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## RESEARCH ARTICLE

### BIOLOGICAL RESPONSE OF MALE WISTAR RATS TO CRUDE EXTRACT OF *Ficus exasperata* (VAHL)

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#### ABSTRACT

Activities of *F. exasperata* (Vahl) leaf extract on the liver function of albino rats were studied. Thirty two mature albino rats weighing between 130-150g were divided into four groups of eight rats. Group 1 (control) received 0mg/kg BW, and Group 2 received 50mg/kg BW, Group 3 received 100mg/kg BW, and Group 4 received 150mg/kg BW for 8 weeks. The rats in each group were sacrificed and blood samples collected by cardiac puncture into heparinized sample bottles. The results showed that the leaf extract of *F. exasperata* caused significant effect ( $P < 0.05$ ) on Aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin and conjugated bilirubin levels. The histological architecture of the liver and kidney cortex revealed several damages, especially in the kidney cortex. This is an explicit indication that the use of *F. exasperata* leaf extract in herbal medicine without proper scientific evaluation might be dangerous to health.

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#### INTRODUCTION

Despite the availability of modern medicine, many people in the developing countries, especially in the rural areas still rely on traditional healers and medicinal plants to meet their primary healthcare needs and that of their domestic animals. In recent times, however, herbal remedies are becoming indispensable and constitute an integral part of primary health care systems in so many nations. Several documentations on the medicinal importance of traditional plants in Nigeria and their active ingredient(s) have been reported (Adesina, 1999). *Ficus exasperata* is a small tree or shrub up to 20m tall with scabrous, ovate leaves. It bears figs, which usually appear in pairs in the leaf axils. The bark is smooth, grayish cream with brown streaks and it exudes gummy sap. Several parts of *F. exasperata* have been used in traditional medicine for treatment of several pathological disorders (Keita, 1999; Ake, 1990; Akah *et al.*, 1998). The ethnomedicinal uses of plants, especially *F. exasperata* would be useful to scientists for drug production (Fasola and Egunyomi, 2008). It is a high time that we began to conserve and domesticate through tissue cultured and genetically manipulating /modifying these plants of medicinal import as not to allow them to go into extinction. On the other hand, the active substances could be isolated and purified as is done with artemisinin in *Artemisia annua*, which has become an active component of most anti-malarial drugs ie Artemisinin Combined Therapies (ACTs).

The efficacy of any drug is dependent on the non-toxic effects on the system of the recipient but exerting its positive effects on the target ailment. Most herbs (drugs) when taken are primarily metabolized by the liver and accumulation of their products can cause cell injury and death. Incidentally, this affects patients with liver diseases, where the processes of detoxification and excretion may have been dangerously altered. Interestingly, there are liver enzymes that act as indicators to either normal functioning or malfunction/dysfunction of the liver. Example is the alkaline phosphatase in the cells lining of the biliary duct of liver whose level in plasma may rise with large bile duct obstruction, interphatic cholestasis or infiltrative substances and diseases of the liver (Kelsey, 1980). The ratio of aspartate aminotransferase (AST) to alkaline phosphatase (ALP) is sometimes useful in differentiating causes of liver damages (MacSween and Whaley, 1992). Significantly, elevated levels of ALT often suggest the existence of other medical problem such as viral hepatitis, congestive heart failure, liver damage, biliary duct problems (MacSween and Whaley, 1992). It has also been reported that albumin level is decreased in chronic liver disease as well as in cirrhosis and nephritic syndrome (Varley *et al.*, 1991). A study by Ijeh and Agbo (2006) indicated that high doses of the ethanolic leaf extract of *F. exasperata* could lead to toxic injury in the kidneys, which might interfere with renal tubular function and induce renal failure.

This present study is aimed at evaluating the impact of leaf extract of *F. exasperata* on liver biochemistry and its effect on cyto-architecture of the liver and kidney. This

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will help in no small measure to elucidating its suitability for use as a therapeutic herb.

## MATERIALS AND METHODS

### Plant collection and preparation of extraction

Leaves of *F. exasperata* was collected from Calabar Metropolis and certified by the herbarium unit of the Department of Botany, University of Calabar, Calabar, Nigeria. The leaves were washed and dried at room temperature (25°C) and subsequent drying in the oven (Continent, MG800G) for ten minutes. The dried leaves were then ground using an electric blender (Orbit, BL 919) to a powdery form. Two hundred grammes of the ground material were soaked in 500ml of 98% ethanol for 48hrs stirring at intervals of 10 minutes. The extract was filtered through a muslin cloth and the concentrated extract was allowed to dry at room temperature and stored in a refrigerator at about -4°C until required.

