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Effect of *Costus afer* Leaves' Juice on Nitrocellulose Thinner Induced Nephrotoxicity in Rats

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ABSTRACT

This study assessed the effect of oral administration of *Costus afer* leaves' juice (CALJ) on the functional integrity of the renal tissues in rats orally exposed to nitrocellulose thinner (NCT). Three groups of six rats each, were orally administered distilled water, NCT (30.0 mg kg⁻¹ b.wt.) and NCT (30.0 mg kg⁻¹ b.wt.) in combination with 600 mg kg⁻¹ b.wt. of CALJ (one hour before NCT administration), respectively for 28 days. The animals were sacrificed after 12 h fast, on the 29th day of the experiment, blood collected through cardiac puncture for serum urea, Blood Urea Nitrogen (BUN), uric acid, creatinine, kidneys for renal tissues malondialdehyde (MDA), Glutathione Peroxidase (GPx) and Superoxide Dismutase (SOD) activities determination. The results showed that NCT caused a significant ($p < 0.05$) increase in serum urea, BUN, uric acid, creatinine and renal tissue MDA levels, as well as decrease in renal tissue GPx and SOD activities, compared to control group. These results indicated that NCT's constituents and their metabolites are nephrotoxic. However, it was observed that administration of CALJ protected the renal tissues against the NCT-induced nephrotoxicity, as indicated by the restoration of serum urea, BUN, uric acid and creatinine levels, as well as renal tissue MDA, GPx and SOD activities to the control range. Also the tubular epithelial necrosis and atrophy of the glomeruli, observed to be associated with exposure to NCT were restored to normal on treatment with CALJ. This study strongly suggested that CALJ's constituents possess a protective effect against NCT-induced renal tissues damage and reflected the beneficial role of *Costus afer* in the treatment of various clinical disorders.

Key words: Nitrocellulose thinner, *Costus afer* leaves', nephroprotection

INTRODUCTION

Nitrocellulose thinner is one of the industrial solvents commonly used in furniture, paints and automobile spray painting industries. It contains such organic chemical agents as ethyl benzene or toluene and butyl acetate. These chemical agents are very volatile and have been reported to constitute environmental pollutants in the household and occupational environments where they are used (WHO, 1996, 2005). Hence, the effects of exposure to these environmental pollutants become a matter of research concern. It has been reported that exposure to various organic solvents cause diverse adverse effects on the functional integrity of different tissues in the biological systems (Robert-Gnansia and Saillenfait, 2002; Faber *et al.*, 2006; Saillenfait *et al.*, 2006; Saillenfait *et al.*, 2007; Uboh *et al.*, 2008; Uboh *et al.*, 2009; Uboh *et al.*, 2010). Particularly, mixtures certain of

hydrocarbon, gasoline vapours, lead, insecticides, pesticides and other chemical solvents have been reported to induce some degrees of adverse effects on the functional integrity of the renal tissues in humans and experimental animals (Dioka *et al.*, 2004; Boogaard *et al.*, 2005; Adeniran *et al.*, 2006; Hernandez-Serrato *et al.*, 2006; Patil *et al.*, 2007; Uboh *et al.*, 2008, 2009, 2011; Salawu *et al.*, 2009). These adverse effects generally result in the impairment of the renal function. Various biological tissues are known to be highly prone to attack by generation of excessive concentration of free radicals. Many pharmaceuticals and chemical pollutants may cause toxicity to these organs through various mechanisms. Particularly, exposure to gentamycin, ivermectin, albendazole, nitrocellulose thinner and petroleum products has been reported to exert deleterious effects on the renal tissues, hence nephrotoxicity (Arise and Malomo, 2009; Padmini and Kumar, 2012; Uboh *et al.*, 2009, 2010, 2012; Varghese *et al.*, 2013). Chemical-induced nephrotoxicity is therefore an important cause of renal failure. Many antioxidants have been used to protect the biological tissues against the free radical challenges. While most of the antioxidants are of natural origin, various classes of phytochemicals are well established to be antioxidants. Among these phytochemicals include such phenolic compounds as flavonoids, quinones, coumarins, lignans, stilbenes and tannins, nitrogen compounds as alkaloids, amines and betalains, vitamins and terpenoids, including carotenoids (Varghese *et al.*, 2013). In the recent times, there have been several research investigations on the possibilities of using plant extracts containing antioxidant principles as organ tissues' protective agents. In the present study, the possible nephroprotective effect of *Costus afer* leaves' uice on nitrocellulose thinner -induced nephrotoxicity was assessed in male rats.

