Global Advanced Research Journal of Agricultural Science (ISSN: 2315-5094) Vol. 7(3) pp. 080-087, March, 2018 Issue.
Available online http://garj.org/garjas/home

Full Length Research Paper

The regenerative efficacy of aqueous and methanolic extracts of watermelon, *Citrullus lanatus* seeds on physiological saline and acetaminophen-induced kidney damage in female albino rats

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Accepted 01 February, 2018

Kidneys are important organs that are responsible for osmoregulation in animals. In this research work, extracts of watermelon seeds, *Citrullus lanatus* L were used for the correction of saline and acetaminophen-induced kidney damage in female albino rats. Aqueous and methanolic extracts were made from watermelon seeds and fed together with vital feed to rats. Forty two (42) female swiss albino rats were purchased and divided into7 groups (A-G). There were seven rats in each group. The rats in Group A were only given vital feed without any extracts (normal). The rats in Groups B, D and E were given 10g/kg body weight of salt solution while the rats in Groups C, F and Gwere given 3g/kg body weight of paracetamol. The rats in Groups B and C were the experimental controls. The rats in Groups D and E were fed aqueous extract of watermelon seeds at dosages of 200 mg/kg body weight and 400 mg/kg body weight respectively while the rats in Groups F and G were fedmethanolic extract of watermelon seeds at dosages of 200 mg/kg body weight and 400 mg/kg body weight respectively. All the rats were given 40% body weight of vital feed twice daily and they all had access to plenty supply of good drinking water. The experiments were monitored for 28days. At the end of the 28th day, all the rats were sacrificed and their kidneys were removed for histopathological studies. The results of the histopathological analysis of the kidneys revealed that aqueous and methanolic extract of C. lanatus seeds had healing/regenerative and nephoprotective effects on the damaged doneto the kidneys of rats by overdose of salts and paracetamol.

Keywords: Aqueous extract, methanolic extract, histopathological, nephroprotective, *Citrullus lanatus*, apoptosis.

INTRODUCTION

Kidneys are bean-shaped organs that serve essential regulatory roles in vertebrates. They are located at the dorsal region of the abdominal cavities of vertebrates. The kidneys regulate fluid balance in the body and filter out waste products from the blood in form of urine, hence, they

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are referred to as organs of osmoregulation. Urine collects in the middle of each kidney, in an area called the renal pelvis , which is a funnel-shaped structure that drains down into tubes called ureters and then to the bladder. The functional unit of the kidney is the nephron. The nephron- a functional unit of the kidney filters the blood to separate urine and reabsorb useful salts back into the system.

Normal kidneys perform their functions well but a diseased or damaged kidney cannot function optimally. Kidneys damage are caused by a number of factors which include overdose of drugs (paracetamol overdose), aspirin (anagelsic), high sugar intake, vitamin B6 deficiency, magnesium deficiency, not drinking enough water, consuming too much sodium and not emptying of bladder early. Tzanakaki *et al.* (2014) were of the opinion that the major causes of hospitalization were catheter related infections and pulmonary oedema in human. The symptom of kidney damage varies according to the cause of the damage. The symptoms may be acute, sub- acute or chronic depending on the severity of the toxicity. Factors such as age and dehydration may also influence the severity of the symptoms.

When the damage of the kidney is caused by acetaminophen, the symptoms are as follows; fatigue, increased blood pressure, hepatic necrosis, increased hydrogen ion level in the blood, anemia, increased urea level in the blood and proteinuria. When the damage of the kidney is caused by Aspirin (Analgesics), the symptoms are as follows: shortness of breath, fever, chills, non-productive cough, Enzymuria, increased blood electrolyte, impaired body water balance, proteinuria, tubular necrosis, anemia and increased blood pressure. Other things that can cause damage to the kidney include: The common symptom of all the above mentioned is proteinuria, cause that is an early sign when the kidneys have been damage, but at this stage the damage can still be reversible.

