INTERNATIONAL JOURNAL OF APPLIED SCIENCE RESEARCH
FEDERAL POLYTECHNIC OKO, ANAMBRA STATE

IMPACT OF AQUEOUS AND ETHANOLIC LEAF EXTRACTS OF *CELOSIA ISERTII* AND *COSTUS LUCANUSIANUS* ON LIVER ENZYMES AND SOME KIDNEY FUNCTION PARAMETERS IN WISTAR RAT

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ABSTRACT

There is a rise in the use of *Celosia isertii* and *Costus lucanusianus* in the treatment of many ailments and diseases around Nigeria and Africa either by oral consumption or by consuming it in liquid form. However, the safety of these plants is not known and has not been established. Despite claimed success in treating diseases, it is imperative that a safety evaluation of the plants are carried out. This study was aimed at evaluating the safety of the aqueous and ethanolic extracts of *Celosia isertii* and *Costus lucanusianus* on the liver and renal function in Wistar rats administered varying doses of the extracts of *Celosia isertii* and *Costus lucanusianus*. Sixty five (65) adult Wistar rats, weighing between 120-130kg were randomly divided into thirteen (13) groups with n=5 rats per group. Twelve (12) groups were treated with varying doses (250, 500, 1000 mg/kg/d) of either aqueous or ethanolic extract of each plant as single daily dose for twenty-eight (28) days using oral canula. The remaining one (1) group was treated with potable water in lieu of extract. The animals were euthanized under chloroform anaesthesia and certain organs (liver and kidneys) were excised. Serum homogenates were used for enzyme (aspartate aminotransferase, AST, alanine aminotransferase, ALT and alkaline phosphatase, ALP) as well as to determine the concentrations of urea, and creatinine of the animals. Results show AST/ALT ratio to be approximately 2; with a significant ($p< 0.05$) decrease in the activity of liver enzymes of the treated groups in a dose dependent manner when compared to the control However, no significant ($p> 0.05$) changes in the concentration of serum urea and creatinine of the treated groups compared to the control of the animals. A high AST/ALT ratio suggest impaired liver function, however, the liver is not the only site of AST or ALT synthesis. As a result of the lower values of AST, ALT and ALP obtained from treatment groups as compare to the control as well as the insignificant ($p>0.05$) changes in levels of urea and creatinine in serum of both control and experimental rats, *Costus lucanusianus* and *Celosia isertii* extracts could be safe at the doses mentioned as they did not show marked toxic effects on the liver enzymes and some selected kidney markers. Hence, they are likely to be beneficial in treating diseases without affecting the integrity of the liver and kidney.

INTRODUCTION

Plants have been used in medicine from time in memorial, they are essential in the treatment of free radical-linked diseases before knowing the exact basis of their benefits. Their uses include treatments of malaria, burns, oedema, allergies and prevention of lipid peroxidation, some cancers and several other diseases (Emudainohwo *et al.*, 2012). Plants are crucial to the medical health care implementation in the developing countries (Akharaiyi and Boboye, 2010). Compared to conventional medicine, the use of tropical plants comes with less side effects. Hence, efforts have been made to show scientifically their use as alternative medicine.

Celosia are commonly referred to as wool flowers or cockscombs and is well known among the East Africans as 'Mfungu" and other West-Africa Countries (such as Nigeria), where it is called "Fulfulde" or "bokangida" (Edeoga *et al.*, 2005). *Celosia isertii* has been shown to be well-cultivated in Nigeria due to the humid weather. *Celosia isertii* is a straggling herb, reaches up to 3.0 mm height. It is generally seen in stream-banks, damp sites, clearings and rarely in savanna. Traces of flavones have been found to be present in the entire plant from the Congo area. The leaves are used for the treatment of inflammations, fever and itching; they are boiled and applied hot for rheumatism in Sierra Leone (Ojieh *et al.*, 2013). The seeds are bitter, useful in blood diseases and mouth sores (Thangarasu *et al.*, 2002). They are an efficacious remedy in diarrhea (Emudainohwo *et al.*, 2012). Based on ethno botanical practice, the plant has been investigated for anti-inflammatory (Patil *et al.*, 2003), antipyretic, anti-diabetic, antibacterial and diuretic properties (Park *et al.*, 2008). In West Africa the plant is often eaten as a vegetable or prepared in soups and sauces.

