Journal of Stress Physiology & Biochemistry, Vol. 19, No. 3, 2023, pp. 178-186 ISSN 1997-0838

ORIGINAL ARTICLE

OPEN ACCESS

Influence of Aqueous Extracts of *Nauclea latifolia* on Serum Biomarker Enzymes of Liver Injury and Serum Electrolytes in Streptozotocin-induced Diabetic Wistar Albino Rats.

Dickson Owoicho Ochalefu [1], Godwin Ichekanu Adoga [2], Carrol Domkat Luka [2], Adakole Hyacinth Abu [3], Blessing Kenechi Myke-Mbata [4] and Iorhemba Cyprian Mfaga [1]

[1] *Department of Medical Biochemistry, College of Health Sciences, Benue State University, Makurdi, Nigeria*

[2] *Department of Biochemistry, College of Health Sciences, University of Jos, Jos, Nigeria*

[3] *Department of Veterinary Physiology, Pharmacology and Biochemistry, College of Veterinary Medicine, Federal University of Agriculture, Makurdi, Nigeria.*

[4] *Department of Chemical Pathology, College of Health Sciences, Benue State University, Makurdi, Nigeria.*

*E-Mail: **dickochalefu@gmail.com**

Received April 9, 2023

Background. The management of diabetes mellitus and its complications is increasingly becoming difficult as new type and subtypes are being discovered. There is, therefore, a continuous search for more effective drug agents for its management. In this work the aqueous extracts of leaves, stem-bark and root-bark of *Nauclea latifolia* were investigated for their effects on serum liver enzymes and serum electrolytes in streptozotocin- induced diabetic Wistar albino rats. Serum levels of aspartate aminotransferase and alanine aminotransferase were determined using assay kits (Randox laboratories, LTD, UK). Alkaline phosphatase level was estimated using kits from Teco Diagnostic Anaheim, United States of America. The electrolytes were analysed using Ion Selective Electrode (ISE) Automated Analyser Machine (SFRI, 3000 model).

Results. The results showed significant reduction ($p < 0.05$) in the levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase by the *Nauclea latifolia* extracts. The diabetic rats treated with aqueous extracts of *Nauclea latifolia* had their sodium and potassium levels reduced non- significantly when compared with the diabetic control rats.

Conclusion. This plant demonstrates a potential for being used in clinical medicine for the management of abnormally high levels of serum liver enzymes in diabetic patients.

Key words: Nauclea latifolia. Extracts. Liver enzymes. Electrolytes

Diabetes mellitus is a common metabolic disorder of the endocrine system which affects adversely glucose, lipid and protein homeostasis (Effiong *et al.,* 2013). It results from insufficiency or lack of insulin secretion by the pancreatic β – cells of the islets of Langerhans or reduction of sensitivity of tissue cells to insulin (Effiong *et al.,* 2013; Nirmala *et al.,* 2009). It is a life-long disease that influences the general well- being of the individual leading to regular close monitoring and control (Okoronkwo *et al.,* 2015). This disease has been intensively researched into in recent times with type 1.5 and type 2 subtypes 1 - 5 being proposed to be added to its classification (Ahlqvist *et al.,* 2018; Appel and Wadas 2018).

The growing epidemics of diabetes mellitus and its complications globally has become a major concern (IDF, 2019). This ailment has resulted in many premature deaths including that of several leaders who have distinguished themselves and scholars of high reputation (Oputa and Chinenye 2015). It has also resulted in complications like foot infections and ulcers which often precede amputation of the lower extremity, kidney, liver and heart diseases (Lipsky *et al.,* 2012). In addition, diabetes mellitus poses disastrous financial costs particularly in Africa where most of the expenditures are paid by the patients and family (Smith-Spangler *et al.,* 2012). For example, in 2017 the International Diabetes Federation (IDF) estimated the total health expenditure because of diabetes mellitus to be $ 3.3 billion globally (IDF, 2019). In Nigeria, $1.071 billion to $1.639 billion per year was estimated to be national annual direct costs of diabetes mellitus whereas in Cameroon the monthly direct medical cost per individual was estimated to be $148. In Sudan, the direct cost of type 2 diabetes mellitus control was $175 per year. This included the cost of medications and ambulatory care only (IDF, 2019).

