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EVALUATION OF THE HEPATOPROTECTIVE EFFECT OF *UVARIA AFZELII* AGAINST PARACETAMOL INDUCED LIVER TOXICITY IN WISTAR RATS.

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ABSTRACT: *Uvaria afzelii* (UV) Sc Elliot (Annonaceae) locally is used in the treatment of kidney disorders, digestive problems, liver disorders, diabetes as well as gonorrhea. This study aims to investigate the possible hepatoprotective activities of the crude aqueous root extract of *Uvaria afzelii* against Paracetamol-induced hepatotoxicity with Silymarin being used as a reference standard. Twenty five (25) adult wistar rats were randomly assigned into a control group (A) and four treatment groups (B, C, D and E) each containing five rats (n=5/group). Animals in each group were allowed access to 200g/day growers' mash and water *ad libitum*. Rats in the treatment groups were administered paracetamol orally at a dose of 800mg/kg body weight daily for fourteen days. Rats in group B were not pretreated while groups C, D and E rats were pretreated daily with 50mg/kg body weight of Silymarin, 250mg/kg and 500mg/kg body weight of crude aqueous extract of UV root respectively. The animals were sacrificed on the 15th day of the experiment and several serum markers, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP) and total protein (TP) was measured to assess the effect of the extract on paracetamol -induced hepatic damage. The study included histopathological examination of liver sections. Paracetamol induced a significant rise in AST, ALT, ALP and TP. Treatment of rats with the crude UV extract significantly ($P<0.05$) altered serum marker enzymes levels to near normal against acetaminophen treated rats. The activity of the extract was comparable to the standard drug, silymarin (50 mg/kg.). Histopathological changes of liver tissues were compared with respective control. Results indicate that *Uvaria afzelii* possesses hepatoprotective effect on paracetamol-induced hepatotoxicity in rats.

INTRODUCTION: *Uvaria afzelii* (UV) Sc Elliot (Annonaceae) is a small tree or spreading shrub growing up to 5 meters tall and is used locally, being harvested from the wild for food and medicines. It is mostly found in West tropical Africa - Sierra Leone to Nigeria. It is widely distributed and grown in the south and eastern part of Nigeria, where it is known by various local names such as; "gbogbonishe" (Yoruba), "Umimiofia" (Igbo) and "Osu-umimi" (Ukwani) [1].

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Locally it is used in the treatment of cough, vaginal tumour, breast aches, swollen hands and feet, diabetes as well as leucorrhoea and gonorrhea [2, 3]. Previous studies carried out on the plant to ascertain the claimed uses include it's reported bacteriocidal activity against gram positive and acid fast bacteria [4 ,5], anti-helminthic and anti-parasitic activities [6].

More so, some compounds have been isolated from the plant and they include; Syncarpic acid, Dimethoxymatteucinol, Emorydone, 2-hydroxydemethoxy matteucinol, Uvafzelic acid, syncarpurea and Afzeliindanone [7, 8]. Some of these compounds have been credited with specific biological activities as Afzeliindanone and Emorydone are reported to possess potent activity

against *trypanosomiasis brucei.* Silymarin is a standardized extract of the milk thistle plant (*Silybum marianum*) which majorly contains flavonoids; silybin, silybinin, silydianin and silychristin [9]. The seeds of this plant have been used over time for the treatment of liver and gall bladder disorders, including hepatitis, cirrhosis and jaundice. More so, the seeds protect the liver against poisoning from chemicals, environmental toxins, snake bites, insect stings, mushroom poisoning and alcohol [10]. Research overtime has demonstrated its use as a standard drug with exhibition of potent hepatoprotective activity at the dose range from 25-200 mg/kg [11, 12].

The liver is the key organ regulating homeostasis in the body. It is involved with almost all the biochemical pathways related to growth, fight against disease, nutrient supply, energy provision and reproduction [13]. More than 900 drugs have been implicated in causing liver injury [14] and it is the most common reason for a drug to be withdrawn from the market. Drug-induced liver injury is a potential complication of nearly every medication that is prescribed, because the liver is central to the metabolic disposition of virtually all drugs and foreign substances [15].

Paracetamol which is safe for use at recommended doses can also cause potential fatal liver damage in cases of acute overdose as it is it is one of the most common causes of poisoning worldwide and also the most common cause of acute liver failure in the United States and United Kingdom [16, 17]. An over dosage of paracetamol is known to be the cause of acute hepatic necrosis in both experimental animals [18, 19] and humans [20, 21].

