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RESEARCH PAPER

EFFECT OF SIDA CORYMBOSA LEAF EXTRACT ON SERUM URIC ACID, UREA AND CREATININE LEVELS OF ALLOXAN-INDUCED DIABETIC ALBINO WISTAR RATS.

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ABSTRACT

This study was designed to investigate the effect of *Sida corymbosa* (SC) leaf extract on serum uric acid, urea and creatinine levels in alloxan induced diabetic albino wistar rats. A total of 30 albino wistar rats each weighing 100g were assembled and divided into three groups (A-C) consisting of 10 rats in each group. Group A received SC treatment, B did not receive SC treatment, while group C served as the control group. 400mg/kg of aqueous extract of SC leaf was administered orally to the rats in group A but not in group B, while group C received only water for 7 days. Blood samples were collected into plain containers for estimation of serum uric acid, urea and creatinine. Serum uric acid, urea and creatinine were analyzed using Uricase, Urease-Berthlot and Jaffe Slot Alkaline picrate methods respectively. Results showed a significant increase in the mean serum levels of uric acid, urea and creatinine after SC treatment, when compared to the pre- treatment status. Similarly, there was a significant decrease in the mean weight of the rats after SC administration. Therefore, SC may have potential harmful effect on the kidney.

Keywords: *Sida corymbosa*, Kidney, Urea, Uric Acid, Creatinine.

INTRODUCTION

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been derived from natural sources, many of these isolations were based on the uses of the agents in traditional medicine (Cragg and Newman, 2001). Herbal Medicine is defined as a branch of science in which plant based formulations are used to alleviate diseases. It is also known as botanical medicine or phytomedicine (Cragg and Newman, 2001). Lately phytotherapy has been introduced as a more accurate synonym of herbal or botanical medicine. In the early twentieth century herbal medicine was prime healthcare system as antibiotics or analgesics were not as yet discovered. With the advent of allopathic system of medicine, herbal medicine gradually lost its popularity among people, which is based on the fast therapeutic actions of synthetic drugs (Singh, 2007). Recently there has been a shift in universal trend from synthetic to herbal medicine, and it can be said a "Return to Nature". Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments (Sharma *et al.*, 2008).

The search for eternal health and longevity and for remedies to relieve pain and discomfort drove the early man to explore his immediate natural surroundings and this led to the use of many plants, animal products, minerals etc for medicinal purposes as well as the development of a variety of therapeutic agents (Nair and Chanda, 2007). The importance of medicinal plants and traditional health systems in solving the health care problems of the world is gaining increasing attention. Because of this resurgence of interest, the research on plants of medicinal importance is growing phenomenally at the international level, often to the detriment of natural habitats and mother populations in the countries of origin (Nair and Chanda, 2007). Most of the developing countries have adopted traditional medical practice as an integral part of their culture. Historically, all medicinal preparations are derived from plants, whether in the simple form of raw plant materials or in the refined form of crude extracts, mixtures, etc (Krishnaraju *et al.,* 2005).

Sida is one of ethnomedicinally important genus of plants (Pradhan *et al.,* 2013) which belongs to the family called malvaceae (Ajithabai *et al.,* 2012). *Sida* plants have over 200 species which are used in treatment of diseases such as diarrhea, ulcer, gonorrhea and hepatic diseases (Narasihna *et al.,* 2013). *Sida corymbosa* popularly called broom weed or wire weed has been reported to have potentials of curing liver diseases (Narasihna *et al.,* 2013). It is found growing in most parts of Nigeria as common weeds. In the South Eastern part of Nigeria, it is called 'Udontike', 'Udonwatakaike', 'Udoike' and 'Acharaike' in the Northern Nigeria, it is called 'Miyartsanya' or 'Karkashinkwado' (Lucy *et al*., 2014), while in the South Western part of Nigeria, it is called 'Ose patu, 'Ose putu' or 'Sanrin'. In Sierra Leone, it is known as 'Kissi soso', Kona sum', 'Mende lelu', 'Nanande', 'Susu Legeti', 'Tenne', Kuruike and 'Port loko (Lucy *et al*., 2014). The plant is an erect, basally perennial shrub with hairy stem (Lucy *et al.,* 2014) which measures between 0.5 m to 2 m in height. The flower and seed are yellow and dark in colour. *sida corymbosa* survives in all seasons (rainy and dry seasons) (Agyakwa and Akobundu, 2005). *Sida corymbosa* is one of popular plants in Nigeria used by a lot of local people to treat disease such as diarrhea, dysentery and stomach ulcer (Alebiosu *et al*., 2012). The kidneys and the liver are the major sites for elimination of waste products of metabolism. These include urea (from metabolism of amino acids), creatinine (from muscle creatine), uric acid (from nucleic acid metabolism) and metabolism of various hormones. Free creatinine is a waste product of creatine metabolism, which is present in all body fluids and secretions, and freely filtered by the kidney glomeruli (Newman, 2001).