Diabetes mellitus poses dangerous threat to humanity in terms of its impact on health, social and economic well- being. However, insulin and other conventional orthodox drugs like the biguanides and sulfonylureas currently being used in the management of this disease have serious side effects like hypoglycaemic coma, haematological and gastrointestinal reactions and disturbances of kidney, liver and heart functions. The search for more effective and safer therapeutic agents for the management of diabetes mellitus and its complications has continued to be a significant area of research (Akomas *et al.,* 2014; Ayinla *et al.,* 2014). In this study we investigated the influence of *Nauclea latifolia* aqueous extracts of leaves, stem- bark and root-bark on serum biomarker enzymes of liver injury and serum electrolytes in streptozotocin-induced diabetic Wistar albino rats.

Damage to liver cells by diabetes mellitus leads to release into the plasma from the cytosol the liver function marker enzymes: alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase (Mankhatithan *et al.,* 2011). The analyses of the activities of these enzymes in the plasma are utilized to indirectly assess the function of the liver. An increase in the plasma concentration of these enzymes above the homeostatic limits implies a disorder to the liver tissue (Friday *et al.,* 2010).

Poorly controlled diabetes mellitus has been implicated as a cause of serum electrolytes imbalance. For instance, it has been found to cause abnormally high concentration of sodium in some cases (Sarguru *et al.,* 2016; Yang *et al.,* 2010). This disease also causes increased serum potassium levels (George *et al.,* 2014).

Nauclea latifolia is an evergreen multi-stemmed shrub found widely spread in the humid tropical rainforest zone or in savannah woodlands of West and Central Africa (Okwori *et al.,*, 2008). This plant called Oya among the Idoma natives of North Central Nigeria is widely used by traditional healers in Idoma land for the management of type 2 diabetes mellitus.

MATERIALS AND METHODS

Drug used for induction of diabetes mellitus

Streptozotocin (Sigma-Aldrich, Germany) was the drug used for the induction of diabetes mellitus in the experimental Wistar albino rats. Streptozotocin was freshly prepared and given intra- peritoneally in a dose of 60mg / kg. body weight in 0.01 M citrate buffer (pH 4.5).

The Reference Drug

Glibenclamide (Sanofi- Aventis, Nigeria Limited) was the reference drug used for the management of the streptozotocin-induced diabetes mellitus in the experimental rats. The drug was given orally at the dose of 5mg/ kg. body weight.

Preparation of the plant extracts

The stem-bark, leaves and root-bark of *Nauclea latifolia* plant used for the study were harvested from the environs of the Federal University of Agriculture, Makurdi, Benue State, Nigeria; identified and authenticated at the Federal School of Forestry, Jos, Plateau State, Nigeria where voucher specimen was deposited with voucher number: FHJ 279.

The stem-bark, leaves and root-bark were air- dried at room temperature for at least 4 weeks, pulverized to fine powder using mortar and pestle and sieved with a porcelain sieve. One hundred grammes (100g) of the stem-bark, leaves and root-bark powder were separately weighed using an electronic weighing balance (Mettler Toledo). The stem-bark, leaves and root-bark powder were separately soaked in 1000 ml of distilled water at a ratio of 1:10 (powder/ solvent) (Das *et al.,* 2010). These were stirred intermittently for 48 hours at room temperature. The soaked powder was filtered using muscillin cloth after which sterile cotton wool and Whatman filter paper No. 1 size 110mm were used to obtain pure filtrates. The filtrates were then concentrated on a water bath at 45^{o}C and dried to constant weights. The percentage yields of the extracts were calculated using the expression:

$$\%\ yield = \frac{Weight\ of\ extract\ (g)}{Weight\ of\ dry\ sample\ (g)}\ X\ 100$$

Induction of Diabetes Mellitus

Diabetes mellitus was induced in overnight fasted rats by single intra-peritoneal injection of freshly prepared streptozotocin (Sigma-Aldrich, Germany) 60mg/kg body weight in 0.1M citrate buffer (pH 4.5) (Adoga and Ibrahim 1990; Ghoraishian, 2006; Rao and Naidu 2010). Diabetes was confirmed in the streptozotocin treated rats by measuring fasting blood glucose concentration using Glucometer (Accu-Chek, Mannheim, Germany) 48 hours after streptozotocin injection. Rats with fasting blood glucose of more than 200mg/dl were considered diabetic and included in the study.