### Experimental animal and administration of extract

Thirty two clinically healthy male Wistar rats of about two months old weighing between 130-150g were housed in cages under standard laboratory condition of 12h light/dark cycle throughout the experimental periods. The rats were left to acclimatize for two weeks with free access to water and feed. Four experimental groups of eight rats each were used for the study. Rats in group 1 served as control and received 1ml of the vehicle (normal saline) and normal chow throughout the experimental periods. Group 2 rats received 50mg/kg BW of *F. exasperata* extract while rats in group 3 and 4 received 100mg/kg BW and 150mg/kg BW of the extract, respectively. The administration lasted for eight weeks through oral gavage. 24 hours after the expiration of the treatment regimen, the rats were sacrificed using chloroform anaesthesia. The liver and kidney were removed and weighed. Blood was taken from the heart through cardiac puncture and placed in heparinized sample bottles. The liver and kidney were stored in bouin's solution for histological studies.

### Data Collection

Data on Aspartate Aminotransferase (AST), Alkaline Phosphate (ALP), Alanine Transaminase (ALT), Total Bilirubin and Conjugated Bilirubin were collected and subjected to analysis of variance (ANOVA) while Least Significant Different Test (LSD) was used to separate significant means (Obi, 2002).

## RESULTS

### Aspartate Aminotransferase (AST)

The administration of *F. exasperata* leaf extract on male albino rats had significant effect ( $P < 0.05$ ) on the Aspartate aminotransferase (AST) level. The trend was not consistent, though it seems dose dependent as the effect increased till 100mg/kg (582.33 I $\mu$ /L) but reduced to 437.0 I $\mu$ /L when the rats were administered with the extract dosage of 150mg/kg (Table 1).

### Alkaline phosphate (ALP)

The effect of *F. exasperata* leaf extract on alkaline phosphate (ALP) level did not follow the pattern of the effect on Aspartate aminotransferase. When the rats were treated with 150mg/kg, the alkaline phosphate (ALP) level reduced significantly ( $P < 0.05$ ) but at 50mg/kg, the ALP

level increased at its peak, when compared with the control and other treatment groups (Table 1).

### Alanine Transaminase (ALT)

There were significant differences ( $P < 0.05$ ) between the levels of Alanine transaminase (ALT) among the treated groups compared to the control. The level of alanine transaminase was highest in the rats administered with 50mg/kg of the extract. However, there was no significant difference ( $P > 0.05$ ) between the rats administered with 100mg/kg and 150mg/kg of doses of the leaf extract (Table 1).

### Total Bilirubin/ Conjugated Bilirubin

The total bilirubin level differed significantly ( $P < 0.05$ ) as the dosage of *F. exasperata* leaf extract administration increases while conjugated bilirubin did not differ significantly ( $P > 0.05$ ) (Figure 1).

### Histology of the liver

The normal liver cell showed central vein with its endothelium intact. It shows normal liver architecture with hepatocytes arranged in plates radiating outwards from the central vein, and separated by endothelial lined sinusoids (Plate 1). The sinusoids bear the liver macrophages known as Kupffer cells. Treating rats with 50mg/kg of *F. exasperata* extract shows central vein with its endothelium intact though there are some areas of hepatocellular hypertrophy, hepatocellular hyperplasia and sinusoids sclerosis, indicating a damaging effect (Plate 2). When rats were treated with 100mg/kg of *F. exasperata* extract, the liver cells show denudation of the central veins endothelium. Hepatocellular hypertrophy and hyperplasia and sinusoidal sclerosis were also observed (Plate 3). There was central vein erosion when rats were treated with 150mg/kg of *F. exasperata* extract (Plate 4). The liver cells show areas of disorganized hepatocellular cyto-architecture having hepatic cells.