The plant, *Costus lucanuscianus* commonly known as spiral ginger is a perennial rhizomatous herb growing up to 3 millimetres tall (Obinna and Kagbo, 2018). It is a common specie in the forest zone of tropical Africa (Saliu and Fapohuda, 2016). *C. lucanuscianus* is a medicinal plant locally called 'monkey sugar cane' in the Niger Delta region of Nigeria. Ethno-medicinally, the plant is used in the management of several ailments and conditions including diabetes, eye problems, cough and threatened abortion (Obinna and Kagbo, 2018). The leaf sap of *C. lucanuscianus* is used to treat eye troubles and headaches.

The plants *Celosia isertii* and *Costus lucanuscianus* are popular in traditional medicine, their medicinal potentials and benefits are not unknown and however, there are infinitesimal accounts on their safety. On that note, this study investigates the effects of the aqueous and ethanolic extracts of these plants on activities of liver enzymes and some kidney functions biomarkers in Wistar rats.

MATERIALS AND METHODS

Plant Harvest and Authentication: The plants were collected among free growing plants in Abraka, Ethiope East Local Government Area of Delta State, Nigeria and transported to the Department of Plant Biology and Biotechnology, University of Benin, Benin City. The plant materials were identified and authenticated by Professor M. I. Idu and voucher specimens (*Celosia isertti*: UBHa 0208 and *Costus lucanusianus*: UBHa02010) were deposited in the herbarium.

Preparation of Plant Materials: Fresh leaves of each plant were plucked, washed and air dried over a period of four weeks and pulverized to fine powder using mechanical blender (Kenwood, Japan), and stored in dark bottles.

Preparation of Aqueous Extract: Five hundred grammes (500 g) each of the ground powder of *Celosia isertii* and *Costus lucanusianus* leaves were separately soaked in 4 L of distilled water. The mixture was vigorously stirred at intervals of 2 h for 6 h and thereafter, left to stand for the next 18 h. The suspension was separated by filtration using muslin cloth and the filtrate was taken for freeze drying, and therefore kept for further analyses.

Preparation of Ethanolic Extract: Five hundred grammes (500 g) each of the ground powder of *Celosia isertii* and *Costus lucanusianus* leaves were separately soaked in 4 L of ethanol. The procedure used to prepare the aqueous extract was followed except that ethanol replaced distilled water.

Animal Grouping and Treatments

Sixty five (65) adult Wistar rats obtained from the Department of Biochemistry Animal House, University of Benin, kept in well ventilated cages for two weeks to acclimatize were divided into thirteen groups of five rats each. The rats were treated as follows: Group 1: Rats + distilled water, Group 2: Rats + CIAE (250 mg/kg/bwt), Group 3: Rats + CIAE (500 mg/kg/bwt), Group 4: Rats + CIAE (1000 mg/kg/bwt), Group 5: Rats + CIEE (250 mg/kg/bwt), Group 6: Rats + CIEE (500 mg/kg/bwt), Group 7: Rats + CIEE (1000 mg/kg/bwt), Group 8: Rats + CLAE (250 mg/kg/bwt), Group 9: Rats + CLAE (500 mg/kg/bwt), Group 10: Rats + CLAE (1000 mg/kg/bwt), Group 11: Rats + CLEE (250 mg/kg/bwt), Group 12: Rats + CLEE (500 mg/kg/bwt), Group 13: Rats + CLEE (1000 mg/kg/bwt).

CIAE = Celosia isertti aqueous extract, CIEE = Celosia isertti ethanolic extract, CLAE = Costus lucanusianus aqueous extract, CLEE = Costus lucanusianus ethanolic extract, bwt: body weight

The extracts were administered orally using oral canula as a single daily dose for twenty eight (28) days.

Euthanizing of Animals and Blood Sample Collection

On day 28 the rats were fasted overnight, weighed and anaesthetized with chloroform the following morning. Then, the animals were euthanized and blood samples were collected and prepared for enzyme assay (aspartate aminotransferase, (AST), alanine aminotransferase, (ALT) and alkaline phosphatase, (ALP) and estimation of urea and creatinine concentrations. The blood samples were collected by cardiac puncture into heparinized bottles, centrifuged, and plasma transferred into plain bottles and stored in the freezer (below - 4^0C).

Analysis of Serum Samples: AST and ALT (Reitman and Frankel 1957), ALP (Furuno, and Sheena, 1965), creatinine (Bartels *et al.*, 1972) and urea (Fawcet and Scott, 1960) were assayed using methods already documented.