Urea is synthesized in the body of many organisms as part of the urea cycle, either from the oxidation of amino acids or from ammonia (Sakami and Harrington, 1963). Urea production occurs in the liver and is regulated by N-acetylglutamate. Urea is found dissolved in the blood and is excreted by the kidneys as a component of urine (Sakami and Harrington, 1963). The handling of urea by the kidneys is a vital part of human metabolism. Besides its role as carrier of waste nitrogen, urea also plays a role in the countercurrent exchange system of the nephrons that allows for re-absorption of water and critical ions from the urine. Urea is reabsorbed in the inner medullary collecting ducts of the nephrons (Walter and Boron, 2004), thus raising the osmolarity in the medullary interstitium surrounding the thin ascending limb of the loop of Henle, which in turn causes water to be reabsorbed. By action of the urea transporter, some of this reabsorbed urea will eventually flow back into the thin ascending limb of the tubule, through the collecting ducts, and into the excreted urine. This mechanism, which is controlled by the antidiuretic hormone, allows the body to create hyperosmotic urine that has a higher concentration of dissolved substances than the blood plasma. This mechanism is important to conserve water, to maintain blood pressure, and to maintain a suitable concentration of sodium ions in the blood plasma (Jacki *et al.,* 2007).

Uric acid production and metabolism are complex processes involving various factors that regulate hepatic production, as well as renal and gut excretion of this compound. Uric acid is the end product of an exogenous pool of purines and endogenous purine metabolism. The exogenous pool varies significantly with diet, and animal proteins contribute significantly to this purine pool. The endogenous production of uric acid is mainly from the liver, intestines and other tissues like muscles, kidneys and the vascular endothelium (Chaudhary *et al.,* 2013). Humans cannot oxidize uric acid to the more soluble compound allantoin due to the lack of the enzyme uricase. Normally, most daily uric acid disposal occurs via the kidneys (Jin *et al.,* 2012). The kidneys eliminate approximately two-thirds, while the gastrointestinal tract eliminates one-third of the uric acid load. Almost all uric acid is filtered from glomeruli, while post-glomerular reabsorption and secretion regulate the amount of uric acid excretion. The proximal tubule is the site of uric acid reabsorption and secretion, and approximately 90% is reabsorbed into blood. This is primarily accomplished at the proximal tubular level by transporters that exchange intracellular anions for uric acid. Almost all reabsorption of uric acid occurs at the S1 segment of the proximal tubule. In the S2 segment of the proximal tubule, uric acid is secreted to a greater extent than that which undergoes reabsorption. Post-secretory reabsorption occurs at a more distal site of the proximal tubule, and approximately 10% of the filtered uric acid appears in the urine (Chaudhary *et al*., 2013). Hyperuricemia is a key risk factor for the development of gout, renal dysfunction, hypertension, hyperlipidemia, diabetes and obesity. Hyperuricemia occurs as a result of the increased uric acid production, the impaired renal uric acid excretion, or a combination of the two (Su *et al.,* 2014). It is characterized by high uric acid level in the blood, causing deposition of urate crystals in the joints and kidneys (Wu *et al.,* 2014).

Creatinine is a breakdown product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body depending on muscle mass. Serum creatinine is an important indicator of renal health because it is an easily-measured by-product of muscle metabolism (Taylor and Howard, 1989). Creatinine itself is an important biomolecule because it is a major by-product of energy usage in muscle (Brown, 2006) via a biological system involving creatine, phosphocreatine and adenosine triphosphate. Creatinine is chiefly filtered out of the blood by the kidneys. There is little or no tubular reabsorption of creatinine. If the filtering of the kidney is deficient, creatinine blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance, which reflects the glomerular filtration rate (Allen, 2014).