### Histology of the kidney

Rats in the control group reveal kidney cortex with glomerulus, Bowman's capsules, proximal convoluted tubules and other normal cyto-architecture of the kidney (Plate 5). The kidney cortex of rats treated with 50mg/kg of *F. exasperata* extract shows that there were segmental areas of glomerular tissue necrosis, reduced urinary space, denudation of proximal tubular epithelium and the presence of mononuclear cells in the renal cortical interstitial. This suggests chronic glomerulo-tubular necrosis (Plate 6). There was increase in intra glomerular mesangial tissue of rats treated with 100mg/kg of the leaf extract of *F. exasperata*. The urinary space was widening, thickening of the Bowman's capsule was seen and erosion of the tubular epithelial cells, interstitial edema and the presence of mononuclear cells in the interstitial (Plate 7). Micrograph of the kidney cortex of rats treated with 150mg/kg *F. exasperata* shows the presence of diffused necrosis of glomerular tissue and tubular epithelial necrosis (Plate 8). The kidney cortex shows areas of disorganized cyto-architecture of the renal cortical structures and diffused infiltration of the tissue with mononuclear cells.

## DISCUSSION

Majority of the world's population is dependent upon traditional medicine – the use of plants and plant extracts such as *Ficus exasperata*. This is particularly true of

**Table 1: Effect of *Ficus exasperata* leaf extract on biochemical indices**

Biochemical parameters ( $\mu\text{L}$ )	Leaf extract dosage (mg/kg BW)			
	0	50	100	150
Aspartate Aminotransferase (AST)	295.33 <sup>a</sup> ±2.97	390.67 <sup>b</sup> ±4.64	582.33 <sup>d</sup> ±2.85	437.0 <sup>c</sup> ±3.22
Alkaline Phosphate (ALP)	29.87 <sup>b</sup> ±0.77	65.08 <sup>d</sup> ±0.11	36.67 <sup>c</sup> ±0.24	23.5 <sup>a</sup> ±0.550
Alanine Transaminase (ALT)	44.13 <sup>a</sup> ± 0.35	76.57 <sup>c</sup> ±0.34	58.77 <sup>b</sup> ±2.00	58.77 <sup>b</sup> ±1.09
Total bilirubin	5.27 <sup>a</sup> ±0.270	9.97 <sup>b</sup> ±0.09	14.50 <sup>c</sup> ±0.44	37.57 <sup>d</sup> ±0.90
Conjugated bilirubin	2.03 <sup>a</sup> ±0.09	2.97 <sup>b</sup> ±0.09	3.80 <sup>a</sup> ±0.12	4.23 <sup>a</sup> ±0.09

Biochemical induces of rats reacted with *F. exasperata* (IU/l)

**Fig. 1. Effect of *F. exasperata* on liver enzymes of rats**

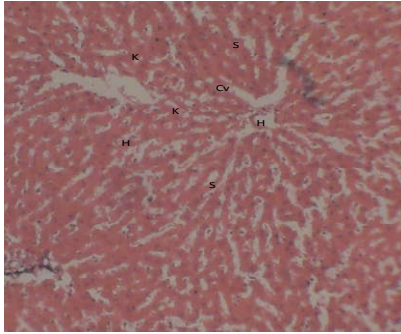
poorer section countries. This is cheaper than medicine available today tend to depend on herbal remedies which they believe is holistic in curing ailment. Oral drugs are meant to be reabsorbed in the intestine and transported to the portal vein in the liver. Substances such as these drugs are meant for metabolism (biotransformation) by the liver and can occur in five pathways: Activation of pro-drug (inactive drug) from the inactive form to an active form, conversion of an active drug into an inactive product, increase in activity of an active drug, increase / reduction in activity of an active drug, and elaboration of a total new drug, different from the one taken, which aimed at detoxifying these drugs (Katzung, 2004, Kumar et al., 2008).

Our results on AST, ALP and ALT indicated that as the doses of the extract increase, there was significant reduction in the levels of the enzymes in the liver. It does suggest that the liver cells have a mechanism of reducing the excess substances within the cells. At an optimal concentration of the extract in the system, the liver cells tend to metabolize it leading to the reduction of effect. This might be the reason underlying the low serum level of AST (437.01  $\mu\text{L}$ ), ALP (36.67  $\mu\text{L}$ ) and ALT (58.77  $\mu\text{L}$ ) observed when rats were administered with 150mg/kg, 100mg/kg and 50mg/kg, respectively of the *Ficus* extract. The extracts showed a dose-dependent

effect on the total bilirubin. However, the effect of the extract on the liver enzymes tends to be enzyme-specific. Apparently, the biosynthetic pathways leading to their production are different and as such the extract may have acted upon them differently and at varying intensities. There is no doubting the obvious that *F. exasperata* leaf extract contains different bioactive components at varying concentrations, which individually or synergistically might either boost or impede the production process of the different enzymes. Most of their contents are hepatic enzyme inducers that mean that they have the potential to cause an increase in the synthesis of the enzymes in the liver. When this happens the sizes of the liver cells increase