Research Design

Animal studies

Thirty male albino rats of Wistar strain weighing 153.5 – 177.0 g used for the study were obtained from the Animal House, College of Health Sciences, Benue State University, Makurdi, Nigeria. They were kept in polypropylene cages under room temperature, with 12-hour light and 12-hour dark cycle. They were allowed to acclimatize for two weeks before the commencement of the experiment. The rats were divided into six groups of five rats each. Group A was normal control and group B was streptozotocin-induced diabetic control. The controls were administered 1 ml distilled water orally. Groups C, D and E were streptozotocin-induced diabetic rats treated with 500mg/ Kg. body weight of stem-bark, leaves and root-bark extracts of *Nauclea latifolia* respectively for 28 days and group F was streptozotocin-induced diabetic rats given 5mg/kg. body weight of the standard anti-diabetic drug, glibenclamide, daily for the same duration (Effiong *et al.,* 2013). The extracts and glibenclamide were administered orally through intra-pharyngeal feeding canula. The rats were fed ad libitum with pellet diet (Grand Cereals Ltd, Jos, Nigeria) and clean tap water. Good hygiene was maintained by constant cleaning and removal of faeces and spills from cages daily. The experiment was conducted between the hours of 9.00A.M and 11.00 A.M. The protocols for these experiments were in accordance with the ethical guidelines on the care and use of laboratory animals (NIH, 1985).

Blood Collection

Twenty – four hours after treatment with the last dose of the extracts, glibenclamide and the placebo on the test groups and the control respectively, the albino rats were sacrificed by inhalation of overdose of Diethyl ether vapour. Whole blood was collected through retro-orbital sinus. A capillary tube was inserted into the medial canthus of the eye, about 30 degrees angle of the nose. A slight thumb pressure was applied to puncture the tissue and to enter the sinus (plexus). The puncturing of the sinus resulted in blood coming out

through the capillary tube. After the collection of 5 mls of blood, the capillary tube was gently removed and wiped with sterile cotton wool.

The blood was put in clean plain specimen bottles and allowed to stand for 2 hours, then spun with centrifuge (Lemfield Medical England, Model 80 – 2) at 3000 rpm for 5 minutes. There after serum was harvested from each blood sample with clean Pasteur pipettes and put into clean Bijou bottles until use.

Biochemical Analyses

Biochemical assays of serum aspartate aminotransferase and alanine aminotransferase (Reitman and Frankel, 1957) were carried out according to procedures outlined in the manuals by reagent kits manufacturer (Randox Laboratories Antrim, United Kingdom). Serum alkaline phosphatase was determined using kits from Teco Diagnostic Anaheim, United States of America.

The electrolytes, sodium, potassium and chloride, were analysed using Ion Selective Electrode (ISE) Automated Analyser Machine (SFRI, 3000 model).

Statistical Analysis

Statistical analysis was done using the statistical package for social sciences (SPSS version 24) software package programme. The results were expressed as Mean ± SEM (standard error of mean), where n = 5, analysed by one- way Analysis of Variance (ANOVA) and the level of significance determined by least significant difference (LSD). The p values of 0.05 and less were taken to imply statistical significance between the means.

RESULTS

Effects of Aqueous Extracts of *Nauclea latifolia* Stem – bark, Leaves and Root – bark on Serum Liver Enzymes Levels of Diabetic Wistar Albino Rats.

The results of aqueous extracts of *Nauclea latifolia* on serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels are shown on Table 1. Serum AST, ALT and ALP were raised significantly ($p < 0.05$) in the diabetic control rats relative to non-diabetic control rats. Treatment of the diabetic rats with aqueous extracts (stem – bark, leaves and root – bark) and glibenclamide for 28 days resulted in significant reduction ($p < 0.05$) in AST and ALT. The administration of the stem – bark and root – bark extracts to the diabetic rats significantly lowered ($p < 0.05$) alkaline phosphatase level in them compared with that of the diabetic control. Glibenclamide and the leaves extract caused non- significant reduction ($p > 0.05$) in the alkaline phosphatase (Table 1).

Effects of aqueous extracts of *Nauclea latifolia* stem – bark, leaves and root-bark on serum electrolytes

There was non-significant ($p > 0.05$) increase in the sodium and potassium levels in the diabetic control rats when compared with the normal control. The diabetic rats treated with the aqueous extracts of *Nauclea latifolia* had their sodium and potassium levels reduced non- significantly ($p > 0.05$) when compared with the diabetic control rats. There was no significant difference in the chloride levels of the normal control, diabetic control and the diabetic rats treated with the plant extracts. (Table2).