However, conventional or synthetic drugs used in the treatment of liver diseases are sometimes inadequate and can have adverse effect [22]. So there is a worldwide trend to go back to the traditional medicinal plants [23, 24, 25]. In view of the undesirable side effects of synthetic agents researchers have develop scientific basis to evaluate traditional herbal medicines which are claimed to possess hepatoprotective activity [26]. Therefore, paracetamol mediated hepatotoxicity was chosen as the experimental model for liver injury in this study. The aim of this research was to investigate the effect of roots extracts of *Uvaria afzelii* on paracetamol induced liver damage and to compare the observed effects with a known hepatoprotective drug (Silymarin).

MATERIALS AND METHOD:

Plant Material

The roots of the plant *Uvaria afzelii* were gotten from a forest in Orhionmwon near Benin City during the month of July 2013. The plant was identified by Mr. Sunny Nweke, the curator of the Department of Pharmacognosy, Faculty of Pharmacy, University of Benin Edo state.

Preparation of Extract:

The roots of *Uvaria afzelii* were chopped into little bits and allowed to dry at room temperature for 5 weeks. The dried roots were pounded in a wooden mortar and pestle and milled into fine powder in an electric blender. 1.5kg of the powder was obtained soaked in 2litres of distilled water for 24hours. The mixture was filtered with a white filter paper and to obtain the filtrate which was evaporated at 60^{o}C in a vacuum rotary evaporator. The residue obtained was dried and stored in a refrigerator. A measured portion of the extract was dissolved in distilled water and an appropriate dose was administered to the animals daily.

Animal Care and Management:

A total of 25 adult male wistar rats were used for this study. The animals were inbred rats obtained from the rat Colony of the Animal House, Department of Anatomy, University of Benin, Benin City. The animals were housed and maintained in accordance with the guidelines of the Research Ethics Committee of the College of Medical Sciences, University of Benin, Benin City.

Treatment Regimen:

The rats were randomly assigned into a control group (A) and four treatment groups (B, C, D and E) each containing five rats (n=5/group). Animals in each group were allowed access to 200g/day growers' mash and water *ad libitum*. Rats in the treatment groups were administered 800mg/kg body weight of paracetamol daily for fourteen (14) days during the experimental period. Rats in group B were not pretreated while groups C, D &E rats were pretreated daily with 50mg/kg body weight of

Silymarin, 250mg/kg and 500mg/kg body weight of crude aqueous extract of UV root respectively.

Sacrifice of the Animals:

The experimental period lasted for 14 days and on the 15th day animals were sacrificed by cervical dislocation. A midline incision was made through the anterior abdominal wall of the rats. 5ml blood samples were collected from the descending abdominal aorta, in heparin coated bottles for biochemical analysis and the liver were excised and fixed in 10% buffered formal saline.

Assay of Marker Enzymes of Liver Damage:

The blood samples collected were centrifuged at 3000 revolutions/minute using a table-top centrifuge (Shanghai Surgical Instrument Factory, Shanghai, China) at 37 ºC for 15 min to separate the sera. Serum alanine (ALT) and aspartate (AST) aminotransferases and alkaline phosphatase (ALP) as well as (TP) Total Protein were assayed using Randox diagnostic kits [27].

Histological Procedure:

Following fixation, the tissues were dehydrated in ascending grades of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. Serial sections of 5 microns thick were cut using a rotatory microtome. The sections were later de-paraffinized for routine Hematoxylin and Eosin (H and E) staining using the method of Drury *et al.* [28]. The photomicrographs were obtained from sections using a research photographic microscope in the Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin City, Edo State, Nigeria.

Statistical Analysis:

The data generated were analyzed using descriptive and inferential statistics. All values were presented as mean ± Standard Error of Means (S.E.M.). All statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) (version 17). The significance of difference in the means of all parameters was determined using one way analysis of variance (ANOVA; 95% confidence interval). Least Significant Difference (LSD), post hoc test was carried out for all groups with control and comparison of all pairs of groups respectively. Values were statistically significant when probability is less than 0.05 ($P < 0.05$).

