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HEPATOPROTECTIVE ACTIVITY OF AQUEOUS AND METHANOLIC EXTRACTS OF WATERMELON SEEDS ON SALT AND PARACETAMOL-INDUCED LIVER DAMAGE IN FEMALE WHITE RATS

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ABSTRACT: *Paracetamol is the commonest over the counter drug for the treatment of body pains. However, an overdose of this drug has detrimental effects on the liver and other internal organs such as the kidneys. This experiment was conducted to investigate the hepatoprotective and regenerative effects of aqueous and methanolic extracts of watermelon seeds on the liver of rats given overdose of common salt and paracetamol. Thirty five (35) female albino rats were used for this experiment and the rats were randomly distributed into seven groups with each group containing five (5) rats. The rats in group A were given only vital feed (40% of the body weights of the rats) without any extract. This was the normal group. The rats in groups B, D and E were given physiological saline at the dosage of 10g/kg body weight once orally. In addition, 200 mg/kg and 400 mg/kg (body weight) of aqueous extract of watermelon seed were given to rats in groups D and E orally twice daily respectively. The rats in groups C, F and G were given paracetamol at dosage of 3g/kg body weight once orally at the beginning of the experiment. In addition, 200 mg/kg and 400 mg/kg (body weight) of methanolic extracts of watermelon were given to rats in groups F and G orally twice daily respectively. These experiments were monitored for 28 days. The results of the histopathological analyses showed that overdose of salt and paracetamol damaged the liver cells of the rats. However, treatments of the rats with aqueous and methanolic extracts of the seeds of watermelon have hepatoprotective and regenerative properties.*

KEYWORDS: Citrullus Lanatus, Liver, Hepatoprotective, Histopathology, Hepatotoxicity, Necrosis, Paracetamol, Cirrhosis, Extracts.

INTRODUCTION

The liver is the largest gland in the body of mammals after the skin and it is involved in many metabolic activities among which are; detoxification of toxic substances, glycogen storage and bile secretion[1, 2]. Bile is a greenish-yellow fluid which aids both the digestion of fats and the absorption of fat-soluble nutrients. Most proteins are synthesized in the liver before they enter the blood[3]. The liver is located behind the ribcage of mammals and it has the unique ability to regenerate its own tissue. The liver can grow back or expand to its original size within several weeks. About 90% of the body's nutrients pass through the liver from the intestines.

The liver converts foods into energy, stores nutrients, and produces blood proteins. Apart from acting as a filter which removes harmful substances from the blood, the liver also produces blood cells in developing foetus. The liver is responsible for the breakdown of insulin and other hormones as well as the breaks down of ammonia into urea as part of the urea cycle while the urea is excreted in urine. The liver breaks down bilirubin via glucuronidation and facilitates its excretion into bile. It also plays a key role in the breaking down or modifying toxic substances (e.g., methylation) and most medicinal products in a process called drug metabolism.

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A normal liver performs its functions adequately. However, if the liver is damaged, it can no longer carry out its normal functions. Damage to the liver can be caused by toxins, drugs, alcohol and insecticides and all these lower the ability of the liver to perform optimally[4, 5]. If the liver is unable to filter out toxins and metabolic by-products such as ammonia, these chemicals may build up in the blood and lead to impaired brain and mental functioning, personality changes (encephalopathy), and (in severe cases) coma and death. People with long-term liver damage may also develop liver cancer.

The use of natural plant products for therapeutic purposes is growing and is largely embraced by the general population[6]. Of interest, are the therapeutic uses of *Carica papaya*, *Homalium letestui*, walnut leaf and *Curcuma longa* (Curcumin)[7, 8, 9]. In Nigeria, *Carica papaya* is one of the most popular, cheap and economically important fruits grown and consumed for its nutritional content.

Watermelon, *Citrullus lanatus*, a Cucurbitanceae is another important fruit which is highly relished for its flesh. Cucurbitaceae plants are known to contain bioactive compounds such as cucurbitacin, triterpenes, sterols and alkaloids[10]. It is an important source of carotenoids, including lycopene and beta-carotene, a precursor of vitamin A[11, 12]. Watermelon seeds are one of the common protein supplements like cotton seeds, groundnut seeds, soybean seeds and rap seeds. Watermelon seeds are cultivated in large quantities in western Sudan. They are used as non-conventional animal feed because of their availability, low cost and are not eaten by humans. Watermelon seeds are excellent sources of protein (both essential and non-essential amino acids), oil, nutrients and minerals[13]. This experiment was conducted to determine the hepatoprotective and the regenerative effects of the aqueous and methanolic extracts of watermelon seeds on saline and paracetamol induced livers of female white rats.