Table 1 Effects of aqueous extracts of *Nauclea latifolia* stem – bark, leaves and root – bark on serum biomaker enzymes of liver injury in streptozotocin – induced diabetic Wistar albino rats.

Group	Treatment	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
A	Normal Control	51.60 ± 4.62	25.80 ± 6.26	17.32 ± 1.32
B	Diabetic Control	75.80 ± 6.87**	42.60 ± 5.77**	20.98 ± 4.79**
C	Stem –bark extract	43.20 ± 6.67*	17.60 ± 2.07*	16.30 ± 1.91*
D	Leaves extract	48.00 ± 12.44*	20.60 ± 2.70*	20. 46 ± 1.54
E	Root – bark extract	49.80 ± 5.89*	19.40 ± 2.79*	16.16 ± 2.08*
F	Glibenclamide	45.00 ± 14.11*	18.60 ± 1.67*	19.99 ± 1.10

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ALP = Alkaline phosphatase. Values are Mean ± SEM of 5 determinants.
*= Statistically significant when compared with diabetic control at ($p < 0.05$)
** = Statistically significant when compared with normal control at ($p < 0.05$)

Table 2 Effects of aqueous extracts of *Nauclea latifolia* stem- bark, leaves and root-bark on serum electrolytes in streptozotocin-induced diabetic Wistar albino rats

Group	Treatment	Sodium (Na+) (Mmol / L)	Potassium (K+) (Mmol/L)	Chloride (Cl-) (Mmol/L)
A	Normal control	142.57± 12.87	7.64± 0.80	105.32±7.50
B	Diabetic control	144.12± 8.21	8.04± 1.20	104.68± 2.07
C	Stem- bark extract	143.20± 3.25	7.81± 0.31	103.90± 1.30
D	Leaves extract	142.93± 2.56	7.55± 1.20	104.12± 8.01
E	Root-bark extract	143.35± 5.74	6.92± 0.42	104.49± 6.26
F	Glibenclamide drug	143.00± 10.19	7.68± 1.28	103.76± 4.39

Values are Mean± SEM of 5 determinations.

DISCUSSION

Our study shows increased serum levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in the streptozotocin- induced diabetic Wistar albino rats when compared to the normal group. These are highly sensitive biochemical tools for the assessment of hepatocellular injury (Item *et al.,* 2007). These findings agree with research work carried out by Sunitha et al (2015) in which they found significant rise in aspartate aminotransferase and alanine aminotransferase levels in diabetes mellitus. Furthermore, Mohammed et al (2019) in their study on the activities of liver marker enzymes in diabetic rats had similar results of significant increase in aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase when compared with the normal control rats.

The increased levels of these enzymes are due to hepatic cell damage (Howida and Abon 2016). Many critical pathways have been identified to cause hepatic cell damage in diabetes mellitus. The decline in target tissue sensitivity to insulin (insulin resistance), the major cause of hyperglycaemia and compensatory hyperinsulinaemia, is the common causative factor (Jamaludin *et al.,* 2016; Palsamy *et al.,* 2010). This results in the disorder of protein, carbohydrate and lipid metabolism, thereby, causing a rise in oxidative stress which triggers inflammatory cascade. Both oxidative stress and inflammatory response cause hepatic cell damage leading to the abnormal levels of these enzymes in circulation in diabetes mellitus (Palsamy *et al.,* 2008; Ebong *et al.,* 2008). Research has revealed that even subtle membrane changes are enough to permit the passage of intracellular enzymes to the extracellular space. A huge concentration gradient between the liver cells and sinusoidal space normally exists for enzymes. Damage to the cell increases permeability resulting in cytosolic enzymes spillage into the sinusoids from where they find their way into the peripheral blood (Muhammed *et al.,* 2009).

