the results of fasting blood glucose (FBG) levels. In day 1 blood glucose were obtained for all the groups and there were only marginal changes across the groups. The day 4 fasting blood glucose was significantly ($p < 0.05$) increased in all the diabetic group compared with the control group value and the value of day one of the same group. Moreover, day 7 fasting blood glucose levels showed significant increases in the different groups compared with control but there were some reductions in some groups when compared with day 4 blood glucose within group. The changes also showed some significant differences ($p < 0.05$) across the groups. On day 14, the glucose levels observed were still higher than control group value, but significantly ($p < 0.05$) lower than day 4 and 7 glucose within the groups. There were also some significant ($p < 0.05$) changes across the groups. On day 21, the glucose levels were still significantly ($p < 0.05$) higher than control group although reductions were observed to be significant ($p < 0.05$) compared with diabetic group.

Days	Control	Diabetic	Diabetic+ Methanol	Diabetic+ ethanol	Diabetic+ Aspirin	Diabetic+ insulin
Day 1	77.4 ± 5.49	82.6 ± 2.58a	83.4 ± 2.34	90.2 ± 2.60	83.8 ± 3.09	91.6 ± 4.93
Day 4	83.40 ± 1.44	359.4 ± 23.47*a	248.6 ± 16.35*	300.0 ± 16.40*	378.2 ± 17.86*	380.8 ± 21.90*a
Day 7	73.60 ± 4.47	234.4 ± 12.22*a	219.4 ± 26.81*	134.0 ± 12.62*	194.0 ± 19.21*	108.0 ± 2.35*a
Day 14	77.0 ± 0.45	205.4 ± 7.59*a	224.8 ± 20.12*	115.2 ± 7.10*	154.0 ± 18.93*	81.20 ± 7.95
Day 21	86.80 ± 2.87	317.0 ± 11.84*a	182.0 ± 5.0*#	155.6 ± 9.16*	260.0 ± 8.50*	165.6 ± 15.51*a

Table 1: Fasting Blood Glucose Level (mg/dL).

*$p < 0.05$.

Fasting Blood glucose level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$. a = test compared with control, * = test compared with day 1, # = test compared with day 4.

Serum total protein level

The results of serum total protein level (figure 7) show marginal increase with mean value of 67.00+5.48 mg/dL in diabetic group compared with 64.20+5.72 mg/dL in control group. The methanol extract group total protein was 61.00+1.64 mg/dL and ethanol extract mean value was 60.20+2.89 mg/dL. The diabetic aspirin treated group has 64.40+2.84 mg/dL which was same with control value but slightly lower than the diabetic group value and insulin treated group value was 67.80+2.35 mg/dL slightly above control value but same with diabetic group value.

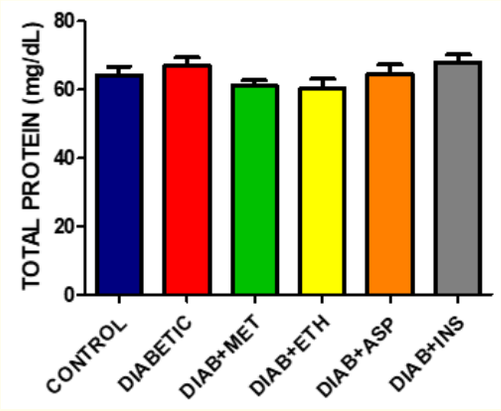

Figure 7: Serum Total protein level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$.

Serum albumin level

Serum albumin levels were assessed and the results are represented in figure 8. In the control group the mean value for serum albumin was 40.80+2.06 mg/dL. this value was elevated to 42.00+2.05 mg/dL in diabetic group but this elevation was not significant. Treatment with methanol and ethanol extracts caused decrease to 39.40+1.44 mg/dL and 38.40+1.89 mg/dL respectively compared to control and diabetic groups. However, there was no significant change in the albumin levels of aspirin treated group with 42.20+1.53 mg/dL and insulin treated group with 42.00+1.52 mg/dL.

