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ANTIOXIDANT EFFECT AND NEPHRO PROTECTIVE POTENTIAL OF TERMINALIA CATAPPA LEAF ON KIDNEYS OF WISTAR RATS EXPOSED TO AUGUMENTIN – INDUCED DAMAGE

Erigbali P. P.*[1], Arhoghro E. M.[2], Sule O. J.[2] and Nordee J. V.[2]

[1]Department of Human Physiology, Faculty of Basic Medical Sciences, Niger Delta University, Wilberforce Island, Bayelsa State.
[2]Department of Biochemistry, Faculty of Basic Medical Sciences, Niger Delta University, Wilberforce Island, Bayelsa State.

***Corresponding Author: Erigbali P. P.**
Department of Human Physiology, Faculty of Basic Medical Sciences, Niger Delta University, Wilberforce Island, Bayelsa State.

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ABSTRACT

This research was aimed at studying the potential protective benefit of ethanol extract of *Terminalia catappa* to the kidneys of rats exposed to tissue damage by treatment with augmentin. Thirty rats were placed in five **groups a – e**. Each group had 6 rats at random weighting between 150g to 200g. They were treated as follows; **group a and b** (that served as normal and positive control respectively) were administered 10ml/kg normal saline**, group c and d** (that served as test group 1 and 2) were given 200 mg/kg and 400 mg/kg per body weight doses of the extract in that order and **group e** (standard) was orally administered 200 mg/kg dose of vitamin E for the first 14 days. From the 15th to 21st day, the group b, c, d, and e were all administered oral dose of 30mg/kg augmentin daily. On the 22nd day, the rats were sacrificed and blood sample was obtained by cardiac puncture to analyze function of kidney. Two grams portion of Kidney tissues was obtained for homogenate used in the antioxidant studies. Results showed that in the positive control group that was subjected to augmentin treatment, augmentin administration caused a significant increase ($p<0.05$) in serum concentrations of urea (110.46±14.18), creatinine (1.87±0.15) and total bilirubin (1.01±0.07) relative to normal control rats. But, treatment with 200 mg/kg b.wt and 400 mg/kg b.wt of *Terminalia Catappa* showed a significant ($p<0.05$), dose dependent decrease in serum concentrations of urea (92.55±15.01 and 79.08±2.93), creatinine (1.20±0.13 and 1.04±0.15), and total bilirubin (0.60±0.05 and 0.44±0.04) respectively, compared to the augmentin treated group. Meanwhile, antioxidant analysis shows that augmentin administration caused a significant reduction ($p<0.05$) in kidney SOD (3.89±1.06), Catalase (2.51±0.24) and GSH (2.59±0.33) activities in the positive control and a significant increase ($p<0.05$) in kidney MDA concentration (4.80±0.44) compared to the normal control group. Meanwhile, treatment with 200 mg/kg b.wt and 400 mg/kg b.wt doses of *Terminalia Catappa* caused a significant ($p<0.05$) elevation of kidney activities of SOD (7.46±1.15 and 9.73±1.46) Catalase (3.85±0.24 and 4.18±0.39) and GSH (4.15±0.55 and 4.80±0.26) in a dose dependent manner, and a significant decrease in the kidney MDA (3.15±0.21 and 2.90±0.11) concentration when compared to the augmentin treated group. In conclusion, administration of the extract of *T. catappa* to albino rats that are exposed to tissue damage provides protective health benefit for the kidneys in a manner that appears to be dose dependent. Although, additional studies may be required if the precise mechanisms involved could be elucidated.

KEYWORDS: Augmentin, CKD, creatinine, antioxidant, terminalia catappa, nephroprotective.

Chronic kidney disease with the general acronym (CKD), is reportedly emerging as one of the most prominent causes of death and suffering in the 21st century; in part due to some rising risk factors, such as obesity and diabetes mellitus (de Boer *et al*., 2020; CDC., 2021). lt is also alarming that there is report of an upward rise in the number of patients affected by CKD estimated at 843.6 million globally in 2017 (Jager *et al*., 2019). The surge and scourge of the risk factors as well as complications associated with CKD has increasingly contributed in no little way to CKD being listed among the leading causes of mortality, among the Global Burden of Disease; even though the rate of mortality in patients with end-stage kidney disease (ESKD) has declined (Hill *et al*., 2016; Kovesdy, 2022). Furthermore, the significant association between hypertension (which is the highest cardiovascular risk factor) and prevalence of CKD that was reported by Hill *et al* (2016) in a meta-analysis which included 75 global studies is more worrisome; particularly when one considers the projected trajectory of about 23.3 million annual mortality from cardiovascular disease by the year 2030, if interventions are not made (Akumiah *et al*, 2023). The prevalence of CKD has been reported to be higher in females than in males. In the United States, the age-adjusted prevalence of CKD stages 1–4 in 2015 to 2016 was 14.9% in females and 12.3% in males (Hill *et al*., 2016).