In some instances, diabetes mellitus results in excessive accumulation of fat cells in the liver causing fatty liver. Fat cells accumulation disrupts liver cell membrane as well as causing dysfunctional mitochondria. Dysfunctional mitochondria release excessive amount of oxidants which in turn injure hepatic cells (Howida and Abon, 2016). Furthermore, there is also a resultant lipid perioxidation that leads to generation of free radicals such as peroxyl, alkoxyl and aldehyde that cause cell damage resulting in the release of the biomarker enzymes. The disruption of the well arranged lipid bilayer of the cell membrane structure may be due to the presence of reactive oxygen species that were produced by oxidative stress. This results in the escape of detectable quantity of these enzymes out of the cell into the extracellular fluid. The reactive oxygen might have oxidized the polyunsaturated fatty acids which constitute the lipid bilayer causing its disruption (Howida, 2016; Choudhary and Devi, 2014)

The treatment of the streptozotocin-induced diabetic rats with the aqueous extracts of *Nauclea latifolia* and glibenclamide brought about significant reduction in levels of the marker enzymes when compared with the diabetic control rats. These results are in consonance

with earlier reports by Effiong and Akpan (2015) and Ebong *et al.,* (2008) who administered some plant extracts to diabetic rats. The significant reduction in the levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in the rats treated with the aqueous extracts of the plant might be that the antioxidants such as flavonoids and tannins contained in the extracts (Ochalefu *et al.,* 2018; Rajamanikandan *et al.,* 2011) scavenge free radicals that cause liver cell damage resulting in the increased serum levels of these biomarker enzymes in circulation (Effiong and Akpan 2015; Hassan *et al.,* 2019). The antioxidants donate hydrogen to reactive oxygen and nitrogen species thereby terminating their destructive activity and removing them (Lopez-Cobo *et al.,* 2015). Furthermore, medicinal plant extracts with these antioxidants have been known to boost biomembrane stability by decreasing lysosomal enzyme activity thereby maintaining cell membrane fluidity and ion gradients (Sandhya *et al.,* 2010).

Electrolytes play a very vital role in the control of acid - base balance, blood clotting, body fluid distribution and contraction of muscle. The concentration of the electrolytes is often used to assess a patient's clinical condition. It is associated with morbidity and mortality. The major electrolytes in the body are sodium, potassium and chloride. These are regarded as the major determinants of electrophysiological activities of myocardial membrane (Kughapriya and Evangeline, 2016; Onyiriuka and Oyenusi 2018).

Diabetic patients often present with electrolyte imbalance. This disorder results from insulin deficiency, hyperglycaemia and hyperketonaemia. Hyperglycaemia predisposes the internal environment to osmotic diuresis while causing a dilutional effect on electrolyte concentrations (Khanduker *et al.,* 2017). The non-statistically significant difference among serum sodium, potassium and chloride ions in the diabetic control rats when compared with the normal control observed in this study is in consonance with earlier finding by Akpanabiatu *et al.* (2005). However, Rashid *et al*. (2019) reported significant decrease in serum sodium and chloride ions and a significant increase in potassium ion levels in diabetes mellitus whereas Adewole and Ige (2016) found that both sodium and chloride ions were significantly increased in diabetic control rats when compared with the normal control. In this study the aqueous extracts of *Nauclea latifolia* reduced non-significantly ($p > 0.05$) the serum levels of sodium and potassium ions in the diabetic treated rats compared to the diabetic control rats.

Sodium is the major positive extracellular ion. This ion controls the total amount of water in the body. The transmission of sodium into and out of individual cell plays a very critical role in body function (Ezekwesili and Nwodo 2013). It is associated with blood pressure and in many hypertensive patients a decreased in sodium intake lowers blood pressure (Akpanabiatu *et al.,* 2005). The excretion of sodium and chloride ions from the body is a function of arterial blood pressure. Sodium ion depletion provokes renin release which subsequently leads to the production of angiotensin II, a potent vasoconstrictor (Eteng *et al.,* 2006). Increased blood sodium level inhibits renin release from the justaglomerular cells with subsequent withdrawal of angiotensin II. It is, therefore, important to strike a balance in the levels of blood sodium and chloride ions to avoid extremes of hypotension or hypertension (Eteng *et al.,* 2006).

Potassium is a major cation inside the cell fluid with only about 10% of the total potassium in the body found extracellularly. Low potassium in the body may cause hypotonia and muscular weakness. On the other hand abnormally high potassium level in the body leads to cardiac arrest and even sudden death (An *et al.,* 2012; Enemor and Okaka 2013). Potassium ion has been reported to be one of the protective electrolytes against hypertension (Akpanabiatu *et al.,* 2005).

