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EFFECT OF AQUEOUS EXTRACT OF *Irvengia gabonensis* ON ACETAMINOPHEN INDUCED NEPHROTOTOXICITY IN RATS

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ABSTRACT
The use of medicinal plant to prevent and/or cure liver problems is a practice not peculiar to developing countries. This research work evaluated the nephrocurative ability of aqueous seed extract of Irvengia gabonensis on Acetaminophen Induced Nephrotoxicity. A total of thirty albino rats were grouped into six groups (GI – GVI) of five rats each. GI served as normal control, GII served as positive control, GIII, GIV and GV were administered with the extract at a dose of 50mg/Kg, 100mg/Kg and 150mg/Kg respectively while GVI rats were administered with standard drug (Vit E) at a dose of 10mg/Kg. Kidney damage was induced in groups (II-VI) using 800mg/Kg of acetaminophen administered orally, rats from group I and II were euthanized24 hours after acetaminophen administration to confirm inducement of kidney damage. Groups III, IV, V and VI were administered with the respective doses for two weeks. A significant decrease ($p<0.05$) in mean serum level of Urea, Potassium (K^+), Chloride (Cl^-) and Creatinine with a significant increase ($p<0.05$) in the level of serum Sodium (Na^+) and Bicarbonate ($HCO3^-$) was observed when compared with positive control. The nephrocurative effect of the plant could be due to its reported secondary metabolites contents.
Keywords: Acetaminophen; Irvengia gabonensis; Kidney function indices and Nephrocurative.

INTRODUCTION

Medicinal plants are the back bone of traditional medicine. The use of plant preparation for treatment and prevention of ailments traditionally depends on experience and superstitious beliefs passed from generation to generation, virtually by the word of mouth (Sofowora, 1993). Researches on medicinal plants are on the increase globally. Various parts of medicinal plants (stem, bark, seeds and roots) have been used in various systems as they have potential effects against numerous diseases. Medicinal plants have been used as a source of medicine to treat/manage diseases for centuries (Sofowora, 1993).

Irvingia gabonensis, popularly known as 'ogbono' and commonly called 'African mango' or "Wild mango", is an indigenous forest tree belonging to the group of plants classified as "non-timber forest products (NTEP). It belongs to the Irvingiaceae family of plants. The tree attains a height of up to 30 meters and about 1.0 meter in girth when fully developed. The leaves are simple and alternate, up to 10 cm long with deciduous stipples up to 1.2cm long, with leaves encircling scares on the branchlets (Matos *et al*., 2009)

Studies undertaken on the nutritional and medicinal value of *Irvingia gabonensis* have been reported and methanol extract of *Irvingia gabonensis* was reported to be effective in the treatment of bacterial and fungal infections. Seeds oils have extensive demands both for human consumption and for industrial applications and also have been rated as the second most valuable commodity in the world trade today. Numerous researchers, among others have carried out a lot of analytical works on seeds primarily because of extensive and increasing demands for both human consumption and numerous industrial applications (Tchoundjeu and Atangana, 2007). Traditionally, *Irvingia gabonens* bark is used as analgesic, antiseptic, antipyretic and also in the treatment of diarrhea and hernia, while leaf extract is used as a febrifuge and the kernels in

the management of diabetes (Burkill, 1985; Okolo *et al*., 1995). Raji *et al* (2000) reported that methanol extract of its stem bark has anti-diarrheal and antiulcer properties in rats. It has been used wholly or as supplement in the treatment of type II diabetics and in reducing obesity (Omoruyi and Adamson, 1994). Oben *et al*(2008) stated that *Irvingia gabonensis* seed extract resulted in a significant inhibition of intracellular triglycerides.

Kidneys are organs that serve several essential regulatory roles in most animal species, including vertebrates and some invertebrates. They are essential in the urinary system and also serve homeostatic functions such as the regulation of electrolytes, maintenance of acid-base balance, and regulation of blood pressure (via maintaining salt and water balance). They serve the body as a natural filter of the blood, and remove wastes which are diverted to the urinary bladder. Nephrotoxicity is a poisonous effect of some substances notably toxic chemicals and drugs on the kidneys (Galley, 2000). It's the most common kidney problem and occurs when the body is exposed to a drug or toxin that causes damage to the kidneys. When kidneys damage occurs, the body is unable to get rid of excess urine and wastes. This cause a rise in blood electrolytes such as Potassium, Sodium, Chloride and Magnesium.