Therefore, it is pertinent that concerted efforts to promptly identify, monitor, and manage CKD be expedited. More so, of paramount concern is the need for a global, systematic implementation of preventive and therapeutic measures in addressing CKD to be put in place.

Meanwhile, it is known that orthodox or modern medicine had benefitted closely from traditional herbal therapeutic practice whilst evolving; as buttressed by how often extracts of the active ingredients from historical medicinal plants are used for development and production of orthodox medication (*Salmerón-Manzano et al*., 2020).

Generally, plants are known to make some natural chemicals which enable them evade agents that could cause disease and also serve as deterrence for their herbivorous predator. These phytochemicals, produced by plants as protection against bacterial, fungal, and viral disease, are found in parts such as roots, stems, barks, leaves, fruits, flowers and seeds. These natural chemicals are considered non-essential for human survival since they do not have nutritional value. However, they have been found to offer numerous health benefits, including protection against life-threatening diseases (Salehi *et al*., 2019). So far, more than 1,000 phytochemicals have been identified, some of which are flavonoids, isoflavones, and lycopene from fruits, soy and tomatoes in that order; that have fewer or no adverse side effects, but higher therapeutic efficacy (Salehi *et al*., 2019).

One of the numerous advantages of plants in health is some of their constituents' (antioxidant) properties which could enable them mop free radicals or reactive oxygen species (ROS); such as ozone (O3) and hydrogen peroxide (H_2O_2); that all play role in oxidation processes (that are degenerative) inside the body as a result of their chemical instability. Some ROS, such as the superoxide anion (O^{2-}) and nitric oxide (NO), are free radicals characterized by an unpaired electron. In the body, antioxidants form a complex network that acts as a defense system, neutralizing free radicals and reactive species to maintain cellular homeostasis (Sharifi-Rad *et al*., 2020). There are some enzymes in the body that also have antioxidant activities that they carry out in a network of interaction; and include superoxide dismutase enzymes (SODs), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase - GRd (Górny *et al.*, 2020). However, when the concentration of oxidants overwhelms the available antioxidants or when the body's antioxidant reserves are depleted due to illness or a poor diet, this may result in oxidative stress and compromised cellular function (Rogers & Cismowski, 2018). Many antioxidants are derived from natural sources outside the body (exogenous), such as plants or minerals ingested. When endogenous antioxidants involved in free radical defenses are unable to protect the body from ROS, exogenous antioxidants becomes essential requirement (Górny*et al.* 2020).

Terminalia catappa also known as Indian almond *is one plant whose* leaves have been associated with ethno medicinal reports. It is rich in alkaloids, anthraquinones, carbohydrate, cardiac glycosides, flavonoids, phenol, saponins, tannins, triterpenes, reducing sugar (Olutokun *et al*., 2018). The leaves have been used in the treatment of skin infections, leprosy, inflammation, malaria and pain. It has been indicated from studies that Indian almond possesses anticancer, anti-HIV reverse transcriptase, antidiabetic, antioxidant effects as well as hepatoprotective activities (Zhang *et al*., 2020). Healthy and accelerated growth of fishes that are bred in ponds to which *T. catappa* leaves were added has been asserted (Anand *et al*., 2015).

METHODS

Sample *of T. catappa* was collected from Niger Delta University, in Bayelsa state of Nigeria. Professor Kola Ajibeshin of the Department of Pharmacognosy, in the University identified it. Then fresh leaves were dried for 14 days under room temperature, and afterwards ground into powdered form. 500g of the powder was diluted with 2 litres of ethanol. This mixture was kept 48 hours while stirring intermittently. Whattman filter paper (110 mm size) was then used to collect the filtrate, evaporated at 40 ^{0}C using a rotary evaporator. Distilled water was now used to re-dilute the powdery residue.

