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Gum Arabic (*Acacia senegalia*) Sap Exacerbates Diclofenac-induced Liver and Kidney Damage in Albino Rats

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ABSTRACT

Introduction: gum arabic is a complex polysaccharide used in traditional folklore as a restorative agent useful for its curative purposes for patients with renal and liver disorders. Diclofenac is one of the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) in the world well-known for its analgesic and anti-inflammatory properties. Despite these therapeutic actions of diclofenac, it has adverse effects and has been used to induce hepatotoxicity in research studies. A potential therapeutic agent that could arrest or reverse its cytotoxic action and preserve the histo-architecture of the renal and hepatic tissue is desirable. In this study, gum arabic was selected as the therapeutic agent.

Methods: wistar rats were divided into five groups. There was a control group, four others were administered diclofenac to induce renal and hepatotoxicity. Gum arabic at different concentrations was administered to observe its effect on the histology of the liver and kidney.

Results: rats treated with diclofenac showed atrophied hepatocytes, inflammatory cells and widened sinusoids. The renal tissue showed degeneration in renal tubules, reduced Bowman's space and interrupted Bowman's capsule. Liver tissue treated with gum arabic showed focal haemorrhage in the hepatic tissue and coagulative necrosis of hepatocytes. The kidney showed congestion of the renal glomeruli with degenerative changes in Bowman's capsule.

Conclusion: vitamin C treatment protected the histological architecture of the liver and kidney, restoring the integrity of glomerular cells and re-establishing Bowman's space. In the liver tissue however, the inflammatory cells were increased around the central vein with observed distortion of the hepatocytes and sinusoidal spaces.

Keywords: Diclofenac; Histology; Liver; Kidney; Vitamin C; Hepatocytes.

Introduction

Traditional medicine is recognized as the preferred primary health care system in many populations, with over 60% of the world's inhabitants and about 80% in developing countries depending directly on medicinal plants for their medical purpose[1]. This could be due to several reasons including affordability, accessibility, and low cost[2]. Modern medicine also utilizes active compounds isolated from medicinal plants and about 80% of these active ingredients indicates a positives correlation between their modern therapeutic use and the traditional uses[3]. Medicinal plants are used by 80% of the world population especially in developing countries to cure and improve the general health, principally due to common belief that plant derived drugs have less side effect along with being economically and locally accessible[4].

Out of many medicinal plants, Acacia senegal (Gum Arabic) has recently attracted the attention of scientists across the globe[5-8]. Gum Arabic or Acacia Gum is the term used to refer to the non-viscous liquid collected from the exudate of Acacia senegal stem and branches. It is a complex composite of glycoproteins, polysaccharides and salts that takes the form of solid spheroidal blobs of varying size[7]. The gum of Acacia senegal ranges in colour from pale white to orange-brown and possesses a matt surface texture[8]. When processed to the broken or kibbled state, it acquires a polar and glassy appearances[4]. Gum arabic dissolves well in water and does not interact with other chemical compounds. It is odourless, tasteless, and translucent and has been used pharmaceutically as a vehicle for drug delivery[9]. Gum arabic has been reported to have antioxidant activity and has a curative effect different system abnormality such as the urinary tract, cardiovascular and gastrointestinal disorders[10], lowering blood level of liver enzymes, total proteins and bilirubin as well as reversing the liver damaging effects of gentamicin and alloxan[11].

Diclofenac sodium was introduced in late 1970s as a potent anti-inflammatory and analgesic agent, whose on long term use has shown hepatotoxic effects, which presented in the form of hepatic injury ranging from mild to fatal liver[12]. Non-steroidal anti-inflammatory drugs (NSAIDS) are massively consumed internationally and with some anti-microbial agents are the most frequent causes of drug-induced liver injury[13]. Diclofenac is the most widely used NSAIDS

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in the world[14]. It belongs to non-steroidal anti-inflammatory drug (NSAID) family. It is a phenylacetic acid derivative which is well-known for its analgesic and anti-inflammatory properties[13,15-16]. It has also been found to have antipyretic and anti-bacterial effects[13,17]. Despite these therapeutic actions of diclofenac, it has observed adverse effects and has been used to induce hepatotoxicity in many research studies[18]. Diclofenac was chosen for the current study because it is a commonly used agent and well documented agent for inducing hepatotoxicity in drug induced liver injury (DILI) in many documented research studies.

The mechanism of diclofenac-induced hepatotoxicity has been partially attributed to; mitochondrial injury[19], generation of oxidative stress[20] and immune-mediated mechanisms[21]. Some studies indicated that the metabolites of diclofenac are capable of causing apoptosis in hepatocytes[22].

Many studies have reported the efficacy of Vitamin C in playing a hepato-protective role in animal and human studies. Vitamin C has been reported to have antioxidant properties, being an important free radical scavenger, trapping free radicals and protecting biomembranes from peroxide damage as well as being an electron donor[23].