Acetaminophen is most widely used in the world as an analgesic and antipyretic drug that is safe at therapeutic dosages. However, it is also known to cause hepatic necrosis and renal failure when overdosed in humans and animals (Ghosh *et al*., 2010). In human, acetaminophen represents a growing cause of renal failure in current medical practice. Acetaminophen-induced renal insufficiency is consistent with acute tubular necrosis, an increase in the plasma creatinine level and a decrease in the glomerular filtration rate (GFR).

This study was aimed at determining the curative effect of aqueous seeds extract of *Irvengia gabonensis* on kidney function indices (Urea, electrolytes and Creatinine) on acetaminophen induced kidney damage in order to give an insight on the possible nephrocurative effects of the extract.

MATERIALS AND METHODS

Study Animals

Male and female Albino rats weighing 100-120g were purchased from Department of Biological Sciences, Bayero University Kano. The animals were housed in colony cages at an ambient temperature (30-35^{o}C). The animals had free access to standard palletized grower feed and drinking water. Principle of laboratory animal care and ethical guidelines for investigation of experimental pain in conscious animals were observed during experimentation (NIH, 1996; Zimmermann, 1983).

Collection and Extraction of the Plant Material

Irvengia gabonensis seeds were bought from Yan lemo fruit market Zaria road Kano, Nigeria. The seeds were shade dried and ground into powder form out of which 100g of the powder was weighed and soaked in 500cm3 of distilled water for 24 hours. Thereafter, the solution was filtered and 10mL of the filtrate was evaporated to dryness in an oven at 40°C to produce a dark brown residue. The residue was weighed and the concentration of the filtrate was found to be 200mg/mL. This was administered to the animals according to the required dose using the relation (Muhammad *et al*., 2015).

$$\text{Volume to be administered (cm3)} = \frac{\text{Weight of rats (Kg)} \times \text{dose (mg/Kg)}}{\text{Concentration of the extract (mg/mL)}}$$

Experimental Design

Induction of kidney damage

Kidney damage was induced using acetaminophen according to the method of (Adeneye *et al*., 2008; Cekmen *et al*., 2009). Exactly 800mg/Kg of acetaminophen was administered by single dose orally. The volume of acetaminophen administered was determined by the weight of the rat according to the following relationship (Muhammad *et al*., 2015).

$$\text{Volume to be administered (cm3)} = \frac{\text{weight of rats (Kg)} \times \text{dose (mg/Kg)}}{\text{Concentration of Acetaminophen (mg/mL)}}$$

Effect of aqueous seed extract of *Irvengia gabonensis on* acetaminophen induced Nephrotoxicity

A total of 30 albino rats were grouped into six groups of five rats each.

Group I: Normal control; no kidney damage was induced and no extract was given

Group II: Positive control; induced with kidney damage, no extract was given

Group III: Induced with kidney damage and administered with the extract at a dose of 50mg/Kg

Group IV: Induced with kidney damage and administered with the extract at a dose of 100mg/Kg

Group V: Induced with kidney damage and administered with the extract at a dose of 150mg/Kg

Group VI: Induced with kidney damage and administered with Vit E a dose of 10mg/Kg

The rats from group I and II were euthanized 24 hours after acetaminophen administration and blood samples were analyzed for kidney function indices to confirm inducement of kidney damage. Group III, IV, and V were administered with the respective doses of aqueous seed extract of *Irvengia gabonensis* and group VI with vitamin E for two weeks.

Statistical Analysis

Results were expressed as mean ± standard deviation and analyzed using ANOVA, with P value <0.05 considered significant, a component of GraphPad Instat3 Software version 3.05 by GraphPad Inc.

RESULTS AND DISCUSSION

Table 1 present the result for kidney function analysis after 24 hours of acetaminophen administration. The results shows a significant increase ($p<0.05$) in the mean serum level of Urea, Potassium (K+), Chloride (Cl^-) and Creatinine with a significant decrease ($p<0.05$) in the level of serum Sodium (Na+) and Bicarbonate ($HCO3^-$) in Acetaminophen induced rats (Group II) compared with the control group (Group I).

Table 1. Kidney Function Indices of Rats after 24 hours of Acetaminophen Administration

	Urea (mg/dL)	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	Creatinine (µmol/L)	MDA (nMol/L)
GI	44.42 ± 4.03^{i}	135.75 ± 7.62^{j}	3.37 ± 0.11^{k}	56.09 ± 4.87^{L}	24.72 ± 3.32^{m}	46.00 ± 0.0^{n}	0.15 ± 0.26^{0}
GII	146.74 ± 6.16^{i}	104.67 ± 2.54^{j}	6.56 ± 0.16^{k}	148.78 ± 8.79^{L}	11.64 ± 0.35^{m}	168.67 ± 0.56^{n}	0.53 ± 0.20^{0}

Values are presented as mean ± SD, n = 5. Values bearing the same superscripts in the same column are significantly different ($p<0.05$)

Table 2 shows the result for kidney function analysis after two weeks administration of the extract administration. A significant decrease ($p<0.05$) in the mean serum level of serum Urea, Potassium (K+), Chloride (Cl^-) and Creatinine with a significant increase ($p<0.05$) in the level of serum Sodium (Na+) and Bicarbonate ($HCO3^-$) was observed in a dose dependent pattern in extract administered groups compared with positive control.