CONCLUSION

A significant reduction in abnormally high serum liver enzymes levels in diabetes mellitus has been demonstrated by the aqueous extracts of *Nauclea latifolia.* This plant, therefore, has the potential in clinical medicine for ameliorating complications associated with serum liver enzymes in diabetic patients. The aqueous extracts of the plant was found not to have any significant effect on the serum electrolytes in this study.

Availability of data and materials

The datasets generated for this study could be made available by the corresponding author upon reasonable request**.**

DECLARATION:

Ethical approval

The ethical guidelines for the care and use of animals for research were followed.

Conflict of interest

The authors declare lack of conflict of interest

ACKNOWLEDGEMENT

The authors expressed their profound gratitude to Mr. Michael Onoja of the Federal University of Agriculture Veterinary Teaching Hospital, Makurdi, Nigeria and Mr. Peter Akogwu of the Information and Communications Technology, Benue State University, Makurdi, Nigeria for their technical assistances. The financial support for this work was given by the Presidential Needs Assessment Fund, through the Benue State University, Makurdi

REFERENCES

Adewole E O, Ige A O (2016) lipid profile and electrolyte composition in diabetic rats treated with leaf extract of *Musa sapientum. J Diet* Supp 13(1): 106- 117. Doi : 10.3109/19390211. 2014.965866

Adoga G I, Ibrahim M B (1990) Effect of garlic oil on some biochemical parameters in streptozotocin-induced diabetic rats. *Medical Science Research* 18: 859-860.

Ahlqvist E, Storm P, Karajamaki A, Martinell M (2018) Novel subgroups of adult onset diabetes and their association with outcomes: a data driven cluster analysis of six variables. *The Lancet Diabetes and Endocrinology* 6(5): 361-369.

Akomas S C, Okafor A I, Nnah I S (2014) Glucose level, haematological parameters and lipid profile in *Ficus sur* treated diabetic rats. Comprehensive *Journal of Agriculture and Biological Sciences* 2(1): 5-11.

Akpanabiatu M I, Umoh I B, Udosen E O, Udoh A E, Edet E E (2005) Rat serum electrolytes, lipid profile and cardiovascular activity of *Nauclea latifolia* leaf extract administration. *Indian Journal of Clinical Biochemistry* 20(2): 29-34

An J N, Lee J P, Jeon H T, Kim H, Oh Y K, Kim Y S, Lim C S (2012) Severe hyperkalaemia requiring hospitalization: predictors of mortality. *Crit Care* 16: R225

Appel S J, Wadas T M (2018) Characterization of type 2 diabetes into five subtypes. *Current Research in Diabetes and Obesity Journal* 8, 1.

Ayinla M T, Owoyele B V, Yakubu M T (2014) Antidiabetic activity of aqueous extract of *Senna fistula* leaves in streptozotocin- induced diabetic rats. *Nigerian Journal of Biochemistry and Molecular Biology* 29 (2): 93-106

Choudhary A K, Devi R S (2014) Serum biochemical responses under oxidative stress of aspartame in Wistar albino rats. *Asian Pac. J. Trop. Dis.* 4 (1): 403- 410

Das K, Tiwari R K S, Shrivastava D K (2010) Techniques for evaluation of medicinal plants products as antimicrobial agent: current methods and future trends. *Journal of Medicinal Plants Research* 4(2): 104-111

Ebong P E, Atangwho I J, Eyong E U, Egbung G E (2008) The anti-diabetic efficiency of combined extracts from two continental plants; *Azadirachta indica* (A. Juss) (Neem) and *vernonia amygdalina* (Dei) (African bitter leaf). *American Journal of Biochemistry/ Biotechnology* 4(3): 239-244

Effiong G S, Akpan H D (2015) The effect of *Nauclea latifolia* leaf extract on some biochemical parameters in streptozotocin-induced diabetic rats models. *Journal of Medicine and Medicinal Sciences* 6(3): 47-52

Effiong E E, Igile G O, Mgbeje B I A, Out E A, Ebong P E (2013) Hepatoprotective and antidiabetic effects of combined extracts of *Moringa oleifera* and *Vernonia amygdalina* in streptozotocin-induced diabetic Wistar albino rats. *Journal of Diabetes and*