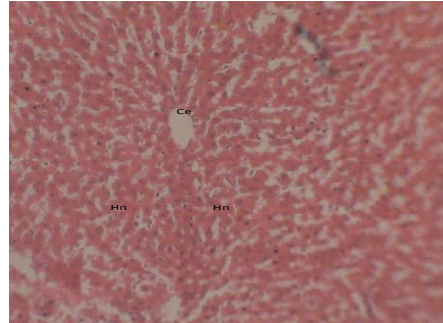
metabolism of these drugs (Guyton, 2006). This might account for the varying effects on the different liver enzymes.

Histological examination after the drug administration revealed that the leaf extract of *F. exasperata* did not have much damaging effect on the liver cells, which could be accounted for by the fact that the liver cells have inherent capacity to metabolize substances reducing them to non-toxic products. However, the kidney cells were worse affected by the administration of the extract. The leaf extract of *F. exasperata* may not have had any direct effect on the kidneys. The result seems to suggest that the by-products obtained affect hepatic metabolism might be responsible for the damage observed in the kidneys. This is consistent with the findings of (Ijeh and Ukwani., 2007, Ijei and Agbo., 2006), which indicate that the leaf extract of *F. exasperata* leads to toxic injury in the kidneys which might induce renal failure and interfere with renal tubular functions. However, it should be noted that the stability and capability of the liver and the kidney in tolerating substances such as drugs are not the same. The kidney might have been more susceptible to the influence of the extract.



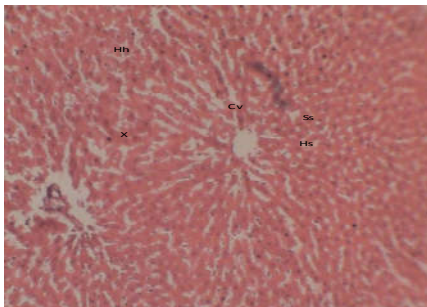
**PLATE 1** H/E  
x400

Photomicrograph of liver from control group 0mg/kg showing the central vein (cv) with its endothelium intact, Hepatocytes (H) (polygonal shaped cells with one to two nuclei) are arranged in plates radiating outwards from the central vein, and separated by endothelial lined spaces Sinusoids (S). Within the sinusoids are seen the sinusoidal lining endothelial cells, red blood cells, and the resident liver macrophages Kupffer cells (K).



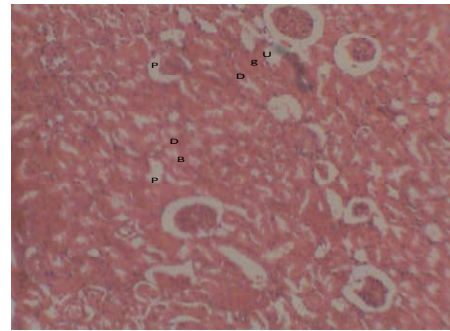
**PLATE 4** H/E  
x400

Photomicrograph of rats treated with 150 mg/kg, showing area of central vein erosion (Ce), areas of disorganized hepatocellular cyto architecture having necrotic hepatic cells (Hn).



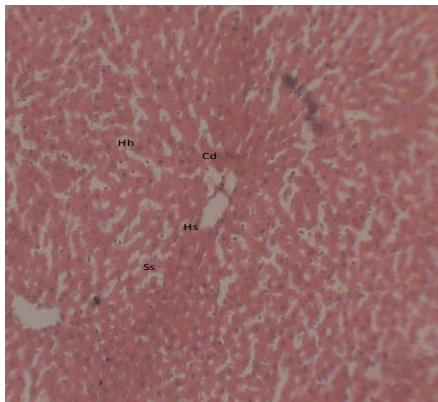
**PLATE 2** H/E x400

Rats treated with 50mg/kg with *f. exasperata*, showing the central vein (Cv) with its endothelium intact, areas of hepatocellular hypertrophy (Hh), hepatocellular hyperplasia (Hs), sinusoidal sclerosis (Ss). X = Artifact