The use of traditional medicine and medicinal plants in Africa especially Nigeria is gaining more awareness due to its efficacy and recent advances in research in this area (Amaeze *et al.,* 2011). The paradigm shift away from the use of synthetic chemicals in food and medicines due to detrimental side effects necessitates the search for therapeutic plants with impressive safety and efficacy compared to costly synthetic drugs, many with adverse effects (Ikpeme, 2012). *Sida corymbosa* has been a component of many remedies by natives for the treatment of diabetes mellitus (Pole and Sebastian, 2006; Radhika *et al.*, 2013). X-raying the above facts, it became important to investigate the effects of *Sida corymbosa* extract on Serum uricacid, urea and creatinine levels of alloxan induced diabetic Wistar rat in Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria.

MATERIALS AND METHODS

Study location: The study was carried out at The Human Biochemistry Laboratory, Nnamdi Azikiwe University. It is located in the suburb of Nnewi - a popular town in Anambra State Nigeria.

Collection and identification of plant: The *Sida corymbosa* plant was collected in Okofia from the premises of College of Health Sciences and Technology, Nnamdi Azikiwe University, Nnewi campus, Anambra State, Nigeria in the month of January, 2016 and identified by Mrs. Aziagba B.O., Department of Botany, Nnamdi Azikiwe University, Akwa.

Animals used for the study: Wistar albino rats (100g) of both male and female were obtained from the Institute's Animal House and maintained at 25±2 ºC temperature and relative humidity 45-55% under 12:12 h light-dark cycle. Rats were fed with standard rat chow and water *ad-libitum*.

Ethical consideration: The protocol was approved by the Faculty of Health Sciences and Technology ethical committee, Nnamdi Azikiwe University, Nnewi campus, Anambra State, Nigeria.

Inclusion and exclusion criteria: Apparently healthy Wistar rats weighing 100g were included for the study while Unhealthy Wistar rats with weight less or above 100g were excluded from the study in order to ensure accuracy and uniformity in result interpretation.

Induction of hyperglycemia in albino wistar rats: This was executed by methods described by Szkudelski, (2001). Generally, the induction of diabetes using alloxan is a useful experimental model for studying the effects of hypoglycemic agents (Szkudelski, 2001). Alloxan and the products of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide with simultaneous massive increase in cytosolic calcium concentration, resulting in the distruction of pancreatic beta cells and severe hyperglycemia (Szkudelski, 2001).

Animal treatment: Animals were divided into three groups each, consisting of ten rats. Rats in the first group (A) received 400mg/kg *Sida corymbosa* dissolved in ethanol while the second group of rats (B) received ethanol. Rats in groups 3 were normal rats and served as the control groups (C). All the animals received their respective assigned treatment daily for a period of seven days. Rats were daily fasted over night before *Sida corymbosa* treatment. On day 8, the animals were anesthetized with ether, and blood was collected using cardiac puncture. Serum was then separated for the estimation of uric acid, urea and creatinine levels. Serum uric acid level was determined using uricase method as described by Trivedi *et al*., (1978); serum urea level was determined using Urease-Berthlot method as described by *Taylor, (1992);* while serum creatinine level was determined using Jaffe Slot Alkaline picrate enzymatic method as described by Burtis and Carl, (2008).

Statistical Analysis: Statistical package for social sciences (SPSS) version 20 was employed in the analysis of the result. The results for the parameters studied were expressed as Mean± SD and the data were analyzed for general group differences

using one-way ANOVA while post-HOC comparison was used to determine the inter-group differences. Level of significance was set at p<0.05.

RESULT

The mean serum levels of all the biochemical parameters studied, (Uric acid, Urea and Creatinine) were statistically significantly increased when the parameters were compared at p<0.05 using ANOVA table. In this study, the serum levels of uric acid, urea and creatinine were significantly increased (186.30±4.4 vs 170.40±5.4; 21.50±3.47 vs 10.77±1.16; 128.60±1.65 vs 100.80±1.99; p<0.05) when compared between alloxan induced diabetic rats with *Sida corymbosa* treatment and those without *Sida corymbosa* (Table 1).