MATERIALS AND METHODS

Collection of watermelon, *Citrullus lanatus*

Citrullus lanatus fruits were obtained from a seller store located opposite Ekiti State University, Ado-Ekiti entrance gate. *C. lanatus* fruits were cut open with knife and the seeds were removed and air dried in the laboratory for 7 days before being pulverised (blended) with a blender (Binatone model) into smooth powder.

Collection and maintenance of rats

Thirty-five female white albino rats of 8 weeks old, whose weight ranges between 180g±30 were purchased from the Animal house of College of Medicine, Ekiti State University, Ado-Ekiti. The rats were allowed to acclimatize for one week before the experiment commenced. The rats were randomly distributed into seven cages. Five rats were put in each of the cages. The rats were fed poultry grower's mash and drinking water was given to them daily (in the morning and in the evening).

Preparation of aqueous extract

Aqueous and methanolic extracts of the seed of watermelon were prepared according to the methods explained by Roy *et al.*[14]. Then 25 g of the watermelon seed powder was measured and dissolved in 250 ml of distilled water, 250 ml of methanol and kept in separate airtight

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glass jars. These mixtures were incubated at 37±1ºC for 72 h in an incubator cum shaker. After 72 h, the separate mixtures were filtered and the solvent of the filtrates were completely removed by rotary vacuum evaporator. The aqueous extract and the methanolic extract were collected. The extracts were dried in desiccator and later stored in refrigerator at 4° C for further use.

Rearing of the rats

The thirty five (35) female albino rats used for this study were randomly divided into seven groups with each group containing 5 rats. The rats in group A were given only vital feed (40% of the body weights of the rats) without any extract. This was the normal group. The rats in Group B, D and E were given physiological saline at the dosage of 10g/kg body weight once orally while the rats in Group C, G and F were given paracetamol at dosage of 3g/kg body weight once orally at the beginning of the experiment. Groups B and C were the control and some of them were sacrificed within 48 h and their livers removed and preserved for histopathological analysis. For their treatments, the rats in Groups D and E were given aqueous extract of watermelon seed at dosages of 200 mg/kg body weight and 400 mg/kg body weight orally twice daily respectively. Moreover, vital feed (40% body weights of the rats) were given to them twice daily. The rats in Groups F and G were treated with methanolic extracts of watermelon at dosages of 200 mg/kg body weight and 400 mg/kg body weight orally twice daily. Also, vital feed (40% body weights of the rats) were given to them twice daily. All the rats in all the groups had access to regular supply of good drinking water. These experiments were monitored for 28 days.

Histopathological analyses

At the end of the 28th day, the rats were separately sacrificed, dissected and their livers were collected for histopathological analyses[15] at the central laboratory of The Federal University of Technology, Akure. The livers of the rats were fixed and processed for histopathological analyses by the methods explained by Palani *et al.*[15]. The livers were fixed in 10% buffered Bouin's reagent and were processed for paraffin sectioning. Sections of 5 mm thickness were stained with haematoxylin and eosin for photomicroscopic observation.

RESULTS

All the rats given saline solution and those given paracetamol were weak, and could not eat for about 48 h after treatments. The result of the histopathological analysis of the liver of female rats fed normal feed is presented in Plate 1. Hepatocytes, central vein, endothelial cells and kupffer cells are distinct in the liver. There was no haemorrhage and cell arrangements in the liver are not distorted.