**PLATE 5** H/E x400

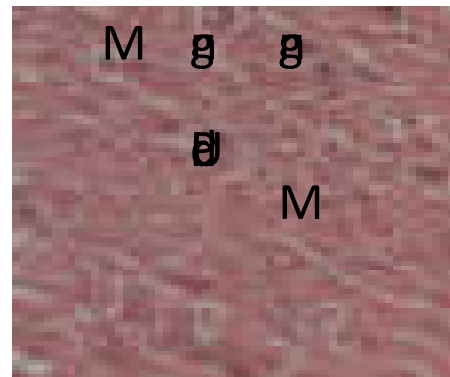
Photomicrograph of the kidney cortex of rats in control group, treated with leaf extract of *F. exasperata* showing the glomerulus (g), Bowman's capsule (B), urinary space (U), many proximal convoluted tubules (P) lined by simple cuboidal epithelial cells with brush borders, distal convoluted tubules (D) lined by simple cuboidal epithelium without brush borders, and the cortical interstitium (ci).



**PLATE 3** H/E X  
400

Treated rats with 100mg/kg of extract of *F. exasperata* showing denudation of the central veins endothelium (Cd).

Hepatocellular hypertrophy (Hh) and hyperplasia (Hs) with a focus of sinusoidal sclerosis (Ss).



Photomicrograph of the kidney cortex of rats treated with 50 mg/kg of *F. exasperata* showing segmental areas of Glomerular tissue necrosis (gn), reduced urinary space (Ur), denudation of proximal tubular epithelium (D), and presence of mononuclear cells (M) in the renal cortical interstitium. This is suggestive of chronic glomerulo tubular necrosis.

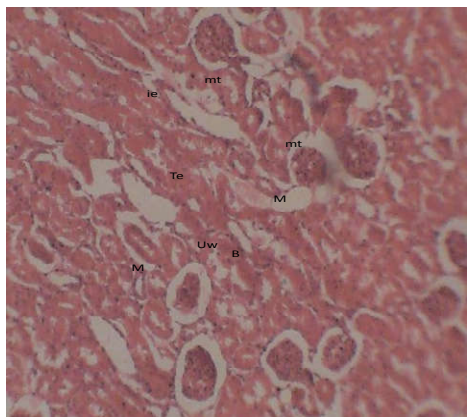


PLATE 7 H/E x400

Photomicrograph of the kidney cortex of rats treated with 100mg/kg, showing increased intra-glomerular mesangial tissue (mt), widening of the urinary space (Uw), thickening of the Bowman's capsule (B), erosion of the tubular epithelial cells (Te), interstitial edema (ie) and presence of mononuclear cells in the interstitium (M).

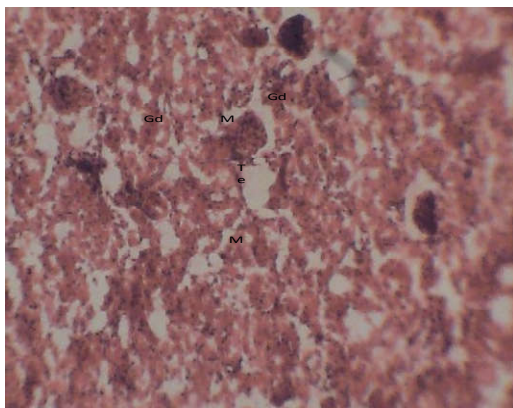


PLATE 8 H/E x400

Photomicrograph of the kidney cortex of rats treated with 150 mg/kg of *F. exasperata* showing, diffused necrosis of the glomerular tissue (Gd), diffused tubular epithelial necrosis (Te), disorganized cyto architecture of the renal cortical structures and diffused infiltration of the tissue with mononuclear cells (M). Features seen is suggestive of irreversible renal tissue destruction.

The results are an indication that medicinal plants, such as *F. exasperata* should be thoroughly screened before recommending it as therapeutic agents. It is arguable that

these effects or distortions as reported in our results are negligible but unfortunately might have a gradual damaging effect un-noticed in the recipient, if proper caution is not taken.

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