Five groups, **a to e** of six wistar rats each were used for the study. All the rats weighting between 150g – 200g were kept in plastic cages under laboratory condition for 14 days, during which they freely accessed grower's mash, water and fresh air with 12 hour light/darkness cycle. During the first 14 days, group **a** and **b** were given 10ml/kg bwt of normal saline every day, as normal and positive control, in that order. 200mg/kg bwt of the extract was administered to **group c** (test group 1) while **group d** (test group 2) was administered 400mg/kg bwt of the extract. 200 mg/kg Vitamin E was given to **group e** (standard group)**.** On the 15th day of the study, rats in **group b, c, d and e** were all given 30mg/kg bwt of augmentin orally, for seven days and thereafter, the rats were sacrificed on the 22nd day. Sample of blood was collected into bottles by cardiac puncture, allowed to settle for 30 minutes to coagulate, and then centrifugation for 10 minutes at 2000 RPM was done. The supernatant was obtained for biochemical analysis of urea, creatinine and bilirubin assay. Two grams portion of tissue from kidneys was extracted for homogenates that were used in antioxidant analysis.

Standard biochemical kits (Randox product) protocol were followed while carrying out all analyses.

Serum urea was estimated according to the instruction on the Randox biochemical kit manual as mentioned in the study of Aronson *et al* (2004).

Estimation of Serum creatinine was performed following protocol on the biochemical kit manual as reported by Dimeski & Treacy (2022); and the serum total bilirubin was estimated by the description on the Randox biochemical kit.

For the antioxidant enzymes analysis, the level of SOD activity was determined by the method of Misra et al (1972) and for reduced glutathione (GSH) the method described by Beutlar (1989). Determination of Catalase Activity was carried out with the method of Sinha A (1971).

Statistical Analysis

The one-way analysis of variance (ANOVA) was applied in analyzing the results, as captured in Turkey Kramer Multiple Comparison Test. All values are expressed in form of mean ± Standard deviation and level of statistical significance was at $p < 0.05$.

RESULTS

The mean serum concentrations of urea, creatinine and total bilirubin as observed in this present study are presented in Table 1, while table 2 captures the mean kidney concentrations of SOD, Catalase, GSH and MDA in the group of wistar rats that were pretreated for 14 days with *Terminalia Catappa* extract and induced 7 days with augmentin.

Table 1: The protective role of *Terminalia Catappa* on augmentin induced albino wistar rats.

EXPERIMENTAL GROUP	Urea (mg/dl)	Creatinine (mg/dl)	Bilirubin (g/dl)
Normal Control with normal saline	56.58±4.76^{a}	0.64±0.02^{a}	0.32±0.063^{a}
Positive Control with 30mg/kg augmentin	110.46±14.18^{b}	1.87±0.15^{b}	1.01±0.07^{b}
Test Group 1with 200mg/kg extract and 30 mg/kg augmentin	92.55±15.01^{c}	1.20±0.13^{c}	0.60±0.05^{c}
Test Group 2 with 400mg/kg extract and 30mg/kg augmentin	79.08±2.93^{d}	1.04±0.15^{d}	0.44±0.04^{d}
Standard Control with 200mg/kg Vitamin E and 30mg/kg augmentin	79.21±3.91^{d}	0.91±0.10^{d}	0.36±0.04^{d}

Data are expressed as the mean ± SD (n = 6). Means within the same column carrying same superscripts are not significantly ($p < 0.05$) different.

Table 1 shows that augmentin administration caused a significant increase ($p<0.05$) in serum concentrations of urea (110.46±14.18), creatinine (1.87±0.15) and total bilirubin (1.01±0.07) in positive control rat relative to normal control rats. But, treatment with 200 mg/kg b.wt and 400 mg/kg b.wt of *Terminalia Catappa* showed a significant ($p<0.05$), dose dependent decrease in serum concentrations of urea (92.55±15.01 and 79.08±2.93), creatinine (1.20±0.13 and 1.04±0.15), and total bilirubin (0.60±0.05 and 0.44±0.04) respectively, compared to the augmentin treated group.

Table 2: The antioxidant effect of *Terminalia Catappa* on augmentin induced wistar albino rats.

EXPERIMENTAL GROUP	SOD (U/mg protein)	Catalase (U/mg protein)	GSH (U/mg protein)	MDA (U/mg protein)
Normal Control with normal saline	9.66±0.86^{a}	5.14±0.45^{a}	5.50±0.38^{a}	1.92±0.61^{a}
Positive Control with 30mg/kg augmentin	3.89±1.06^{b}	2.51±0.24^{b}	2.59±0.33^{b}	4.80±0.44^{b}
Test Group 1with 200mg/kg extract and 30 mg/kg augmentin	7.46±1.15^{c}	3.85±0.24^{c}	4.15±0.55^{c}	3.15±0.21^{c}
Test Group 2 with 400mg/kg extractand 30mg/kg augmentin	9.73±1.46^{a}	4.18±0.39^{c}	4.80±0.26^{d}	2.90±0.11^{d}
Standard Control with 200mg/kg Vitamin Eand 30mg/kg augmentin	8.75±1.61^{a}	4.78±0.23^{d}	4.44±0.20^{d}	2.91±0.37^{d}

Data are expressed as the mean ± SD (n = 6). Means in same column having same superscripts are not significantly ($p < 0.05$) different.