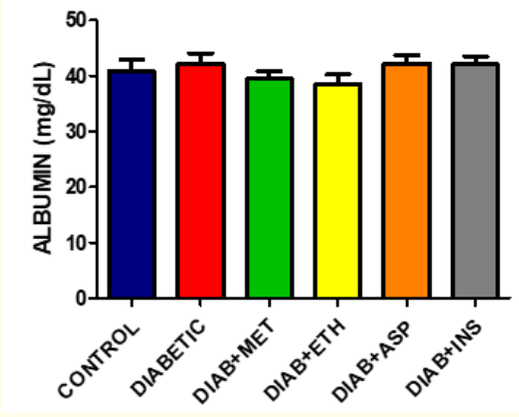

Figure 8: Serum Albumin level in diabetic and test groups compared with control. Values are mean ± SEM and $p < 0.05$.

Discussion

Serum electrolytes and some other parameters are useful tools in assessing renal functions in the body. The study was designed to investigate the biomarkers of renal functions in rats with diabetes mellitus induced by streptozotocin and treated with different *Terminalia catappa* leaf extracts. Sodium ion (Na^+) levels were observed to significantly reduce in all the groups except in diabetic group treated with ethanol extract of *Terminalia catappa*. The observed reduction of sodium ion in diabetic group is consistent with the study of [5]. The reduction in sodium ion in diabetic group indicates development of hyponatremia attributed to urinary loss of Na^+ due to hyperglycemia induced osmotic diuresis [9]. The observed state of hyponatremia was not corrected in the methanol and ethanol extracts treated groups. This implies that these extracts do not possess the ability to remedy the state of hyponatremia experienced in diabetes mellitus. Various diabetic complications consequent upon hyponatremia such as bone disorders; osteoporosis and fracture or cognitive impairments [19] may not be ameliorated by the methanol and ethanol extracts of *Terminalia catappa* leaves. Serum osmolality is normally increased by the presence of hyperglycemia [20] and this causes efflux of intracellular fluid to the extracellular compartment rendering cells dehydrated and reduced sodium concentration by ECF dilution causing dilutional hyponatremia [21]. A similar trend was observed in potassium ion level. The low potassium ion in diabetic group is in line with the work of other researchers [1]. The hyperglycemia induced hypokalemia was again not corrected by neither methanol nor ethanol extract of *Terminalia catappa* leaves. But the group administered with insulin caused the potassium level to rise to same level with control group. However, the increase observed in aspirin treated group was still significantly lower than the control group value but higher than diabetic group. From this results, insulin and aspirin showed capability of reversing hypokalemia in diabetes mellitus. Hypokalemia has been reported to be high in diabetic population [22]. A condition attributed to probable redistribution of potassium ion from extracellular compartment to intracellular compartment, malabsorption of potassium in the gastrointestinal tract or loss of potassium by osmotic diuresis [23].

Another important electrolyte measured was bicarbonate. The changes in bicarbonate levels across the groups were not significant. The diabetic group bicarbonate level was raised marginally contrary to other reports of low serum bicarbonate in diabetes patients [24,25]. The slight elevation of bicarbonate level observed in diabetic group was reduced to a level equivalent to the control group value by both methanol and ethanol extract treatments. The changes in bicarbonate level in extracts treated groups were similar to the values obtained following insulin and aspirin treatments. Serum bicarbonate is a useful marker of metabolic acidosis.