When the alloxan induced diabetic rats with *Sida corymbosa* treatments were compared with the control group, all the parameters showed a statistically significant difference (P<0.05). The serum levels of uric acid and creatinine were statistically insignificant when the alloxan induced diabetic rats without treatment were compared with the control group in contrast to the mean serum level of urea which was statistically significant at p<0.05. More so, there was a significant decrease in the mean weight of the rats treated with *Sida corymbosa* when compared with those without *Sida corymbosa* treatment (98.80±1.03 vs 119.40±1.17; p<0.05). There was a significant decrease in the mean weight of rats with *Sida corymbosa* treatment when compared with the control group (98.80±1.03 vs 100.60±0.84; p<0.05). When the rats without *Sida corymbosa* treatment were compared with the control group, there was a significant increase in the mean weight of the rats (119.40±1.17 vs 100.60±0.84; p<0.05).

Table 1: Serum level of Uric acid, Urea and Creatinine in Alloxan –Induced Diabetic rat with *Sida corymbosa*treatment (A), without treatment *Sida* treatment (B) and in control group (C).

Group	Uric acid (umol/L	Urea (mmol/L	Creatinine (umol/L)	Weight (g)
A (n =10)	186.30±4.4	21.50±3.47	128.60±1.65	98.80±1.03
B (n= 10)	170.40±5.4	10.77±1.16	100.80±1.99	119.40±1.17
C (n=10)	147.40±14.46	8.29±1.51	83.90±10.14	100.60±0.84
F (P)-value	44.537(.000)	94.340 (0.00)	139.653 (000)	150.000 (.000)
AvB	<0.05	<0.05	<0.05	<0.05
AvC	<0.05	<0.05	<0.05	<0.05
BvC	>0.05	<0.05	>0.05	<0.05

All values are expressed as Mean ± Standard deviation (SD) with P<0.05 considered as significant.
Keys: F (P) – Value = Mean ±SD of parameter compared among group A, B and C using (ANOVA); AvB P- Value = Mean ±SD of parameter compared between group A and B using (t-test); BvC P- Value = Mean ±SD of parameter compared between group B and C using (t-test); AvC P- Value = Mean ±SD of parameter compared between group A and C using (t-test).

DISCUSSION

The *corymbosa* plant family has been found to be a potential and promising plant for medical purposes such as diabetes, hyperlipidemia and hypertension in Ayurvedic medicine (Pole and Sebastian, 2006; Radhika *et al.*, 2013). The present study shows a significant increase in the mean serum level of Urea following rats' treatment with *Sida corymbosa* extract when compared with the rats without *Sida corymbosa* treatment (p<0.05). This result is in contrast with the report of Enemor *et al.* (2013) who investigated the effects of ethanol extract of *sida acuta* leaves on some organ function parameters and physiologically important electrolytes in normal wistar albino rats and found that there was a non-significant decrease in mean serum urea level of the rats treated with the *Sida acuta* plant. Again, there was a significant increase in the mean serum creatinine level of the wistar albino rats after *Sida corymbosa* treatment compared to subjects without *Sida corymbosa* treatment. This result agrees with the findings of Enemor *et al.* (2013). Other similar studies in rats also did show the toxic effect of *Sida corymbosa* on the kidneys (Obeten *et al.*, 2013). An increase in blood creatinine level may indicate kidney dysfunction. Any medication that interferes with the normal actions of the kidneys can lead to elevations in blood creatinine

levels. Thus, the significant influence of *Sida corymbosa* extracts on these markers of kidney function is a proof of its toxic effect on the kidneys at the administered dose. This increase in creatinine level in the blood may suggest the functional excretory mechanisms of the kidney nephron in ensuring the removal of toxic materials from the body.

Again, the mean serum level of Uric acid was significantly increased after the Alloxan induced diabetic rats were subjected to treatment. More so, there was a significant decrease in the mean weight of the Wistar rats treated with *Sida corymbosa* when compared to both those rats without *Sida* treatment as well as the control group ($p<0.05$). This finding agrees with the report of Obeten *et al.*, 2013. This decrease in the mean weight of rats may suggest the diuretic effect of Sida plant resulting in weight reduction in the subjects (Kang *et al.*, 2010).

From the foregoing therefore, *S. corymbosa* significantly reduced the mean weight of rats and also had deleterious effects on the kidney function. Caution may be needed in the use of this plant in the herbal treatment of diseases. Further studies are needed in order to find safe dose regimen that will help unravel the full potential and benefit of *S. corymbosa.*

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AUTHORS' CONTRIBUTIONS

All authors (Ogbodo EC, Eriugo RC, Ezeugwunne IP, Oguaka VN,Analike RA, Onyegbule OA, Okwara EC, Ezego AI, Okeke KU) contributed to the completion of this research work and were actively involved in the presentation of this manuscript.