The correction of damaged kidneys is possible through the consumption of nutrient-rich food. Pawpaw intake enhances the immune system: with chronic damaged kidneys, the immune system becomes lower and lower. Vitamin C which is present in pawpaw can help boost immunity largely. Pawpaw also cleanses the blood, if kidneys are damaged severely, they cannot purify blood normally by removing waste products and toxins from the body. Pawpaw is able to eliminate peroxide and other waste from the body, so as to purify the blood. Pawpaw also prevents some disorders like constipation, nephritis and high blood pressure. Aqueous extract of pawpaw seeds contained nephroprotective phytochemicals which helps in preventing kidney damage induced by paracetamol (Naggayi, *et al.* 2015).

Another food that aids in the correction of damaged kidneys is watermelon. Watermelon *Citrullus lanatus L*, is an important fruit crop of the family Cucurbitaceae. Cucurbitaceae plants are plants known to contain bioactive compounds such as cucurbitacin, triterpenes, sterols and alkaloids (Rahman, *et al.* 2008). The crop contains about 90% water. It is also a source of important nutritional compounds such as sugars, lycopene and cardiovascular health–promoting amino acids, such as citrulline, arginine and glutathione (Hayashi, 2005).The fruit contains so many active phyto-constituents and minerals. The watermelon fruit has smooth exterior rind and juicy, sweet, usually reddish, or sometimes orange, yellow, or pink interior flesh (Daniel and Maria, 2000). Watermelon seeds are excellent sources of protein (both essential and non-essential amino acids) and oil. Watermelon is an excellent source of vitamins and minerals (Godwin, *et al.* 2008, Okunrobo, *et al.* 2012). Watermelon seeds were observed to contain minerals such as magnesium, calcium, potassium, sodium and zinc (Okunrobo, *et al*. 2012).

The laxative effect of aqueous fruit pulp extract of*C. lanatus,* antimicrobial activity against bacteria and fungi, the antioxidant and anti-ulcerative activities of the crop have been studied (Alsok, *et al.* 2012, Swapnil, 2011, Loiy and Ahmed, 2011, Loiy and Ahmed, 2011, Naresh, *et al.* 2011). The protective effects of n- hexane extracted *C. lanatus* seed oil against CCl4 induced hepatic damage in rats and the in-vivo and in-vitro evaluation of *C. lanatus* seed oil have been evaluated for their anti-inflammatory activities (Madhavi, *et al.* 2012, Madhavi, *et al.* 2012, Adeneye, *et al.* 2008) while Aruna *et al*. (2012) studied the effects of extracts of *C. lanatus* on hypercholesterolemia-induced atherosclerosis in mice. The aim of this work is to determine the effects of aqueous and methanolic extracts of *C.lanatus* seeds on experimentally damaged kidneys of Swiss albino rats.

MATERIALS AND METHODS

Collection of watermelon, *Citrullus lanatus*

Healthy watermelon fruits were obtained from fruit store at Oja-Oba Market in Ado-Ekiti, Ekiti State of Nigeria. The fruits were cut opened and their seeds were separated from the flesh and air-dried in the laboratory for 7days. The seeds were ground into smooth powdery form with an electric blender, which was turned to the highest speed (Binatonemodel).

Collection and maintenance of rats

Forty two female white albino rats of 8 weeks old, whose weight ranges between 150g±20 were purchased from the Animal house of College of Medicine, Ekiti State University, Ado-Ekiti. The rats were allowed to acclimatise for one week before the experiment commenced. The rats were randomly distributed into seven cages. Six rats were put in each of the cages. The rest were used as spare specimen. The rats were fed poultry grower's mash and they were also allowed unrestricted access to drinking water daily.

Preparation of aqueous extract

Aqueous and methanolic extracts of the seed of watermelon were prepared according to the methods explained by Roy *et al.* (2013). The extracts were dried in desiccators and later stored in refrigerator at 4° C for further use.