Statistical Analysis

To test the level of significance, data was expressed as Mean ± Standard Deviation and subjected to analysis of variance (ANOVA). Significant differences between the treated groups were determined at 5% level using the Duncan Multiple Range Test. Analysis was performed using SPSS software version 19.

RESULTS

Results obtained from investigation into the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in Wistar rats treated with aqueous and ethanolic leaf extracts of *Celosia isertii* and *Costus lunusianus* are presented in Tables 1-2.

Table 1: Activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in Wistar rats treated with aqueous and ethanolic leaf extracts of *C. isertii* leaves

Leaf Extract (mg/kg.bw)	ALT(IU/L)	AST(IU/L)	ALP(IU/L)	AST/ALT
Control	46.69±24.03(46.69±24.03)	98.80±7.92(98.80±7.92)	32.90±12.76(32.90 ± 12.76)	2.12(2.12)
250	39.95±3.77^a(36.52±9.14^a)	91.24±58.16^a(71.75±14.42^a)	31.08±6.39(27.16±4.99^a)	2.28(1.96)
500	36.52±9.14^a(31.28±5.58^a)	83.73±23.76^a(71.10±22.10^a)	24.34±7.85^a(26.80±12.39^a)	2.29(2.27
1000	32.69±1.35^a(26.67±9.46^a)	76.19±32.54^a(69.24±20.65^a)	30.23±6.76(23.38± 5.11^a)	2.33(2.60

Values are expressed as Mean ± SD for n=5 rats per group. The ethanolic leaf extract-induced changes are expressed in parenthesis, [a] Significantly lower from control ($p < 0.05$).

There was a significant ($p<0.05$) decrease in the activities of serum ALT, AST and ALP compared to the control in both the aqueous and ethanolic leaf extracts of the plant administered and these decreases are dose dependent except for ALP activity which showed a higher activity in the group treated with 1000 mg/kg body weight compared to the group treated with 500 mg/kg bodyweight of the aqueous extract of the plant.

Table 2: Activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in Wistar rats treated with aqueous and ethanolic leaf extracts of *C. lucanusianus*

Leaf Extract (mg/kg.bw)	ALT(IU/L)	AST(IU/L)	ALP(IU/L)	ASL/ALT
Control	48.66±9.47(48.66±9.47)	117.73±23.66(117.73±23.66)	36.50±15.88(36.50±15.88)	2.45(2.45)
250	36.52±4.01[a](38.43±2.80[a])	68.16±13.64[a](112.66±25.60[a])	28.20±1.87[a](32.90±12.78[a])	1.76(2.93)
500	31.40±4.01[a](36.52±9.14[a])	64.67±10.19[a](100.91±8.68[a])	19.54±4.21[a](24.78±3.90[a])	2.06(2.76)
1000	31.22±1.41[a](28.87±7.56[a])	64.64±13.16[a](98.80±7.92[a])	16.64±5.95[a](23.32±4.99[a])	2.07(3.42)

Values are expressed as Mean ± SD for n=5 rats per group. The ethanolic leaf extract-induced changes are expressed in parenthesis, [a] Significantly lower from control ($p < 0.05$).

Both the aqueous and ethanolic leaf extracts of *Celosia lucanusianus* induced a significant ($p<0.05$) reduction in the activities of liver enzymes (alanine aminotransferase, ALT, aspartate aminotransferase, AST and alkaline phosphatase, ALP) when compared to the control.

Levels of urea and creatinine in serum of rats administered varying doses (250, 500 and 1000 mg/kg/d) of aqueous and ethanolic leaf extracts of *Celosia isertii* and *Costus lucanusianus* are shown in Figures 1-4.