MATERIALS AND METHODS

Chemicals and reagents: Nitrocellulose thinner (POLYGARD®, MISWA CHEMICALS LTD, England), Randox, Dialab diagnostic, CRESCENT diagnostic and AXIOM Gestllschaft for Dignostica and Biochemica mBH reagent kits were used for the biochemical assays. All the other chemicals used in this study were of high grade of purity, commercially available.

Animal handling and experimental design: Eighteen mature male albino wistar rats, weighing between 180 to 200 g were obtained from Biochemistry Department Experimental Research Animal House of the University of Calabar, Calabar, Nigeria. They were fed with a standard laboratory diet and tap water. Illumination was 12 h light/dark cycle and room temperature was $25\pm 2^{\circ}\text{C}$. The animals were divided into three groups, [i.e., one control (I) and two experimental groups (II and III)], which consisted of 6 apparently normal albino wistar rats per group. The experimental groups II and III were orally administered $30.0\text{ mg kg}^{-1}\text{ b.wt.}$ and NCT ($30.0\text{ mg kg}^{-1}\text{ b.wt.}$) in combination with $600\text{ mg kg}^{-1}\text{ b.wt.}$ of CALJ (one hour before NCT administration), respectively, while the control group I was given distilled water, for 28 days. After the 28th day, the animals were sacrificed following 12 h fast and the required tissues collected for nephrotoxicity studies. In this study, all the animal experimentations were carried out following the guidelines for the care and use of laboratory animals obtained from the Institutional Animal Ethics Committee. The research work was carried out between October and November, 2013.

Collection and handling of blood serum for analyses: Twenty-four hours after the 28th day of exposure, the animals were anaesthetized with chloroform vapors and dissected following 12 h fast. Whole blood from each animal was collected by cardiac puncture into well labeled non-heparinized sample tubes and allowed to clot for 3 h in iced water. The serum was separated

from the clots after centrifuging at 10,000 rpm for 5 min into well-labeled plain sample bottles and used for some serum biochemical assay. The kidney tissues were also collected for some tissue biochemical indices and histopathological assay.

Biochemical assays

Serum urea and blood urea nitrogen: The concentration of urea in serum was estimated by the endpoint colorimetric method using Dialab reagent kits (Searcy *et al.*, 1967). In this method, urease enzyme hydrolyses urea to ammonia and carbon dioxide. The ammonia so formed reacts with alkaline hypochloride and sodium salicylate in the presence of sodium nitroprusside to form a coloured chromophore which was measured with DREL 3000 HACH (England) model spectrophotometer.

Serum uric acid level: The concentration of uric acid in the serum of the experimental animal was estimated by enzymatic colorimetric test using CRESCENT diagnostic kit (Saudi Arabia) according to the procedure given in the kit protocol.

Serum creatinine: The concentration of serum creatinine was assayed based on the reaction of creatinine with an alkaline solution of sodium pirate to form a red complex. The red coloured complex which is proportional to the concentration of creatinine in the sample was measured spectrophotometrically.

Kidney tissue Glutathione Peroxidase (GPx): The activity of glutathione peroxidase in the kidney tissue homogenate was determined following the method described by Paglia and Valentine (1967).

Kidney Tissue Superoxide Dismutase (SOD) Activity: The activity of superoxide dismutase in the kidney tissue homogenates was determined by its ability to inhibit auto-oxidation of epinephrine which was estimated by the increase in absorbance at 480nm as described by Sun and Zigma (1978).