Table 2. Kidney Function Indices of Rats afterTwo Weeks of Extract Administration

	Urea (mg/dL)	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	Creatinine (µmol/L)	MDA (nMol/L)
GI	44.42 ± 4.03^{a}	135.75 ± 7.62^{a}	3.37 ± 0.11^{a}	56.09 ± 4.87^{a}	24.72 ± 3.32^{a}	46.00 ± 0.01^{a}	0.15 ± 0.26^{a}
GII	$146.74\pm6.17^{a,b,c,d}$	$104.24\pm2.54^{e,b,c}$	$6.56\pm0.16^{a,b,c,d}$	$148.78\pm8.79^{a,b,c,d}$	$11.64\pm0.35^{a,b,c,d}$	$168.67\pm0.56^{a,b,c,d}$	$0.53\pm0.20^{a,b,c,d}$
GIII	124.54 ± 6.17	106.48 ± 3.88	3.51 ± 0.05^{a}	102.69 ± 7.04^{a}	13.86 ± 2.71	105.33 ± 0.55^{b}	0.42 ± 0.30^{b}
GIV	86.86 ± 7.27^{b}	111.84 ± 6.80^{a}	2.28 ± 0.06^{b}	92.30 ± 6.14^{b}	15.29 ± 0.06^{b}	59.33 ± 0.60^{c}	0.26 ± 0.26^{c}
GV	45.79 ± 4.21^{c}	131.05 ± 6.40^{b}	3.76 ± 1.00^{c}	55.72 ± 7.45^{c}	23.85 ± 3.55^{c}	43.85 ± 0.27^{d}	0.17 ± 0.42^{d}
GVI	53.87 ± 1.17^{d}	140.37 ± 2.55^{c}	2.18 ± 0.06^{d}	87.38 ± 3.66^{d}	18.64 ± 0.42^{d}	47.07 ± 2.66^{e}	0.19 ± 0.40^{e}

Values are presented as mean ± SD, n = 5. Values bearing the same superscripts in the same column are significantly different ($p<0.05$)

DISCUSSION

Acetaminophen induced renal insufficiency is consistent with hepatic necrosis and renal failure in humans and animals (Ghosh *et al*., 2010). About 5-15 percent of Acetaminophen is oxidized to benzoquinoneimine, a reaction catalyzed by mixed function oxidase enzyme. The benzoquinoneimine is conjugated by the glutathione pathway to form mecaptuic acid and cysteine conjugates. Oxidation occurs to a small extent after therapeutic doses and becomes more significant after large overdose (Murray *et al*., 2006). The benzoquinoneimine formed is conjugated to the nucleophilic GSH in a reaction catalyzed by glutathione-s-transferases which are present in high amount in the liver cytosol (Murray *et al*., 2006). If this potentially toxic intermediate (benzoquinoneimine) was not conjugated to GSH, it would be free to combine with DNA, RNA and cell protein which could lead to serious cell damage. This metabolite appears to be the agent responsible for hepatic necrosis in Paracetamol overdose. It has also been postulated that increased levels of serum urea

and creatinine are linked to kidney disease. The observed increase in serum levels of urea, potassium (K^+), chloride (Cl^-), creatinine and MDA with a significant decrease ($p<0.05$) in bicarbonate ($HCO3^-$) and sodium (K^+) in acetaminophen administered groups compared with the normal control indicates successful induction of kidney damage (Ghosh *et al*., 2010).

The observed a decrease in serum levels of urea, K+, Cl^-, creatinine and MDA, with an increase in $HCO3^-$ and Na^+ when compared with the test control groups may suggest the potential nephrocurative activities of the extract which may be due to its reported phytochemicals (tannins, alkaloids, glycoside, flavonoids and terpenoids) constituent of the plant. A possible mechanism for the nephrocuration may be due to their antioxidant properties, which could counteract the toxic effect of benzoquinoneimine produced through Paracetamol metabolism (Toma*et al*., 2009).

CONCLUSION

The results of the present study showed *Irvengia gabonensis* seed extract to poses nephrocurative effects against acetaminophen induced kidney damage which may be mediated through its antioxidant ability.

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