Endocrinology 4(4): 45-50.Doi 10. 5897/JDE 2013.0069

Enemor V H A, Okaka A N C (2013) Subacute effects of ethanol extract of *Sarcocepalus latifolius* root on some physiologically important electrolytes in serum of normal Wistar albino rats. *Pakistan Journal of Biological Sciences* 16(23): 1811-1814

Eteng M U, Ibekwe H A, Amatey T E, Bassey B J Uboh F U, Owu D U (2006) Effect of vitamin C on serum lipids and electrolytes profile of Wistar albino rats. *Nigerian Journal of Physiological sciences* 21(1- 2): 15-19

Ezekwesili C N, Nwodo OF C (2013) Evaluation of the pharmacological activity of ethanol leaf extract of Acalypha torta (Muell). *The Bioscientist* 1(1): 67-72

Friday E U, Iniobong E O, Moses B E (2010) Effect of aqueous extract of *Psidium guaiava* leaves on liver enzymes, histological integrity and haematological indices in rats. *Gastroenterology Research* (3): 32-38

George L, Evangelos L, Fotios B, Moses E (2014) Diabetes mellitus and electrolyte disorders. *World J Clin Cases* 2(10): 488-496. Dio: 10.12998 / wjcc V2. I10.488

Ghoraishian S M (2006) Effect of Hazel leaf decoction on blood glucose reduction in the diabetic rats. *World Journal of Medical Science* 1(2): 144-146

Hassan B Y, Yazdi V H H, Abdolhossein S, Sara H , Gholamihassan V, Mousa-Al-Reza H (2019) Liver dysfunction and oxidative stress in streptozotocin-induced diabetic rats: protective role of Artessimia. *Journal of Pharmacopuncture* 22(2): 109-114.

Howida S, Abon S (2016) Review article on physiological changes due to hepatotoxicity and the protective role of some medicinal plants. *Beni-Suef University Journal of Basic and Applied Sciences* 5(2): 134-146.

International Diabetes Federation, IDF (2019) Economic impact of diabetes in Africa. Current Diabetes Reports, 19,5.

Item J A, Patrick E, Godwin E E, Mbeh U E, Eyong U E (2007) Effect of *Vernonia amygdalina* del on liver function in alloxan-induced hyperglycaemic rats. *Journal of Pharmacy and Bioresouces* 4(1): 1-7

Jamaludin M, Nazratun N, Zariyantey A H, Budin S B (2016) Mechanism of diabetes – induced liver damage. The role of oxidative stress and inflammation. *Sultan University Medical Journal* 16(2): 132-141.

Lipsky B A, Berendt A R, Cornia P B (2012) Infectious diseases society of American clinical practice guidelines for diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 54(12): 132-173.

Khanduker S, Ahmed R, Khondker F, Aharama A, Afrose N, Chowdhury M A A (2017) electrolyte disturbances in patient with diabetes mellitus. *Bangladesh Journal of Medical Biochemistry* 10 (1): 27-35

Kughapriya P, Evangeline J (2016) Evaluation of serum electrolytes in ischaemic heartdisease patients. *National Journal of Basic Medical Sciences* 6(4): 1-14

Lopez-Codo A, Gomez-Caravaca A M, Svarc-Gajic J, Segura-Carretero A, Fernandez-Gutierrez (2015) Determination of phenolic compounds and antioxidants activity of the Mediterranean plant. The case of *Satureja montana* subspecies *Kitaibelii*. *Journal of Functional Foods* 18: 1167- 1178

Mankhatithan W, Lueaniyomkula A, Manosuthin W (2011) Hepatotoxicity in patients co-infected with tuberculosis and HIV-1 while receiving non-nucleoside reverse transcriptase inhibitors based anti-retroviral therapy and rifampicin containing anti-tuberculosis drugs. *South East Asian Journal of Tropical Medicine. Public Health* 429: 651-658.

Mohammed M S, Mohammed F A, Sivagurunathan M S, Tarique A (2019) Hepatoprotective potential of *Sargassum muticum* against streptozotocin-induced diabetic liver damage in Wistar rats by inhibiting cytokines and the apoptosis pathway. *Analytical Cellular Pathology*. Article ID 7958701.https://doi.org/10.1155/2019/7958701.