Kidney tissue lipid peroxidation: Malondialdehyde (MDA), an index of lipid peroxidation, was determined using the method of Buege and Aust (1978).

Histopathological examination: Sections were cut from the kidney tissues of the rats in the three respective groups for histopathological assay. The sections were fixed in 10% neutral buffered formalin and processed to paraffin wax. Five microns sections were stained with Haematoxyllin and Eosin (H and E) and Periodic Acid Schiff (PAS) and then examined under light microscope at 400 magnifications.

Statistical analysis: All the data obtained for the biochemical assay results were presented as Mean±SEM. These results were analyzed using the Statistical Package for Social Sciences (SPSS for windows, version 17.0). Comparison were made between and within the experimental groups using one-way Analysis of Variance (ANOVA), followed by pair wise comparison between each test and control groups using Student's t-test. Values of less than 0.05 (i.e., $p < 0.05$) were regarded as statistically significant.

RESULTS

The results of this study, on the effect of oral administration of *Costus afer* leaves' juice on the functional integrity of the renal tissues in rats orally exposed to nitrocellulose thinner, are shown in Table 1 and 2, as well as Fig. 1-3. The results showed that exposure to nitrocellulose thinner caused a significant ($p < 0.05$) increase in serum urea, BUN, uric acid, creatinine and renal tissue MDA levels by 160.1, 173.5, 120.0, 162.5 and 178.8%, respectively, as well as decrease in renal tissue GPx and SOD activities by 69.1 and 66.1%, respectively, compared to control group. Histopathological studies showed cell shrinkage and shrunken nucleus, with disruption of glomerular capillaries, vacuolar degeneration of tubular epithelial cells in the renal tissues of rats exposed to nitrocellulose thinner (Fig. 2), compared to the control (Fig. 1). These results indicated that nitrocellulose thinner's constituents and their metabolites are nephrotoxic and that exposure to the solvent may constitute a risk factor for nephrotoxicity.

It was however, observed that administration of *Costus afer* leaves' juice provided protection to the renal tissues against the nitrocellulose thinner-induced toxicity. These nephroprotection properties of *Costus afer* leaves' juice were clearly indicated by the reversal of the serum urea, BUN,

Table 1: Some renal function serum metabolites of rats orally exposed to nitrocellulose thinner and treated with *Costus afer* leaves' juice

Group	Treatment	Urea (mg dL ⁻¹)	BUN (mg dL ⁻¹)	Uric acid (mg dL ⁻¹)	Creatinine (mg dL ⁻¹)
1	Distilled water	14.8±4.6	6.8±2.4	0.5±0.2	0.8±0.3
2	NCT	38.5±9.8*	18.6±7.2*	1.1±0.9*	2.1±1.3*
3	NCT+C. <i>afer</i>	18.1±3.7	8.2±1.6	0.6±0.3	1.1±0.2

All values are presented as Mean±SEM, n = 6, *p<0.05 compared, respectively with groups 1 and 3, NCT: Nitrocellulose thinner

Table 2: Renal tissue MDA, SOD and GPx activities of rats orally exposed to nitrocellulose thinner and treated with *Costus afer* leaves' juice

Group	Treatment	MDA (%TBARS)	SOD (U mg ⁻¹ protein)	GPx (U mg ⁻¹ protein)
1	Distilled water	13.2±3.1	158.6±3.1	147.8±4.8
2	NCT	36.8±5.6*	53.8±2.3*	45.6±9.4*
3	NCT+C. <i>afer</i>	15.1±2.4	149.7±3.5	139.8±5.1

All values are presented as Mean±SEM, n = 6, *p<0.05 compared, respectively with groups 1 and 3, NCT: Nitrocellulose thinner



Fig. 1: Section of rat kidney in control group with normal glomeruli in the cortex, H and E, 400



Fig. 2: Section of rat kidney in group 2 administered NCT only, showing cell shrinkage and shrunken nucleus, with disruption of glomerular capillaries, vacuolar degeneration of tubular epithelial cells, PAS, 400