Besides the electrolytes, other renal biomarkers evaluated were creatinine, urea and uric acid. These biomarkers are of diagnostic relevance for assessment of kidney functioning. In this study, the serum creatinine level was elevated in diabetic group. This finding corroborated the report of Ullah and colleagues [26] on human diabetic patients. Creatinine is a by-product of creatine associated with muscular activity [27] and is normally excreted by the kidney. Therefore, elevation of creatinine signifies abnormal kidney functioning which may be attributed to hyprglycemia [28]. Such abnormalities may include hyperfiltration, micro and macrovascular alterations and high GFR with attendant increase in serum levels of creatinine and urea [19,29]. In methanol treated group, creatinine level reduced indicating the efficacy of the methanol extract in mitigating hyperglycemia-induced renal injury represented by high serum creatinine level. The reduction was comparatively similar to group which received insulin administration but the ethanol group showed no reduction while aspirin treated group creatinine was significantly raised above the control group and other test groups. This may support the assertion that nonsteroidal anti-inflammatory drugs are contraindicated in respect to serum creatinine level in diabetes [30]. The observed increase by aspirin treated group suggest mechanism of renal microvascular injury outside the supposed inflammatory mechanism as the anti-inflammatory drug did not ameliorate the renal disorder characterised by increase creatinine level. Therefore, the decrease of creatinine level in methanol extract group may involve utilization of a different pathway in exerting its effect on the creatinine level other than anti-inflammatory pathway. This may suggest presence of some phytochemicals in the methanol extract which may be absent in ethanol extract and may be responsible for this effect on creatinine. Further studies comparing the phytochemicals of these two extracts is necessary to elucidate the possible differences in their activities on creatinine levels. Furthermore, assessment of serum urea levels showed increase in the diabetic group and this corroborate the report by [26,31] and was considered as indication

of pre-renal damage. Amino acid oxidative deamination produces ammonia and is transported to liver for urea production [32]. The kidney is responsible for cleaning the blood from urea. Therefore, elevated level of urea is indicative of kidney dysfunction [33]. The urea level was reduced to a level similar to control group in the extracts and insulin treated groups but remains elevated in aspirin group. The reduction by the extracts suggest ability to reduce amino acid breakdown in diabetes mellitus. This may be a follow up to the antidiabetic action of *Terminalia catappa* associated with glycemia reduction [17]. A similar trend was observed in uric acid level which was raised significantly in diabetic group but was reduced by the two extracts, aspirin and insulin. The report of [34] supported the findings of high uric acid level in diabetic mellitus. Uric acid level is influenced by a lot of factors such as uric acid production, uric acid excretion and renal injury [35]. Studies in uric acids focus on key enzymes such as xanthine oxidase and adenosine deaminase as well as uric acid transporter in the kidney [36,37]. Hyperuricemia can aggravate impact of diabetes [35] therefore, reduction in serum uric acid is relevant pointer to reduced level of purines breakdown and amelioration of renal injury [38]. In this study, uric acid reduction was higher in the ethanol group compared to all other groups suggesting improvement in the ability of the kidney to increase excretion of uric acid. Further investigation relating this observation on the efficacy of ethanol extracts of *Terminalia catappa* is required.

Although the glucose level reduced by the day, the level of reduction was not much and does not conferred on these extracts the evidence of strong antidiabetic agent. This level of antidiabetic potency in methanol and ethanol extracts is not as much as observed in previous finding on aqueous extract [17]. Therefore, the observed changes in various renal parameters may be associated with pathways other than reduced glycemic status.

Inflammation and oxidative stress damage are known mechanisms involved in diabetes complications [39]. Reversal of the changes in renal biomarkers may be attributed to anti-inflammatory and anti-oxidative stress function as previously reported in aqueous extract of *Terminalia catappa* [40,41]. Renal complications definitely involve microvascular abnormalities in the kidney.

Conclusion

Therefore, the changes might be a correctional function of vascular derangement in the glomerulus allowing proper filtrations and clearance of the metabolites, reduced breakdown of protein, purines and muscles. Therefore, the methanol and ethanol extracts of *Terminalia catappa* may reduce hyperglycemia induced renal dysfunction and abnormal protein and purine metabolism as reflected respectively by creatinine, urea and uric acid regulation but do not change the sodium and potassium derangement in diabetes mellitus in rat model.

Conflict of Interest

There was no conflict of interest.

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