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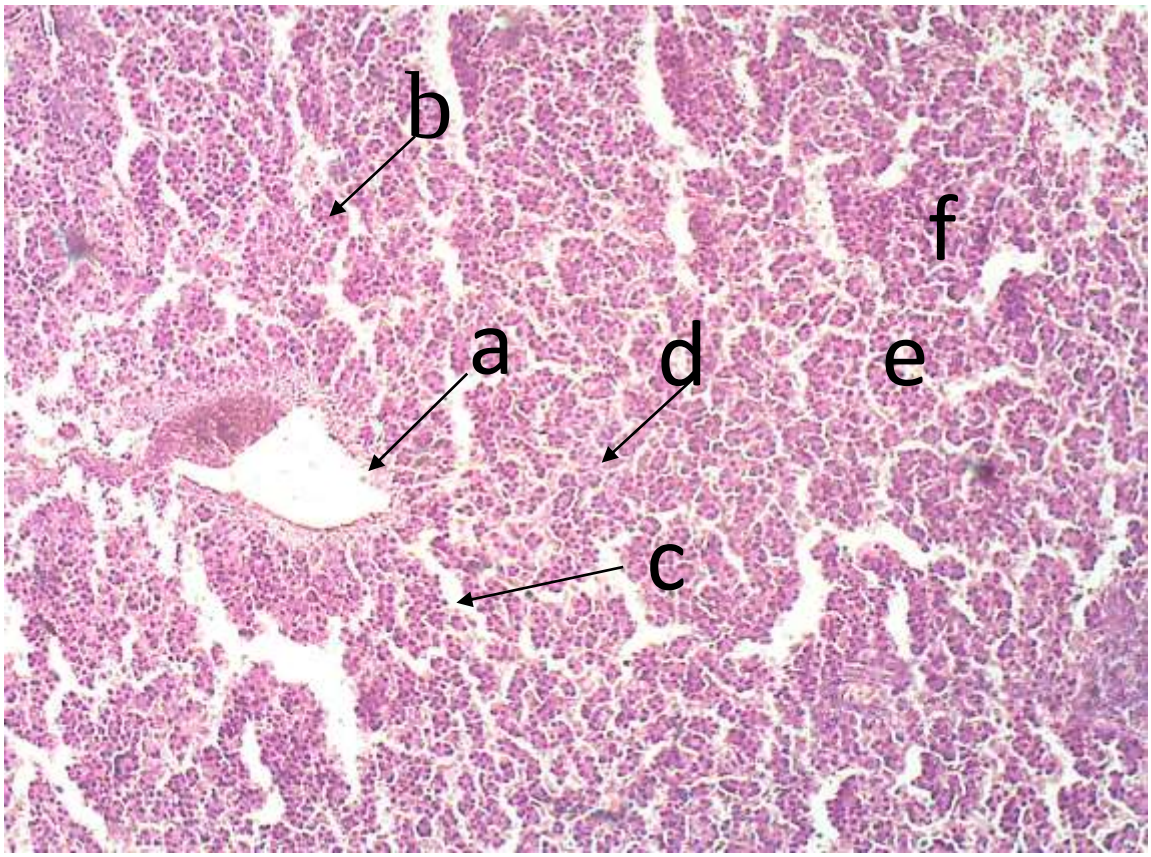

Plate 1. The histopathology of the normal liver of a rat (Mg. x400).

A = Central vein, B = Hepatocytes, C = Sinusoid (passage of flow of blood), D = Cord (hepatocytes are arranged into cords separated by sinusoids), E= Endothelial cell, F= Kupffer cells. There was no haemorrhage.

Plate 2 below shows the result of the histopathological analysis of the liver of female rats given salts 10g/kg body weight. The cells in the liver are distorted, and there were necrosis and widespread haemorrhage. Moreover, vacuolation of the liver cells were observed.

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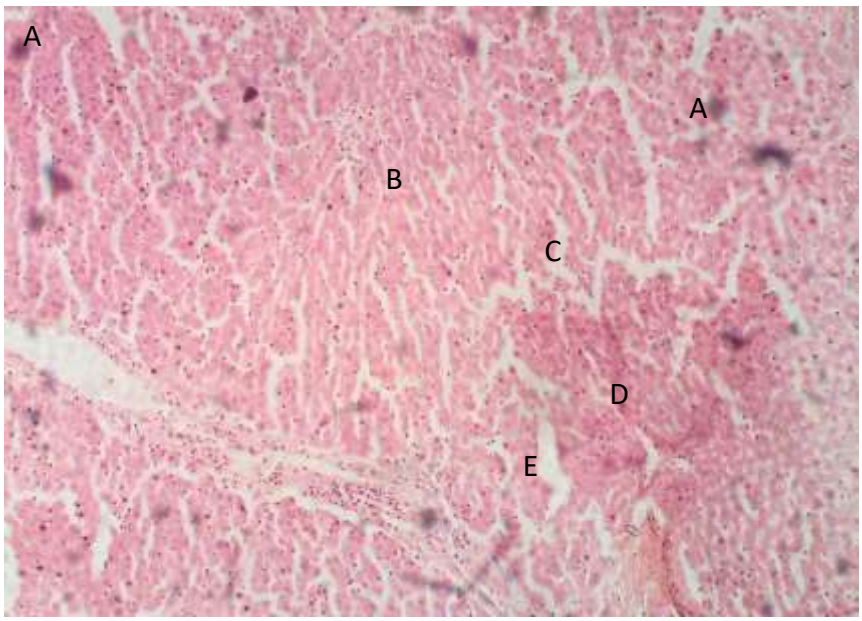