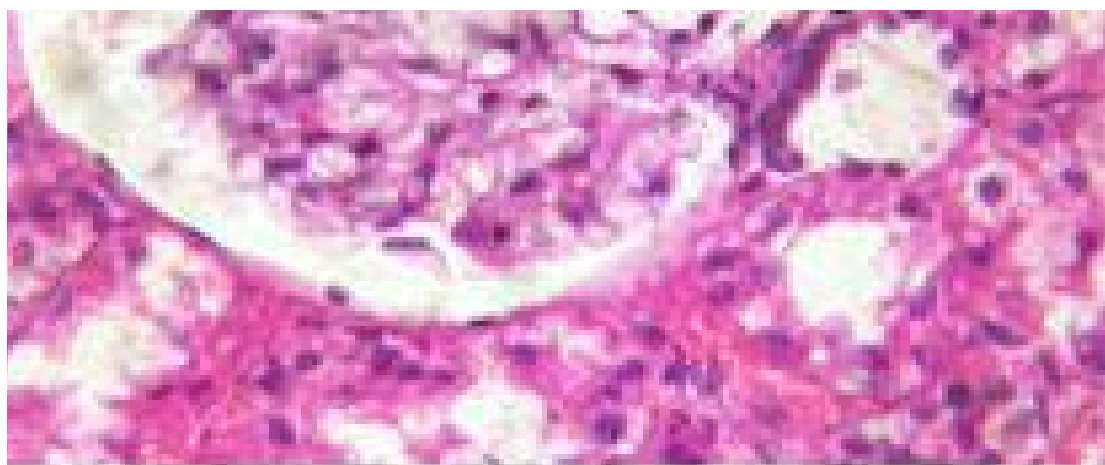


Fig. 3: Section of rat kidney in group 3 with restored normal macula densa, H and E, 400

uric acid and creatinine levels, as well as renal tissue MDA, GPx and SOD activities to the control range. Also, the tubular epithelial necrosis and atrophy of the glomeruli, recorded to be associated with exposure to nitrocellulose thinner were restored to normal on treatment with *Costus afer* leaves' juice (Fig. 3). The results of this present study therefore give a strong indication that *Costus afer* leaves' juice contain some active principles with potent nephroprotective effect against nitrocellulose thinner-induced renal tissues damage and that *Costus afer* leaves' juice may be beneficial in the treatment of various clinical disorders associated with nephrotoxicity.

DISCUSSION

Several chemical pollutants in the environment, drugs of clinical importance, such as acetaminophen and gentamicin and particularly drugs used in the treatment of specific diseased

conditions as cancer and tuberculosis can cause severe organ tissue toxicities. Some of these chemical substances are reported to produce renal toxicity due to generation of free radicals in the course of their metabolism. Increased generation of free radicals overwhelms the endogenous protective mechanism, thereby resulting in the nephrotic damage and necrosis (McGinness *et al.*, 1978). Plant extracts are known to contain a wide variety of free radical scavenging molecules, such as phenolic compounds (e.g., flavonoids, quinones, coumarins, lignans, stilbenes, tannins), nitrogen compounds (alkaloids, amines, betalains), vitamins, terpenoids (including carotenoids) and some other endogenous metabolites, which are rich in antioxidant. Hence, the intake of natural antioxidants has been reported to be associated with reduced risks of organ toxicities (Jain and Agrawal, 2008). In this study, it was observed that oral exposure to nitrocellulose thinner caused adverse alteration of renal functions in rats. This alteration was indicated by increased serum creatinine and urea levels, as well as increased MDA, accompanied with decreased GPx renal tissue contents in rats. The elevation of serum urea and creatinine levels observed to be associated with oral exposure to nitrocellulose thinner in this study was taken as the index of nephrotoxicity. These results are consistent with the result of our previous work on nitrocellulose thinner-induced nephrotoxicity in experimental animals (Uboh *et al.*, 2012). The results also indicated that the increased serum creatinine and urea levels, as well as elevated MDA and GPx renal tissue contents returned approximately to the normal control levels when the animals were administered with *Costus afer* leaves' juice, 1 h before nitrocellulose thinner. This indicates that the active principles in *Costus afer* leaves' juice possess a protective potential on the nitrocellulose thinner-induced nephrotoxicity.