Rearing of the rats

The forty two (42) female albino rats were divided into seven groups containing 6 rats each. The rats in Group A were given only vital feed (40% of their body weight) without any extract. This was the normal group. The rats in Group B were given physiological saline at the dosage of 10g/kg body weight once orally while the rats in Group C were given acetaminophen at dosage of 3g/kg body weight once orally at the beginning of the experiment. These two groups were the control. The rats in Groups D and E were given physiological saline at dosage of 10 g/kg body weight once orally at the beginning of the experiment. For their treatments, the rats in Groups D and E were given aqueous extract of watermelon seed at dosages of200 mg/kg body weight and 400 mg/kg body weight orally twice daily respectively. Moreover, vital feed (40% body weight)were given to the rats twice daily. The rats in Groups F and G were given acetaminophen at dosage of 3g/kg body weight orally once at the beginning of the experiment. The accurate measurement of the extract was done with the use of syringes. 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 weight) were given to the rats 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 experiment the rats were separately sacrificed, dissected and their kidneys were collected for histopathological analyses (Palani, *et al.* 2009) at the central laboratory of The Federal University of Technology, Akure. The kidneys of the rats were fixed and processed for histopathological analyses by the methods analysed by Palani *et al.* (2009). The kidneys 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 photo microscopic observation.

RESULTS

Upon the administration of the physiological saline and acetaminophen to the rats, some of them died within 30 min to 48 h. None of the rats could eat within 24 h but a few numbers of them were able to eat within 48 h. The results of the histopathological analysis of the kidneys of the rats treated with aqueous and methanolic extracts of watermelon seeds are presented below. Plate 1 shows the histology of normal rat kidney. Endothelial cells, podocytes and mesangial cells are present.

The Bowman's capsule, glomerulus's, proximal and distal tubules are normal. There were no deformities in the arrangement of the kidney tissues. Plate 2 showed the histopathology of the kidneys of the rats that were given overdose of saline solution. The cells of the kidneys were deformed and destroyed causing the disruption of the kidney tissues. Apoptosis might have occurred. The Bowman's capsules, glomerulus's and all other parts of the kidney disintegrated. There were evidences of necrosis inside the Bowman's capsules and other parts of the kidneys.

Plate 3 showed the histopathology of the kidneys of the rats that were given an overdose of acetaminophen. Rupturing and necrosis of the kidneys tissues occurred as a result of the exposure to overdose of acetaminophen. The Bowman's capsule and the glomerulus's were washed away. Necrosis occurred in both the Bowman's capsules and the interstitial tissues.

Plate 4 showed the histopathology of the kidneys of the rats treated with 200 mg of aqueous extract of *Citrullus lanatus,* watermelon seeds. Regeneration of the kidney cells were taken place but there were scattered coagulative necrosis.

Plate 5 showed the histopathology of the kidneys of the rats treated with 400 mg of aqueous extract of *Citrullus lanatus,* watermelon seeds. Regeneration has taken place. No evidence of necrosis seen. Distinct proximal and distal tubules as well as interstitial tissues are regenerating.

Plate 6 showed the histopathology of the kidneys of the rats treated with 200 mg of methanolic extract of *Citrullus lanatus,* watermelon seeds. Faster regeneration of the kidney cells were noticed. Bowman's capsules, proximal and distal tubules as well as interstitial tissues are distinct.

Plate 7.Showed the histopathology of the kidneys of the rats treated with 400 mg of methanolic extract of *Citrullus lanatus,* watermelon seeds. So many distinct Bowman's capsules, glomerulus, blood vessels, proximal and distal tubules seen. No evidence of necrosis was observed.