Muhammadu Z, Syed N N, Masood A, Zahid A K (2009) Altered liver morphology and enzymes in

streptozotocin-induced diabetic rats. *Int. J. Morphol* 27 (3): 719- 725

National Institute of Health, NIH (1985) Consensus Statement 5(11): 1-23.

Nirmala A, Saroja S, Vasanthi H R, Lalitha G (2009) Hypoglycaemic effect of *Basella rubra* in streptozotocin-induced diabetic albino rats. *Journal of Pharmacognosy and Phytotherapy* 1(2): 25-30.

Ochalefu D O, Adoga G I, Luka C D, Abu H A, Amali OOE, Agada S A, Alonyenu E I (2018) Phytochemical composition and effect of *Nauclea latifolia* aqueous extracts on blood glucose levels of streptozotocin-induced diabetic Wistar albino rats. *Journal of Biomedical Research and Clinical practice* 1 (2): 157-165

Onyiriuka N A, Oyenusi E E (2018) Prevalence of abnormal serum sodium and potassium concentration in paediatric new onset type 1 diabetes with ketoacidosis: from two Nigerian Teaching Hospitals. *Sri Lanka Journal of Diabetes Endocrinology and Metabolism* 8(1): 32-39. Doi: http://doi.org/10.4038/sjdem.v8i1.7349

Okoronkwo L I, Ekpemiro N J, Okwori U. Edna, Okpala U P, Adeyemo O F (2015) Economic burden and catastrophic cost among people living with type 2 diabetes mellitus attending a tertiary health institution in South –east zone, Nigeria. *BioMed Central Research Notes* 8:527. Dio 10. 1186/s13104-015-1489-X

Okwori A E J, Okeke C I, Uzoechina A, Etukudoh N S, Amali M N, Adetunji J A, Olabode A (2008) The anti-diabetic potentials of *Nauclea latifolia. African Journal of Biotechnology* 7(10): 1394-1399.

Oputa R N, Chinenye S (2015) Diabetes in Nigeria- a traditional medicine approach. *African Journal of Diabetes Medicine* 23(10): 7-10.

Palsamy P, Sivakumar S, Subramanian S (2010) *Resveratrol* attenuates hyperglycaemia-mediated oxidative stress, proinflammatory cytokines and protects hepatocytes ultrastructure in streptozotocin-nicotinamide induced experimental diabetic rats. *Chem. Biol Interact* 186: 200-210.

Rajamanikandan S, Sindhu T, Durgapriya D, Sophia D, Ragavendran P, Gopalakrishnan V K (2011) Radical scavenging and antioxidant activity of ethanolic extract of Mollugo nudicaulis by in vitro assays. *Indian journal of Pharmaceutical Education and Research* 45(4): 310-316

Rao P V, Naidu M D (2010) Anti-diabtic effect of *Rhinacanthus nasuthis* leaf extract in streptozotocin- induced diabetic rats. *Libyan Agricultural Research Centre Journal International* 1: 310-312.

Rashid N K, Farhana S, Muhammad H S (2019) Pattern of electrolytes imbalance in type 2 diabetes patients: Experience from a tertiary care hospital. *Pak J Med Sci.* 35 (3): 797- 801. Doi: 10.12669/pjms.35.3.844

Reitman S, Frankel S (1957) A colorimetric method for the determination of SGOT and SGPT. *American Journal of Clinical Pathology* 28: 56-63.

Sandhya S, Vankatramana K, Vinod K (2010) Membrane stabilizing potency of two *Tephrosia* species. Journal of Phytology 2: 42- 46

Sarguru D, Vanaja R, Balaji R (2016) Evaluation of serum electrolytes in type II diabetes mellitus. *Int J Pharm Sci Rev Res* (40): 251- 253

Smith-Spangler C, Bhattacharya J, Goldhaber-Fiebert J (2012) Diabetes, its treatment and catastrophic medical spending in 35 developing countries. *Diabetes Care* 35: 319-326.

Sunitha S , Gandham R, Wilma D S, Rao S (2015) Evaluation of significance of liver enzymes as screening tests for early detection of clinically asymptomatic non alcoholic fatty liver disease in type 2 diabetes mellitus. *Int J Biomed Adv. Res* 6(12): 860-863

Yang L, Frindt G, Palmer L G (2010) Magnessium modulates ROMK channel-mediated potassium secretion. *J. Am Soc Nephrol* 21: 2109- 2116. Doi. 10.1681 / ASN