Lipid peroxidation was also monitored in this study by measuring the level of MDA resulting from free radical damage to membrane components of the renal tissue cells. A significant increase in the MDA concentration was recorded in the renal tissues of rats treated with nitrocellulose thinner alone. This suggested that nitrocellulose thinner induced free radical production causing oxidative damage to the renal tissues. Various plant extracts have been reported to be effective in protecting against chemical-induced nephrotoxicity (Shirwaikar *et al.*, 2003; Salawu *et al.*, 2009; Gowrisri *et al.*, 2012; Varghese *et al.*, 2013). This study showed that *Costus afer* leaves' juice significantly attenuated the increase of MDA concentration in kidney tissue. According to Anyasor *et al.* (2010), extracts from different parts of *C. afer* possess high phenolic contents, with significant antioxidant and inhibition of lipid peroxidative activities. Plant phenolics have been reported to be the major group of compounds acting as primary antioxidants or free radical scavengers (Kahkonen *et al.*, 1999). Also, the therapeutic potential of antioxidants in controlling degenerative diseases with marked oxidative damage from reactive oxygen species or free radicals have been reported (Tripathi, 1999; Vani *et al.*, 1997). The results recorded in this study may probably be attributed to the free radicals scavenging and antioxidant properties of the chemical principles in *Costus afer* leaves' juice.

The results of study also showed that the activities of renal tissues GPx and SOD significantly decreased on administration of nitrocellulose thinner alone and increased when the animals were administered with *Costus afer* leaves' juice before nitrocellulose thinner administration. GPx and SOD are known to play a multiple role as an antioxidant agent in the biological systems. Particularly, it is reported to function as a scavenger of ROS, including hydroxyl radicals, singlet oxygen, nitric oxide and peroxyxynitrite (Halliwell *et al.*, 1992). It has been reported that some plant extracts increase the activities of reduced glutathione and glutathione peroxidase in various biological tissues (Varghese *et al.*, 2013). Moreover, antioxidant and protective properties

of various plant extracts against different biological tissue damage have been reported (Dash *et al.*, 2007; Oboh, 2008; Arhoghro *et al.*, 2009; Tiwari and Khosa, 2010; Sasidharan *et al.*, 2010). Hence, report of the antioxidant and protective effects of *Costus afer* leaves' juice against nitrocellulose thinner-induced nephrotoxicity are in agreement with the nephroprotective activity of *Benincasa hispida* (Thunb.) Cogn. Fruit extract (Varghese *et al.*, 2013), anti-oxidant and nephroprotective activities of *Cassia occidentalis* leaf extract (Gowrisri *et al.*, 2012) against paracetamol induced nephrotoxicity, protective effect of *Pongamia pinnata* flowers against cisplatin and gentamicin induced nephrotoxicity in rats (Shirwaikar *et al.*, 2003), protective activities of *Cucurbita maxima* aerial parts (Saha *et al.*, 2011) and leaves of *Parkinsonia aculeata* linn (Shah and Deval, 2011) against paracetamol induced hepatotoxicity in rats. The nephroprotective effects of *Costus afer* leaves' juice in nitrocellulose thinner induced nephrotoxicity may be due to active principles in the juice. These active principles are assumed to have played a vital antioxidant role in the nitrocellulose thinner treated rats. This assumption is evidenced by the restoration of the renal tissue GPx level, in the nitrocellulose thinner treated rats administered *Costus afer* leaves' juice, to normal control range. Hence, it may be concluded that *Costus afer* leaves' juice contain some antioxidant principles with nephroprotective potential against nitrocellulose thinner induced nephrotoxicity in rats.

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