DISCUSSION

Kidneys are important organs and they function optimally under favourable condition. The introduction of overdose of physiological saline and acetaminophen into the rats caused nephrotoxicity and renal cellular damage which later lead to the death of the rats. Similar observation has

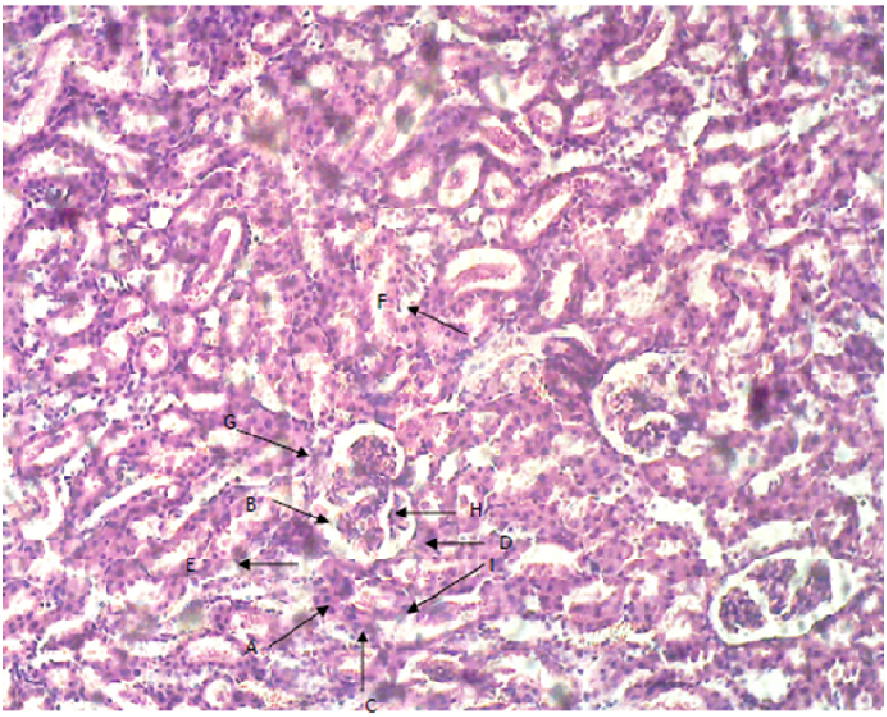

Plate 1. Histology of normal kidney of rat(X400).A = Bowman's capsule, B =Bowman's space ,C= Glomerulus, D =Afferent Arteriole, E =Distal tubule, F =Proximal tubules, G = Macula Densa, H = The Filtration Chamber , I = Basement membrane of the Bowman's capsule, (Normal histology of kidney cells, no evidence of necrosis).

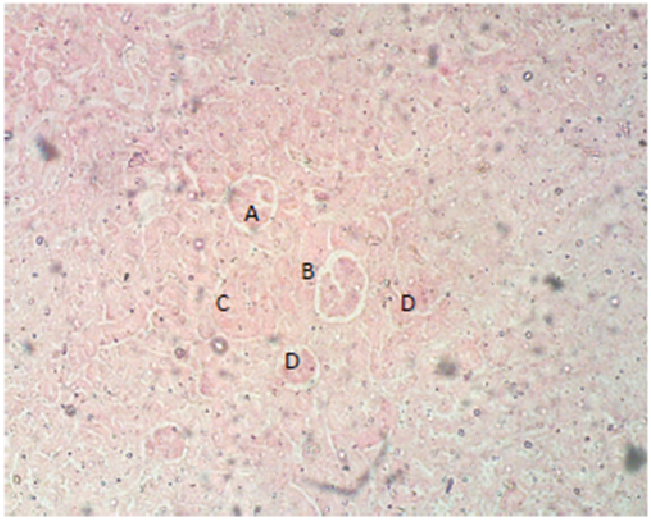

Plate 2. Kidney of the rat given saline solution. (X400) (Cortical part) A= Degenerating Glomerulus, B= Bowman's capsule with collapsing basement membrane, C= Ruptured Bowman's capsule, D= Necrosis inside Bowman's capsules (Total destruction of the histological architecture of the kidney).