RESULT:

TABLE1: EFFECT OF CRUDE AQUEOUS ROOT EXTRACT OF *UVARIA AFZELII* ON SERUM LIVER ENZYMES IN PARACETAMOL INDUCED HEPATOTOXICITY IN RATS

	GroupA Control	GroupB (paracetamol 800mg/kg)	GroupC (Silymarin+paracetamol 800mg/kg)	GroupD UV(250mg/k) +paracetamol 800mg/kg)	GroupE UV(500mg/kg) +Paracetamol 800mg/kg)
ALP (IU/L)	27.50±2.50	48.00±2.89*	31.75±2.87**	37.00±3.03**	36.00±2.27**
(AST IU/L)	10.75±0.85	35.25±2.84*	11.00±1.08**	27.50±3.88**	18.00±4.32**
ALT (IU/L)	34.25±1.11	54.50±1.85*	33.50±1.71**	37.75±2.50**	36.75±2.14**
TP (IU/L)	6.98±0.11	5.73±0.15*	7.40±0.27**	6.58±0.27**	6.60±0.21**

*shows significance when compared with group1

**shows significance when compared with group2

The results of ALP, AST and ALT in control rats were 27.50±1.45, 10.75±1.53 and 34.25±1.11 respectively, whereas in paracetamol treated rats, these levels were elevated to 48.00±2.89, 35.25±2.84 and 54.50±1.85 respectively. *Uvaria afzelii* pretreatment at the dose 250mg/kg significantly ($P<0.05$) prevented the paracetamol induced rise in the ALP, AST and ALT to 37.00±3.03, 27.50±3.88 and 37.75±2.50 respectively when compared with paracetamol treated group. With a higher dose of 500 mg/kg further reduction of ALP, AST and ALT to 36.00±2.27, 18.00±4.32 and 36.75±2.14 respectively were noted. Silymarin (50 mg/kg) pretreatment also prevented the paracetamol induced rise in ALP, AST and ALT to 31.75±2.87, 11.00±1.08 and 33.50±1.71 respectively. Same trend was observed in total protein (TP) values.

Histopathology Findings:

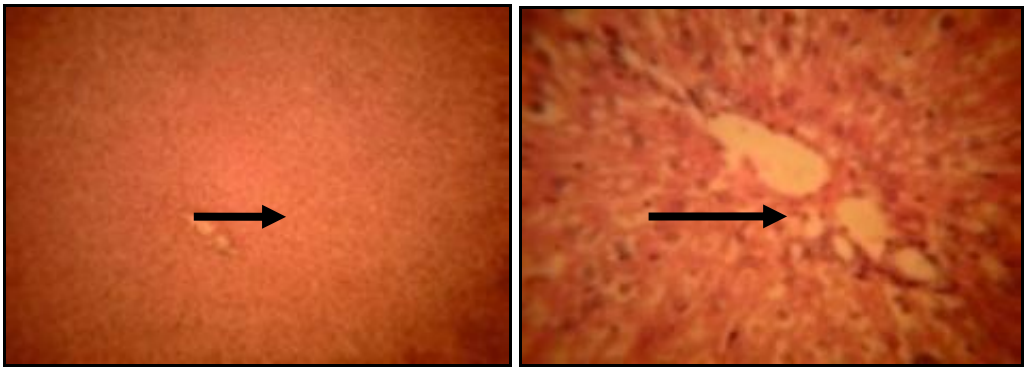

FIG.1: MICROGRAPH OF LIVER TISSUE OF CONTROL ANIMALS (GROUP A) SHOWING A NORMAL PORTAL TRIAD (ARROW) AND HEPATOCYTES (H AND E X 100 AND 400)

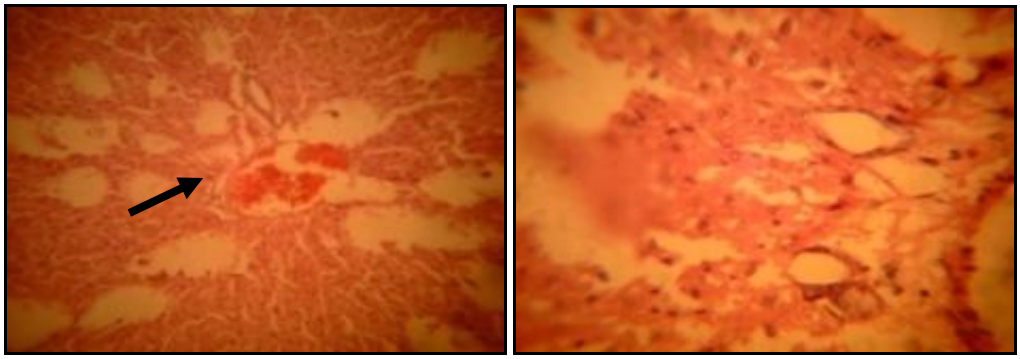

FIG.2: MICROGRAPH OF LIVER TISSUE OF GROUP B ANIMAL ADMINISTERD PARACETAMOL 800MG/KG SHOWING MILD CONGESTED PORTAL VEIN (ARROW), NECROSIS OF HEPATOCYTES AND VACUOLIZATION (H AND E X 100 AND 400)