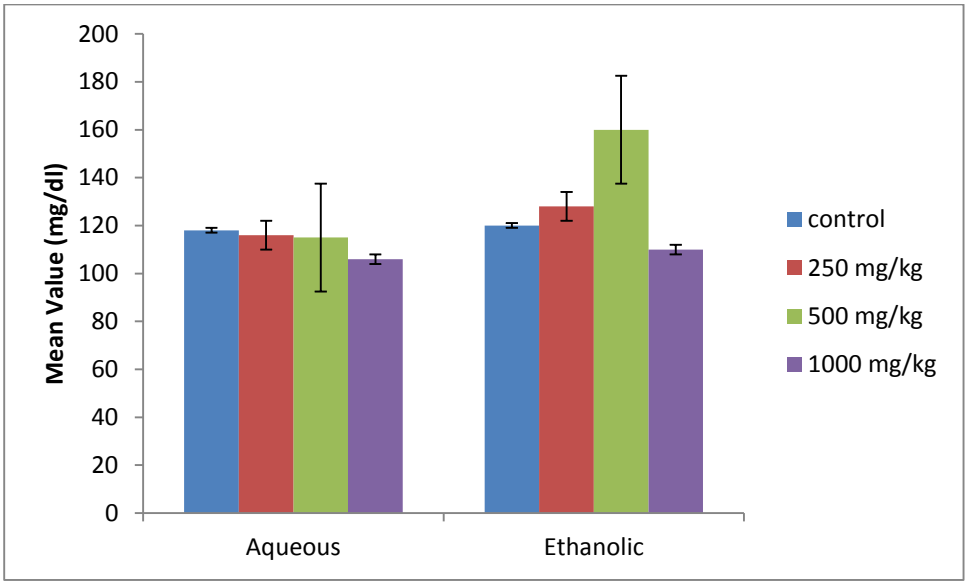

Figure 1: Changes in serum urea levels in rats administered *C. isertii* aqueous and ethanolic leaf extracts

Changes in serum urea for experimental animals were not significantly ($p>0.05$) different from the control except for group treated with 250 and 500 mg/kg ethanolic extract.

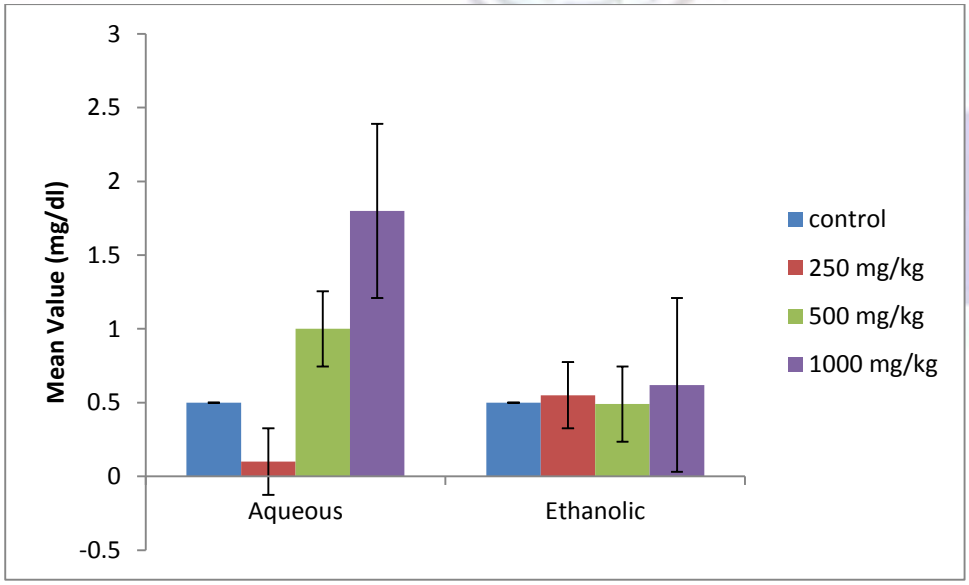

Figure 2: Changes in serum creatinine levels in rats administered *C. isertii* aqueous and ethanolic leaf extracts

There is significant ($p<0.05$) difference in changes in serum creatinine for experimental animals treated with aqueous extract and control; while the 250 mg/kg group is lower than the control, the 500 mg/kg and 1000 mg/kg were higher than the control. In

the ethanolic treatments however, changes in serum creatinine for experimental animals were not significantly ($p>0.05$) different from the control.