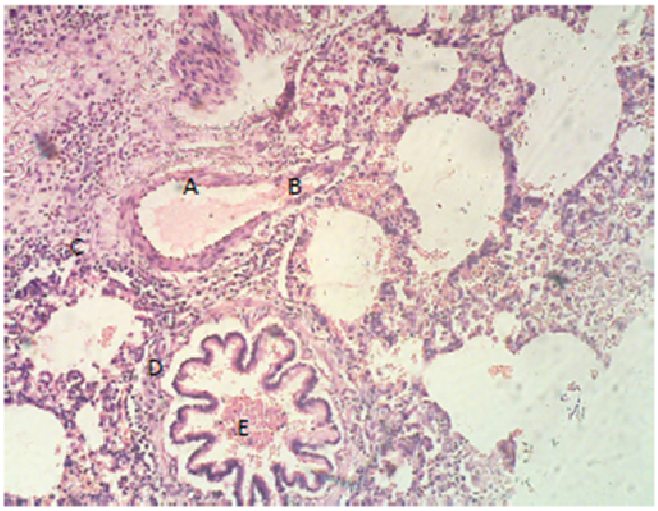

Plate 3. Histopathologyof the kidney of the rat given acetaminophen (X400). A= Ruptured Bowman's capsule, B= Narrowing of proximal tubule, C= Central vein, D= Rupturing Bowman's capsule, E= Necrosis inside glomerulus.

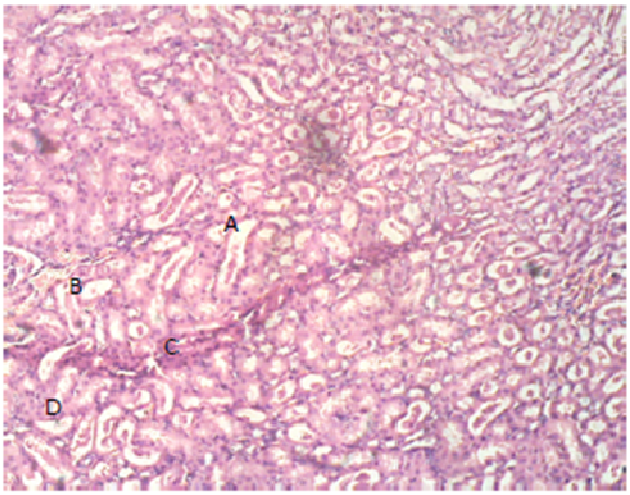

Plate 4. Histopathology of the kidney of rats treated with 200 mg of aqueous extract of *Citrullus lanatus* seeds. (X400). (Medullary part) A= Proximal tubule, B= Distal tubule, C= Necrosis, D= Recuperating Bowman's capsule

been documented by some authors that higher dosages of drugs lead to toxicity and renal damage (Roy, *et al.* 2015). The results of the histopathological analyses of the kidneys of female rats treated with aqueous and methanolic extracts of watermelon seeds showed the healing and nephroprotective effects of the extracts. The result in plate 1 showed the structure of a normal rat kidney. The Bowman's capsules were without deformities and the glomeruli (filtration chambers) were also without deformities. On this plate, the endothelial cells which form a single cell layer that lines all blood vessels and regulates exchanges between the bloodstream and the surroundings is present. Signals from endothelial cells organise the growth and development of connective tissues cells that form the surrounding layers of the blood-vessels. On this same plate 1, podocytes are present. Podocytes are cells in the Bowman's capsule in the kidneys that wrap around capillaries of the glomerulus's. Mesangial cells are also present. Mesangial cells provide structural support for and regulate blood flow of the glomerular capillaries by their contractile activity. The result in plate 2 showed that the saline solution administered to the rats caused disruption of the kidneys, which in turn caused interruption in the normal functioning of the kidney cells. Apoptosis might have occurred here. Apoptosis is programmed cell death or