Plate 2. Photomicrograph of the liver of rats treated with saline solution (10g/kg body weight) (Mg. x400). A= Necrosis (showing lesions), B= destroyed/distorted hepatocytes, C= Sinusoidal dilatation, D= Haemorrhage, E= Cytoplasmic vacuolation of liver cells.

The liver of the rats given paracetamol showed greater histopathological changes (Plate 3). The liver showed cytoplasmic vacuolation, disruption of hepatocytes, blood vessel and collagen fibers deposition. Scattered haemorrhage and lesions were observed.

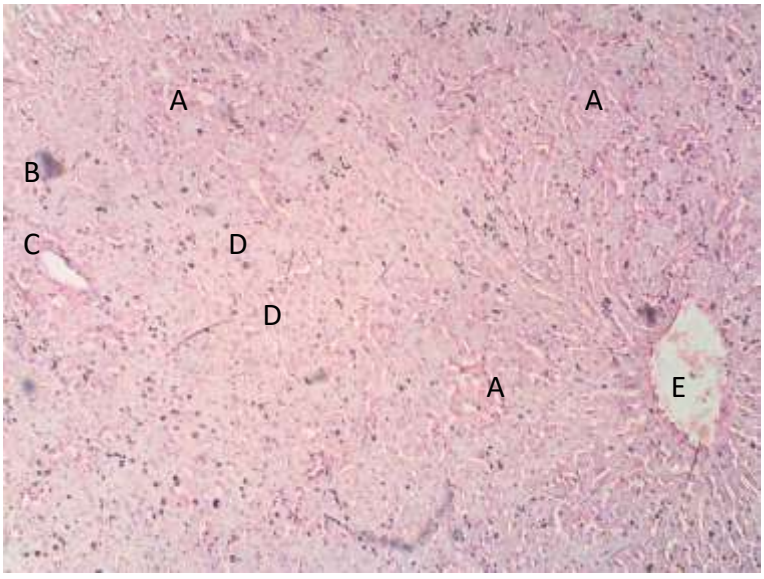

Plate 3. Photomicrograph of the liver of rats treated with paracetamol (3g/kg body weight). (Mg. x400). A= Necrosis, B= Lesion, C= Vacuolation, D= Completely distorted/disorganized hepatocytes, E= shrinking Central vein.

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Plate 4 below, displayed the result of histopathological analysis of the liver of rats treated with aqueous extract of watermelon seeds at dosage of 200 mg/kg. Regenerations of the liver were observed also scattered necrosis were observed. The cells at the periphery of the liver were observed to have suffered destruction more than the ones at the centre.