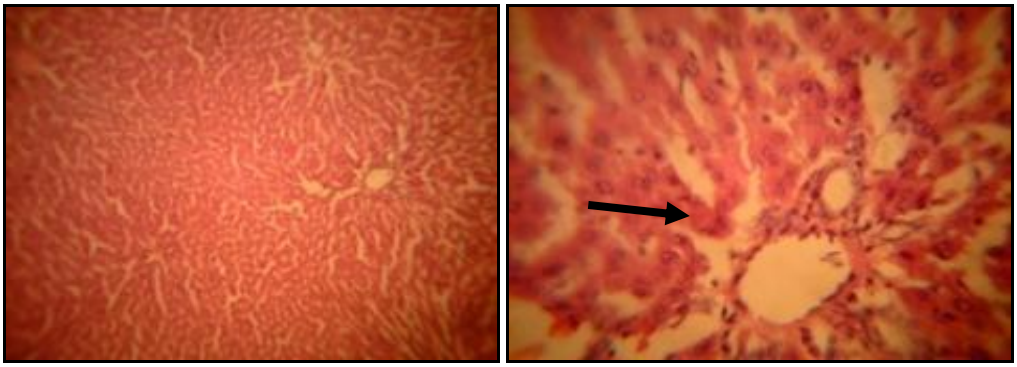

FIG.3: MICROGRAPH OF LIVER TISSUE OF GROUP C ANIMAL TREATED WITH 50MG/KG SILYMARIN AND 800MG/KG PCM FOR 2 WEEKS SHOWING MILD TISSUE SEPARATION AND MILD PERIPORTAL INFLAMMATORY INFILTRATES (ARROW) (H&E X 100 AND 400)

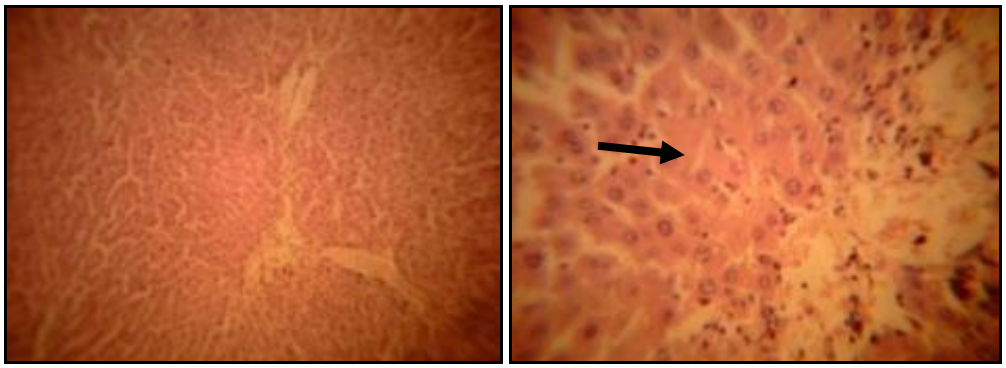

FIG.4: MICROGRAPH OF GROUP D LIVER TREATED WITH 250MG/KG *UVARIA AFZELLI* AND 800MG/KG PCM FOR 2 WEEKS SHOWING ALMOST A NORMAL LIVER ARCHITECTURE WITH MILD TISSUE SEPARATION AND PORTAL AREA (ARROW) (H&E X 100 AND 400)

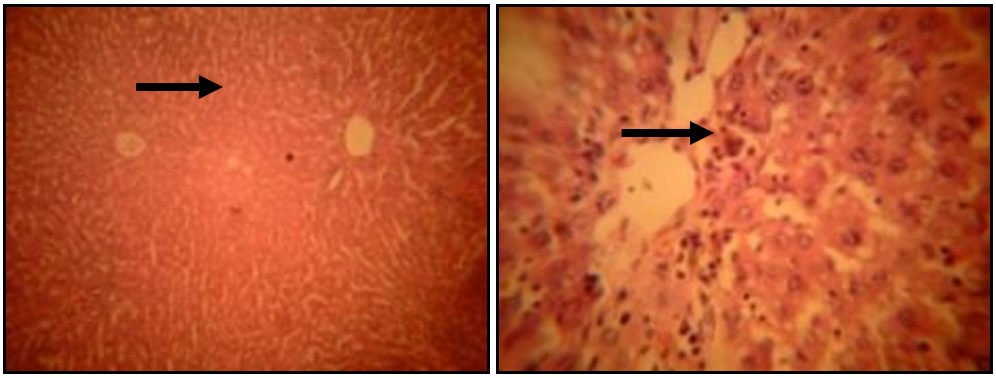

FIG.5: MICROGRAPH OF GROUP E LIVER TREATED WITH 500MG/KG *UVARIA AFZELLI* AND 800MG/KG PCM FOR 2 WEEKS SHOWING A NORMAL LIVER ARCHITECTURE WITH MILD TISSUE SEPARATION (H&E X 100 AND 400)

DISCUSSION: The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market [14].