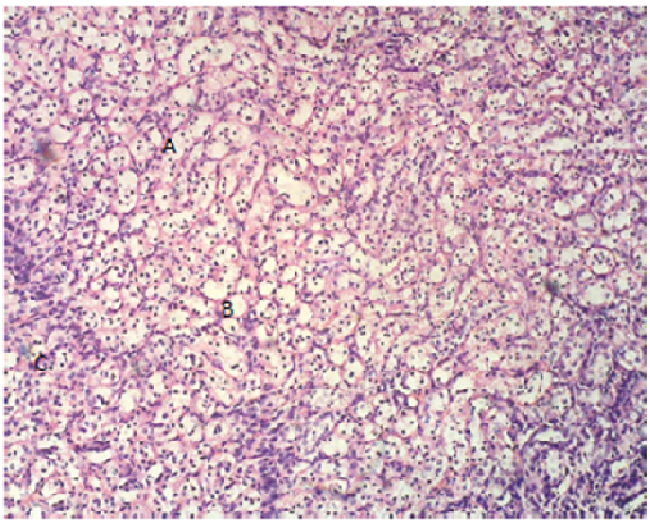

Plate 5. Histopathology of the kidney of rats treated with 400 mg of aqueous extract of *Citrullus lanatus* seeds. (X400). (Medullary part) A= Proximal tubule, B= Distal tubule, C= Interstitial tissues

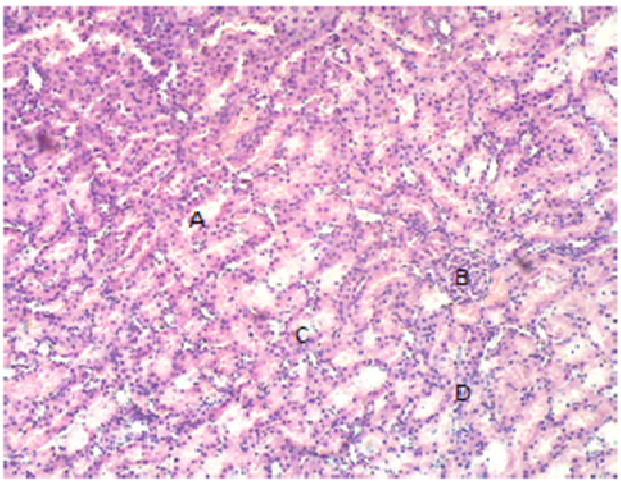

Plate 6. Kidney treated with 200 mg of methanolic extract of *Citrullus lanatus* seeds. (X400). A= Proximal tubule, B= Recuperating Bowman's capsule, C= Distal tubule, D= Interstitial tissue

cell suicide, the cells self-destruct. Apoptosis does not lead to infection.

The result of plate 3 showed that there was necrosis of the kidney cells which occurred as a result of exposure to overdose of acetaminophen. Necrosis is a form of cell injury which results in the premature death of cells in living tissues by autolysis. Necrosis leads to infection. The result of plate 4 showed regeneration of the kidney cells. The kidney cells were in the process of renewal, restoration and growth. Scattered coagulative necrosis occurred. Coagulative necrosis is a type of accidental cell death typically caused by ischemia or infarction. In coagulative necrosis the architecture of dead tissues is preserved for at least a couple of days. The regeneration is due to the 200mg of aqueous extract of watermelon seed administered to the rat. The result in plate 5showedsome degree of regeneration of the kidney cells taking place. It was also visibly noticed that there were fewer coagulative necrosis. This was due to the 400mg of aqueous extract of watermelon administered to the rat. The rate of regeneration observed in plate 5 was higher than that of plate 4, due to the increased dosage of the extract given to the rat. Okunrobo *et al.* (2012) have earlier observed similar occurrence. Extracts of plants have been observed to have nephroprotective ability in animals (Okunrobo, *et al.* 2012, Erhihie and Ekene, 2013, Roy *et al.* 2013, Amjed *et al.* 2016).