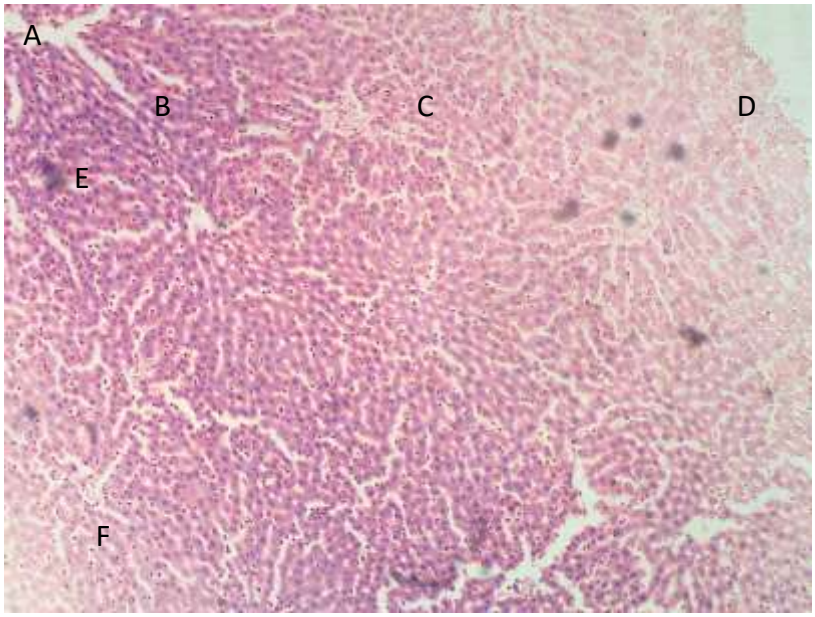

Plate 4. Photomicrograph of the liver of rats treated with aqueous extract of *C. lanatus* (200 mg/kg body weight) (Mg. x400). A= Sinusoid, B= Rejuvinated Hepatocytes, C= Rejuvinating Hepatocytes, D= Disintegrated Hepatocytes, E= Lesion, F= Rejuvinating Hepatocytes.

Recovery of the liver cells were observed in Plate 5. Regeneration of the liver cells and there arrangements were taken place. There was no haemorrhage but scattered lesions were observed. This result is an improvement on the result displayed in Plate 4.

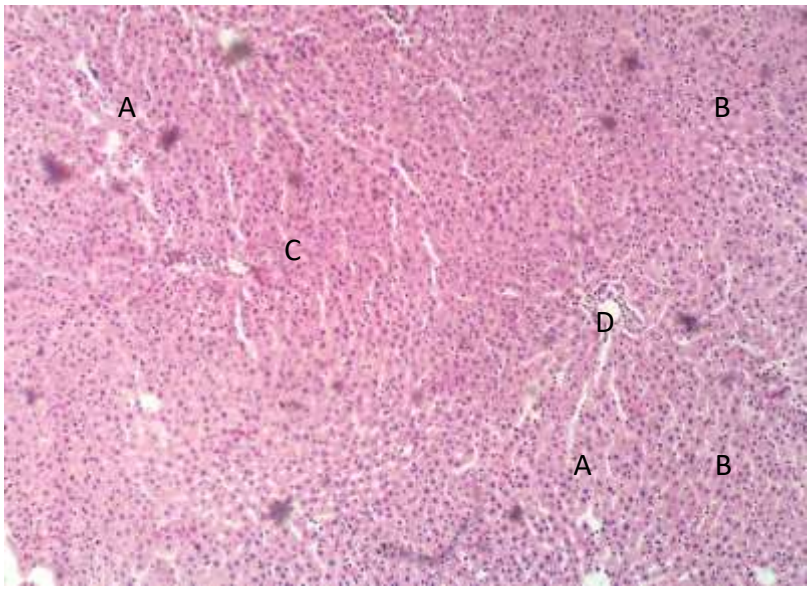

Plate 5. Photomicrograph of the liver of rats treated with aqueous seed extract of *C. lanatus* (400 mg/kg body weight) (Mg. x400). A= Sinusoid, B= Rejuvinated hepatocytes, C= Mild haemorrhage, D= Blood vessel.

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The result of the histopathological analysis of the liver of female rats given 200mg/kg of methanolic extracts of watermelon seeds is shown in Plate 6. Regeneration of the liver cells as a result of *C. lanatus* treatment occurs. Fewer lesions were observed in the cell arrangement.