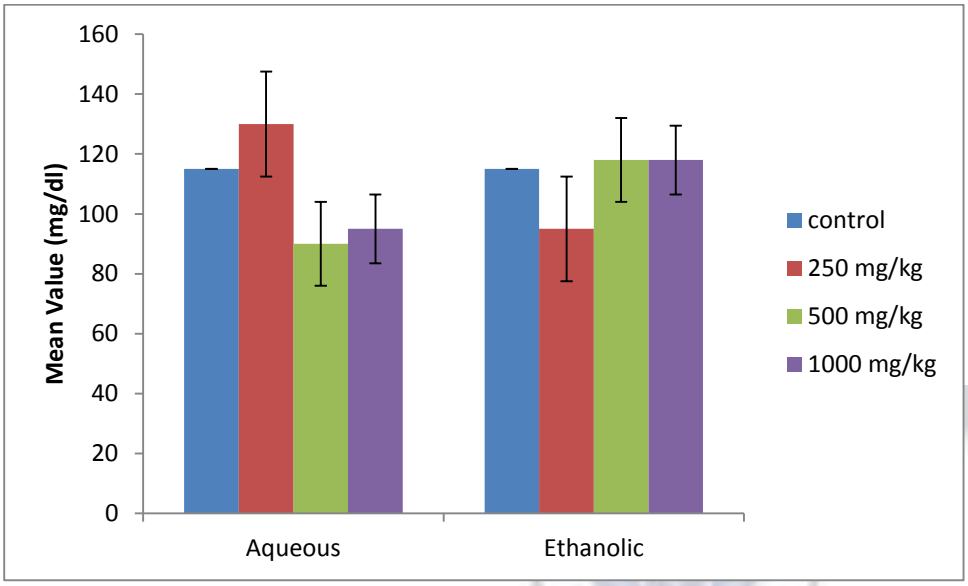

Figure 3: Changes in serum urea levels in rats administered *C. lucanusianus* aqueous and ethanolic leaf extracts

Changes in serum urea for experimental animals were not significantly ($p>0.05$) different from the control.

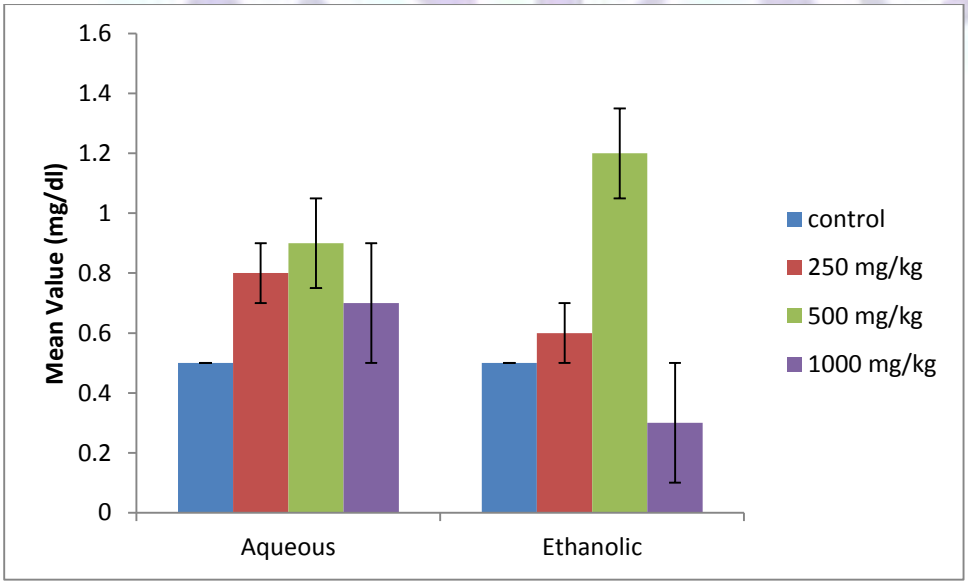

Figure 4: Changes in serum creatinine levels in rats administered *C. lucanusianus* aqueous and ethanolic leaf extracts

Changes in serum creatinine for experimental animals were not significantly (p>0.05) different from the control except in ethanolic group where 500 mg/kg treatment is higher than the control.

DISCUSSION

Despite naturally occurring antioxidant systems in the human body, reactive oxygen species cause lipid, protein, and DNA oxidation. These damages at the molecular level may influence the etiology of diseases, such as cancer, kidney failure, atherosclerosis, diabetes, hepatotoxicity, neurodegenerative disorders, and aging-related diseases. The reactive oxygen species that are constantly generated in the human body cause oxidative stress. The ratio of reactive oxygen species may be increased by the factors such as drugs, chlorinated compounds, deficiency of natural antioxidants, alcohol, stress and unhealthy food (Strzemski *et al.*, 2017).

The kidney is a very important organ of the body which helps in the maintenance of the body's homeostasis. It plays a principal role in excretion of waste products of the body's metabolism, drugs and chemicals (Okolie, 2011). Toxic substances such as chemicals, drugs, heavy metals, and immunological complexes can inflict injury on the kidney and in turn incapacitate it from performing notable excretory functions that may lead to renal failure (Okolie, 2011).

Liver diseases which include liver cirrhosis, fibrosis, liver cancer, hepatitis etc. are common causes of death worldwide (WHO, 2016) and several factors including free radicals have been linked with the diseases (Dokunmu *et al.*, 2018).