The result in plate 6 showed faster rate of regeneration of kidney cells. The endothelial cells, the mesangial cells, and the podocytes were visibly noticed. This was due to

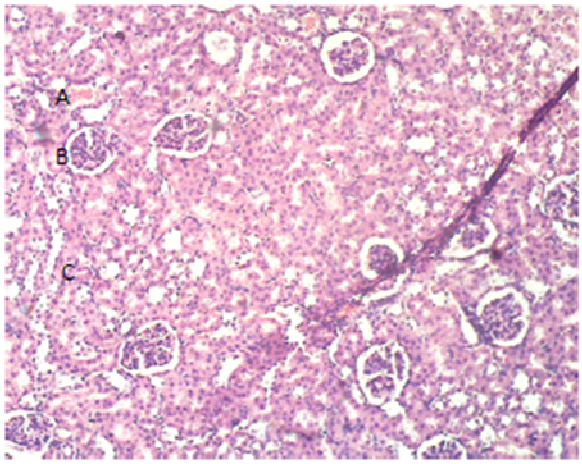

Plate 7. Histopathology of the kidney treated with 400 mg of methanolic extract of *Citrullus lanatus* seeds. (X400).
(Cortical part) A= Proximal Tubule, B= Bowman's capsule, C= Distal tubule, Normal histology of the kidney, No evidence of necrosis.

the 200 mg of methanolic extract administered to the rat. The result in plate 7 showed a near total recovery of the kidney cells. The Bowman's capsules were many and distinct. This occurred due to the 400 mg of methanolic extract administered to the rat. These results revealed that aqueous and methanolic extract of *Citrullus lanatus* have healing/corrective effects on damaged kidneys. From this research work, it had been established that extracts of watermelon seeds have corrective effect on a physiological saline and paracetamol induced kidney damaged in rats, within 28days of administration. This work buttress the previous works of some authors on the correction of kidney damage using plant extracts (Oyewo *et al.* 2012, Erhirhie and Ekene, 2013).

It has been widely known that plant medicine (phytomedicine) plays an important role in healthcare delivery in many parts of Africa and the rest of the world (Elujoba *et al*., 2005). For better and effective healthcare delivery to be achieved, orthodox medicine must be complemented with the use of plant medicine. At least 80% of Africans depends on plant medicine for their health care (Sofowora, 1993). Fruits and vegetables have been recognised as natural sources of various bioactive compounds (Penningtonand Fisher, 2010) which could be attributed to their phytoconstituents shows flavonoids, anthocyanins, vitamin C and vitamin E, phenolic compounds, dietary fiber and carotenoids are present in fruits and vegetables (Gonzalez-Aguilar *et al*., 2005). The extracts used in this research work showed that seed extracts of watermelon has regenerative and nephoprotective effects on the kidneys of rats. The seed has been used in the treatment of ulcer, diabetics, diarrhoea, bed-wetting, gonorrhoea, hypertension, alcohol poisoning, urinary infections, dropsy and renal stones and inhibition of bacteria activity (Naresh *et al.* 2011, Erhirhie and Ekene, 2013, Hussam, 2016). Extract of watermelon seeds possess nephroprotective phytochemicals which were able to correct and heal the kidney damage inflicted by overdose of physiological saline and acetaminophen in female albino rats.

CONCLUSION

Administration of aqueous and methanolic extracts of watermelon seeds on acetaminophen and physiological saline –induced kidney rats for 28days showed regenerative and corrective effects on the damaged kidneys of the rats. Some of the rats were able to regenerate the damaged parts and were able to compete with untreated rats for food and mates after the experiment. This study shows that extracts of watermelon seeds have positive effects on the health of rats. The results of the histopathology showed that the extracts of watermelon seeds were able to activate the immune systems of the rats. It is obvious that watermelons, apart from being valuable fruits containing nutritionally important nutrients are also valuable in correcting renal damage in rats. The crop also contains nutritionally valuable and immunogenic properties which prevented the organ (the kidney) from irreparable damage.

ACKNOWLEDGEMENT

The authors are grateful to Mr. Oguntokun M.O. (Central laboratory, Federal University of Technology, Akure) for the technical assistance.

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