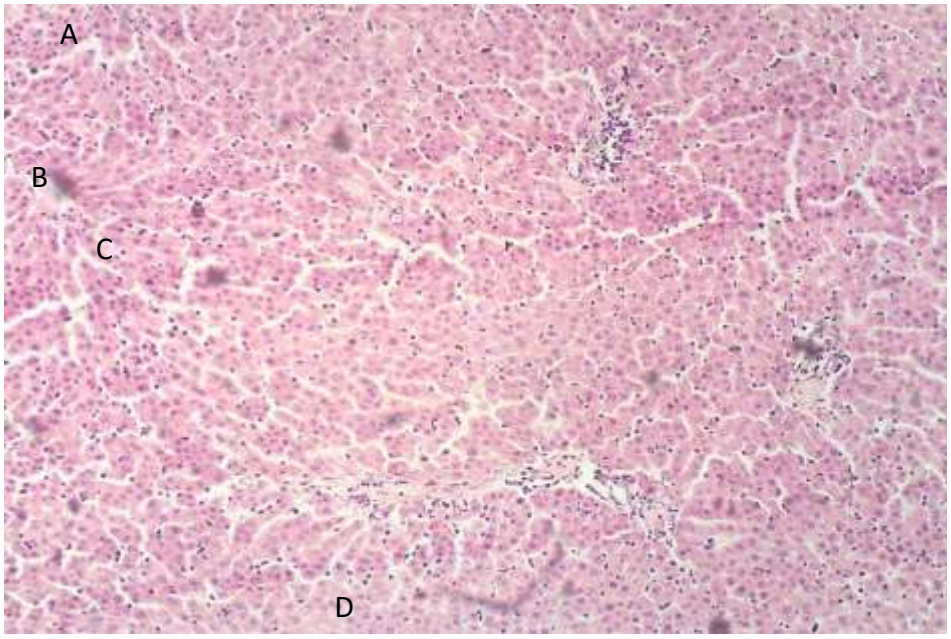

Plate 6. Photomicrograph of the liver of rats treated with methanolic extract of the seed of *C. lanatus* (1g/kg body weight) (Mg. x400). A= Normal hepatocytes, B= Lesion (regenerating), C= Sinusoid, D= Rejenerating Hepatocytes.

The result displayed in Plate 7 shows the liver cells of rats that have fully recovered from the damage done by overdose of paracetamol. The histopathological analysis of the liver compares favourably with than of the normal rats (Plate 1).

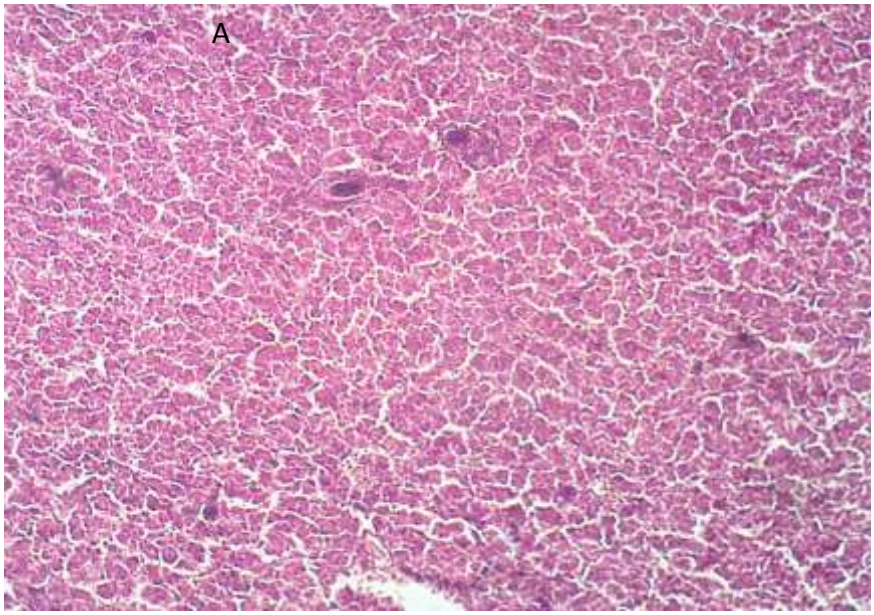

Plate 7. Photomicrograph of the liver of rats treated with methanolic extract of the seed of *C. lanatus* (2g/kg body weight) (Mg. x400). No haemorrhage was observed.

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DISCUSSION

All the rats abstained from food for periods ranging from 1 h to 48 h after treatment with overdose of saline and paracetamol because the livers of the rats were severely damaged. The rats could not eat their foods as a result of the disorderliness and distortion of the liver tissues. These two compounds caused significant alterations in the arrangement of the cells of the liver. These compounds greatly hindered the functions of the liver and could have led to liver failure in the rats. Liver failure is a common attack in mammals. It may be acute or chronic and may be caused by a wide variety of disorders such as drug overdose, poisoning, chemicals and cirrhosis[16, 17]. Cirrhosis causes weakness, loss of appetite, itching and fatigue in animals. The rats in the control did not abstain from their food throughout the duration of the experiment, indicating that no damage was done to the vital internal organs.

Overdose of salt and paracetamol are deleterious to the system hence should be avoided by animals. The damage done to the liver tissues by salt and paracetamol were devastating, thus washing away the liver cells (Plate 2 and plate 3). They caused the distortion of the liver cells, necrosis, widespread haemorrhage and vacuolation of the liver cells. Liver vacuolation is caused by liver injury[18]. From this work, it is evident that high dose of salt and paracetamol are hepatotoxic agents. Similar observations have been made by some authors[19]. Higher dosages of paracetamol have been reported to cause larger percentage of paracetamol to be bioactivated to NAPQI (N-acetyl-p-benzoquinone imine) which depletes the glutathione stored in the liver[20]. When glutathione depletion reaches a critical level NAPQI reacts with cell structures and results in hepatocellular injury[21]. Higher dosage of paracetamol has been observed to adversely affect rats blood[22]. The damage done to the liver by drug overdose equates with the effects of pesticides on the liver. Pesticides deteriorates the liver and the kidneys of albino mice[4] thus hampering the functions of these vital organs in the system.