AST, ALT or ALP levels are a valuable aid primarily in the diagnosis of liver disease. Although, not specific for liver disease, it can be used in combination with other enzymes to monitor the course of various liver disorders. When body tissue or an organ (where these enzymes can be found) such as the liver, kidney or heart is diseased or damaged, additional AST and ALT are released into the bloodstream, causing activity levels of the enzyme to increase. Therefore, the amount of AST and ALT in blood is directly related to the extent of tissue damage. After severe damage, AST level rises 10 to 20 times greater than normal, whereas, ALT can reach higher levels (up to 50 times greater than normal) (Vasudevan *et al.*, 2013).

The ALP test is used to detect blocked bile ducts, liver damages or bone disorders. When the liver cells are damaged it releases increased amounts of ALP into the blood. ALP levels in plasma also rise with large bile duct obstruction, intrahepatic cholestasis, or infiltrative diseases of the liver (Hasan *et al.*, 2018).

The reference ranges of AST, ALT and ALP are 50 to 150 IU/L, 10 to 40 IU/L and 30 to 130IU/L respectively (Hasan *et al.*, 2018).

Table 1 and 2 showed levels of hepatic enzymes AST, ALT and ALP in Wistar rats treated with aqueous and ethanolic leaf extracts of *Celosia isertii* and *Costus lunusianus*.

About all the values generated on enzymes activities are within reference ranges, the few that were not are not far off. Meanwhile, there were significant ($p< 0.05$) difference between the control and all treatment groups (250, 500, 1000 mg/kg) in both the aqueous and ethanolic leaf extract of study plants. Furthermore, in no treatment group was the level of any of the enzymes higher than the control, it can be said that plants did not cause damage to the liver and the significant ($p< 0.05$) decrease between the control and treatments groups (which is dose dependent) shows there is the possibility of the plants protection on the liver by reducing the formation of the enzymes. This pattern of hepatoprotective potential corresponds to Okoro (2018), Adejoke *et al.* (2015), Awogbindin *et al.* (2014) and Ulicna *et al.*, (2003); and oppose that of Hasan *et al.* (2018) and Imafidon and Okunrobo (2012).

Meanwhile, as revealed in Table 1 and 2, aqueous extracts of both plants lower activities of enzymes than their ethanolic extracts.

Another determinant considered in this hepatotoxicity study is the AST/ALT ratio. The AST/ALT ratio is useful to differentiate between causes of liver damage, or hepatotoxicity (Nyblom *et al.*, 2006). Most causes of liver cell injury are associated with a greater increase in ALT than AST; however, an AST/ALT ratio more noteworthy than 1 suggest localized myocardial necrosis, while a ratio <1 might be because of the release of ALT from the impaired liver. An AST/ALT ratio in excess of 2 is characteristics of alcoholic hepatitis or cirrhosis (Ezejiofor *et al.*, 2013). The AST values were higher than ALT's (Table 1 and 2), however the AST/ALT ratio (approximately 2), is an indication of abnormal functioning of the liver.

The fact that extracts treatments elicited decreased values as compare to the control and not increase, this high AST/ALT ratio might not be attributed to liver damage. Muscle inflammation due to dermatomyositis may cause this high AST/ALT ratio, besides AST and ALT do come from other tissues other than the liver (Nyblom *et al.*, 2006).

Urea is the primary metabolite derived from dietary protein and tissue protein turnover while creatinine is the product of muscle creatinine metabolism (Bandebuche *et al.*, 2017). Urea and creatinine are commonly used as markers of kidney function. When the levels of these metabolites increase in serum, it indicates that there is a problem with the kidney excretion (Mahmoud *et al.*, 2015). This is because

the kidney is responsible for filtration of the blood, and when there is a problem with the kidney, urea and creatinine which are supposed to be filtered into the urine accumulates in the blood (Mahmoud *et al.*, 2015).

Over levels of urea and creatinine in serum of rats administered varying doses, (250, 500 and 1000 mg/kg/d) of aqueous and ethanolic leaf extracts of *Celosia isertii* and *Costus lucanusianus* show no significant ($p < 0.05$) difference between the control group and treated groups, although, there were very few deviations from the generally observed trend, and is similar to Ezejiofor *et al.* (2013).

CONCLUSION

The findings in this study suggest that *Celosia isertii* and *Costus lucanusianus* do not impact damage on the liver or kidney and are therefore safe for treatments of diseases and disorders.

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