Acetaminophen hepatotoxicity is now recognized as the most common cause of the potentially devastating clinical syndrome of acute liver failure in many western countries [29]. Acetaminophen (also known as paracetamol or panadol), is reported to induce a wide spectrum of toxicities especially when taken in large single dose either alone or in combination with an equally large amount of alcohol [30, 31]. These toxicities often are pansystemic, involving virtually all organs/systems in the body. For example, in the liver and kidneys, paracetamol overdose causes potentially fatal conditions known as acetaminophen-induced hepatotoxicity and acetaminophen-induced nephrotoxicity, respectively [32].

Because of its wide availability as an over-the-counter analgesic-antipyretic, acetaminophen is liable to abuse and consequent toxicities including hepatotoxicity. However, the toxic dose of acetaminophen is highly variable. For example, in adults, a single dose of above 10 grams or 150 mg/kg or chronic ingestion of doses as low as 4 g/day could induce acetaminophen hepatotoxicity [33], whereas in children, acute doses above 200 mg/kg would be required to induce same degree of hepatotoxicity as in adults [34]. This higher threshold is largely due to children having larger livers relative to body size than adults, hence, being more tolerant of acetaminophen overdose than adults [31]. Paracetamol is documented to mediate its toxic effect on the liver by inducing the process of lipid peroxidation which is mediated principally by the highly reactive intermediate metabolite of acetaminophen, N-acetyl-parabenzoquinonimine (NAPQI) [35].

This intermediate metabolite covalently binds to hepatocyte intracellular and membranal macromolecules to cause cell death and consequent liberation of intracellular contents including the cytosolic liver enzymes.

This present study was designed to evaluate the hepatoprotective activity of *Uvaria afzelii* in paracetamol induced liver damage in rats. Damage to the liver or hepatotoxicity does not result from paracetamol itself, but from one of its metabolites, N-acetyl-*p*-bezoquinoneimine (NAPQI) [35]. NAPQI depletes the liver's natural antioxidant gluthathione and directly damages cells in the liver, leading to liver failure. In the assessment of liver damage by paracetamol, the determination of enzyme levels such as ALP, AST and ALT is largely used.

The increased levels of ALP, AST and ALT in serum are indicative of cellular liver leakage and loss of functional integrity in the cell membrane of the liver [36]. However, administration of the crude aqueous UV extract at various dose levels mediated a reduction in the levels of these enzymes towards

the normal value. This indicates a stabilization of plasma membrane as well as repair of hepatic tissue damage caused by paracetamol. This finding is in consonance with the common view that serum levels of transaminase return to normal following healing of liver parenchyma and regeneration of hepatocytes [37].

Histopathological observations showed severe vacoulations; which were original site of lipid deposit and necrosis of hepatocytes in the paracetamol treated group indicative of liver toxicity. However, on administration of Silymarin (50 mg/kg of body weight) and the crude aqueous UV extract (250mg/kg and 500mg/kg), the severity of these lesions were reduced. These observations suggested the possibility of the plant extract being able to condition the hepatic cells to a state of accelerated regeneration thus reducing the leakage of ALT, AST and ALP into circulation.

Several investigations have shown that silymarin improved liver function related to hepatocellular necrosis and increased membrane permeability through its antioxidant capacity [38]. The protective effect of silymarin observed in our study was attributed to its antioxidant and free radical scavenging properties as reported in earlier studies [39].

The mechanism by which *Uvaria afzelii* exerts its protective action against paracetamol induced damage in the liver may be due to the antioxidative effect of the plant extract. These antioxidative effects might be due to the phytoconstituents such as flavonoids, triterpenoids and phenols present in the plant material as they have been reported to exhibit hepatoprotective activity [40, 41].

CONCLUSION: The findings from the present investigation demonstrate the efficacy of *Uvaria afzelii* plant aqueous extract against experimental hepatic damage induced by paracetamol and these findings were similar to that produced by silymarin. Thus providing preclinical evidence and therapeutic rationale requiring further studies on the above mentioned hepatoprotective activity of the plant extract in attenuation of hepatic insufficiencies, in men as well.

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