Watermelon and its seed extracts have been used by various authors to treat various ailments in animals and they came up with various results. Watermelon has been reported to cause increase in reproductive effeciency in mice[23], reduced prostates weight in rats[24], possess anti-ulcer activity[25] and possess ability to correct bed wetting and dropsy[26]. On the other hand, watermelon has been observed to have antifertility effects on rats[27].

The extracts of watermelon seeds at dosages 200 mg/kg and 400 mg/kg body weights had hepatoprotective and rejuvenating effects on the liver of the treated rats. The quantity of watermelon extracts used in this study compared favourably with the quantity of curcumin (400 mg) used by Soliman, *et al.*[9] but lower than the quantity of milk thistle (500 mg) used in correcting marked destruction of hepatic and renal functions inflicted by paracetamol in rats[28]. Similar observations have been reported by some authors[29, 30, 31]. In this study, watermelon seed extracts were able to reverse the oxidative and hepatological dysfunction in treated rats. This finding was in agreement with the earlier work of Adebayo, *et al.*[32] and Oyenihi *et al.*[33] who observed haematological and hepatoprotective effects of watermelon juice on carbon tetrachloride induced and acute ethanol-induced oxidative stress in rats respectively. Ojo, *et al.*[34] observed similar significant hypoglycaemic, hepatoprotective and nephroprotective effects of aqueous extracts of *C. papaya* seed and leaf on diabetic rats. Seed extracts of plants are always more potent and highly effective in treating toxicity[34]. The importance of stem of *C. papaya* as potent herbal plant for wound healing has been emphasised[35]. However, some authors have observed that extracts of *C. papaya* has potential to cause liver injury and adversely affect reproduction in rats[36, 37]. The use of plant materials in treating ailments and

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infections is an age-long practice since plants are good and rich sources of antioxidants and phytochemicals.

Watermelon is a rich source of antioxidants such as lycopene, β-carotene and phytofluene[11]. In their submission, Alok, *et al.*[38] and Oyenihi *et al.*[33] reported that watermelon possess antioxidant, anti-inflammatory, analgesic, anti-diabetic and anti-ulcerogenic properties. Watermelon is not only rich in minerals and nutrients but contains different phytochemicals and antioxidants which include; phenol, tannin, flavonoids, carotenoids, lycopene[12, 39]. Oxidative stress, ailments and diseases are caused by free radicals which are released as a result of biological activities and they are capable of attacking healthy cells of the body and cause damage, disease and severe disorders[40]. Free radicals are naturally controlled by beneficial compounds known as antioxidants which play important roles in protecting the body against the harmful effects of free radicals[40]. Watermelon, being a rich source of antioxidants must have derived its ability to cause healing and protect body cells from the array of antioxidants it possesses. Apart from being one of the most important components which plays critical role in the maintenance of cells functioning and integrity, antioxidants play important role against the reactive oxygen species and maintenance of normal cells activity[41]. Antioxidants are known for scavenging for free radicals in the body. Radical-inhibiting antioxidant properties that have been attributed to carvedilol are largely or exclusively due to its metabolite components (i.e. 3-hydroxy, 5-hydroxy and 4-hydrocycarvedilol)[42]. The protective ability of antioxidants against toxicity has been reported by Shrivastava, *et al.*[43]. The potency of watermelon extracts in this study must have been due to the presence of antioxidants and phytochemicals in them. Igwe and Omoha[44] reported that the potent antimicrobial and free radical scavenging activities of the seed extract of *C. lanatus* was as a result of the bountiful presence of phytochemicals in them.

CONCLUSION

This work showed that overdose of salt and paracetamol are highly deleterious to the liver. These compounds caused devastating damage to the liver thus hampering its functions. However, the results obtained from this study showed that aqueous and methanolic extracts of *Citrullus lanatus* seeds have healing and rejuvenating effects on the liver. The seed extracts showed anti-oxidative and hepato–protective potentials toward liver damage caused by overdose of salt and paracetamol in rats.

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