Table 2 shows that augmentin administration caused a significant reduction ($p<0.05$) in kidney SOD (3.89±1.06), Catalase (2.51±0.24) and GSH (2.59±0.33) activities in the positive control and a significant increase ($p<0.05$) in kidney MDA concentration (4.80±0.44) compared to the normal control group. Meanwhile, treatment with 200 mg/kg b.wt and 400 mg/kg b.wt doses of *Terminalia Catappa* caused a significant (p<0.05), elevation of kidney activities of SOD (7.46±1.15 and 9.73±1.46) Catalase (3.85±0.24 and 4.18±0.39) and GSH (4.15±0.55 and 4.80±0.26) in a dose dependent manner, and a significant decrease in the kidney MDA (3.15±0.21 and 2.90±0.11) concentration when compared to the augmentin treated group.

DISCUSSION

Plants with medicinal properties have been widely used in various climes as a primary healthcare resource. Numerous plants have been studied for their pharmacological benefits, including their potential as anticancer, antidiabetic, antimicrobial, and antiviral agents (Mohammed, 2019). The current study focused on investigating the impact of ethanol leaf extract of *Terminalia catappa* on kidney injury induced by a high dose of augmentin in male Wistar rats. The kidneys are known to play very crucial role in the excretion of waste products and toxins such as urea, creatinine, and small amount of conjugated bilirubin (Hoilat & John, 2022).

Results obtained from this study as shown in (Table 1) indicates that, the administration of Augmentin to rats (positive control) led to a significant (p<0.05) elevation in serum concentrations of urea, creatinine and bilirubin; implying that there was renal damage and dysfunction. Usually creatinine is produced as the end product of creatine metabolism, biochemically through an irreversible reaction, at about 2% daily, but consistently filtered freely out from the body by kidneys; therefore, its appearance and estimation in serum has made it the best biomarker or indicator (endogenously) for kidney dysfunction or damage (Dimeski & Treacy, 2022). Elevated blood urea has been linked with renal dysfunction that is associated with heart failure (Aronson et al., 2004). However, pretreatment with ethanol extract of *Terminalia catappa at doses of* 200 mg/kg and 400 mg/kg body weights significantly reduced serum concentration of creatinine, urea, and bilirubin (Test groups 1 and 2). The implication of this portrays a potential protective benefit that *T. Catappa* administration might have offered to the renal health of those wistar rats that were pretreated with its extract. More so, this effect of the extract appears to be dose dependent.

Similarly, administration of vitamin E to group e rats (standard group) also reduced serum concentrations of urea, creatinine, and bilirubin significantly (p<0.05). Vitamin E is an established or known antioxidant, which among several health benefits is also reported to improve kidney functions (Rizvi *et al.,* 2014).

The physiological role of antioxidants is to prevent damage to cellular components that may occur due to oxidative reactions or chemical reactions that involves free radicals (Sharifi-Rad *et al*., 2020). In this study, antioxidant parameters were also assessed in the group of rats. It was found that augmentin intoxication significantly (p<0.05) increased kidney MDA concentration and reduced the activities of SOD, catalase, and GSH enzymes in positive control rats. This is indicative of increased lipid peroxidation and impaired antioxidant defense mechanisms in those rats (Bencheikh *et al.*, 2022). Meanwhile, treatment with *Terminalia catappa* extract and vitamin E apparently resulted in a reversal of these effects. Thus, suggesting the expression of antioxidant properties of the extract. These results are in agreement with the report of Umoren *et al* (2023), who showed that *Terminalia catappa* leaf extract attenuated Phenylhydrazine-induced hepato-renal toxicity in male Wistar rat by up-regulation of *in vivo* antioxidant armouries.

The nephroprotective effects of *T. catappa* extract observed in this study may be attributed to its phytochemical composition, which includes compounds such as flavonoids, alkaloids, tannins, cardiac glycosides and others, some of which have antioxidant activities (Olutokun *et al*., 2018). Although, additional studies may be required if the precise mechanisms involved could be elucidated.

CONCLUSION

Administration of the extract of *T. catappa* to albino rats that are exposed to tissue damage provides protective health benefit for the kidneys in a manner that appears to be dose dependent. Although, additional studies may be required if the precise mechanisms involved could be elucidated.

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