Diclofenac affects many organs including many organs including liver in the body, research undertaken by several physicians proves that the drugs used for treatment of diclofenac induced liver damage are expensive and increases risk of adverse side effect. Therefore, a potential therapeutic agent that could arrest any of the pathological pathways activated by diclofenac, could be used to arrest or reverse its cytotoxic action and preserve the histo-architecture of the renal and hepatic tissue. This study was undertaken to find the hepato-protective drug effect of aqueous Acacia senegal (Gum arabic) extract on the liver and kidney tissue in Wister albino rat to observe if it would have an ameliorative effect on diclofenac induced liver damage.

Method and Methodology

Plant Authentication, Preparation, Extraction and Storage

Gum Arabic (sap) was purchased from a local herb store in the local market and was identified and authenticated by a Botanist from the Department of Biological Science, Faculty of Sciences, University of Maiduguri. The Gum Arabic (sap) was crushed to smaller fragments mechanically. 3200g of the extract was soaked in 5 litres of distilled water for 48 hours. The extract was then filtered, the liquid component was removed using an evaporator and allowed to dry.

Animal Husbandry

Thirty-five (35) albino rats weighing 100-200g body weight were obtained from the Department of Human Physiology University of Maiduguri and housed in the Animal House of the Faculty. The cages were kept at room temperature, humidity and 12 hours light, 12 hours dark cycle which were suitable for the rats. The animals were allowed to acclimatize for a period of 21 days before the start of the experiment. The rats were fed with standard rat chow and water ad libitum.

Experimental Design

The rats are grouped into five groups (A, B, C, D and E) as indicated in Table 1. The extract was administered to the rats daily for a period of 7 days.

Table 1. Experimental groups and their respective treatment.

Groups	Treatment
Group A (Control)	Standard pellet and water
Group B (Negative Control)	50mg/kg Diclofenac
Group C (Low Dose)	50mg/kg Diclofenac + 200mg/kg of Gum Arabic
Group D (High Dose)	50mg/kg Diclofenac + 400mg/kg of Gum Arabic
Group E (Positive Control)	50mg/kg Diclofenac + 100mg/kg of vitamin C

Animal Sacrifice

Ketamine hydrochloride (100mg/kg) was used to induce unconsciousness during the sacrifice of the rats at the end of the experimental period. A laparoscopic procedure was performed with a vertical midline incision to expose the abdominal organs. The peritoneal cavity was accessed and the liver and kidney tissue was carefully dissected out. The kidney and liver were quickly weighed to determine of the ratio of kidney and liver to body weight. The kidney and liver tissue were then fixed in 10% formalin solution for routine histological evaluation. After fixing in 10% formalin, the kidney and liver tissue was dehydrated in graded series of alcohol, cleared in xylene, and embedded in paraffin wax. The tissues were sectioned at 4 μm with a rotary microtome and stained with haematoxylin and eosin (H and E).

The kidney index was calculated by dividing the mean weight of the kidneys by total body weight and multiplying by 100%.

Statistical Analysis

The data obtained from measurements made above were analysed using GraphPad Prism 9.1.0. $P<0.05$ was considered significant. The results of all data were presented as mean ± standard error of the mean; the one-way analysis of variance (ANOVA) was adopted.

Results

Effect of Arabic Gum on Weight of Wistar Rats

Figure 1 showed 7.3% increase in the weight of rats at the end of the experimental study in Group A. There was a marked decrease (-12.7%) in the weight of rats in Group B. The weight from the experimental groups showed a decrease in the low dose (-5.6%) and high dose (-9.1%). The positive control group had the greatest reduction of weight (-17.7%).

Table 2 represents the weights of right and left kidneys (as in Figure 2) and the average weight of the kidneys in the rats used in the experimental study. The kidney in Group B were weightiest when compared to the other groups as the kidney mass weighed 0.63g compared to the weight of the kidney in the control group which weighed the lightest at 0.49g. Kidney index was also presented in Table 2 showing that Group A had the lowest percentage (2.8%) and Group B had the highest kidney index (4.1%).

The weights of the liver in experimental animals in all groups was also included in Table 2. Rats in Group B also had the weightiest liver when compared to the other groups as the average weigh of the liver tissue in that group was recorded as 4.9g. The liver index was also highest in Group B and lowest in the control. The liver in the rats in Group E was lightest with a weight of 4.0g (Figure 3).

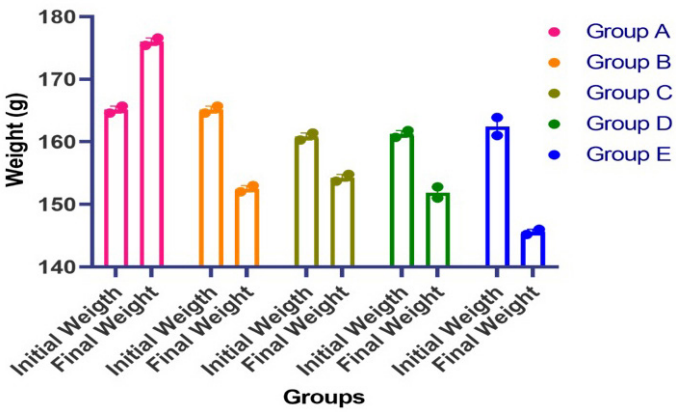

Figure 1. Showing the initial versus the final weight of rats in all groups.

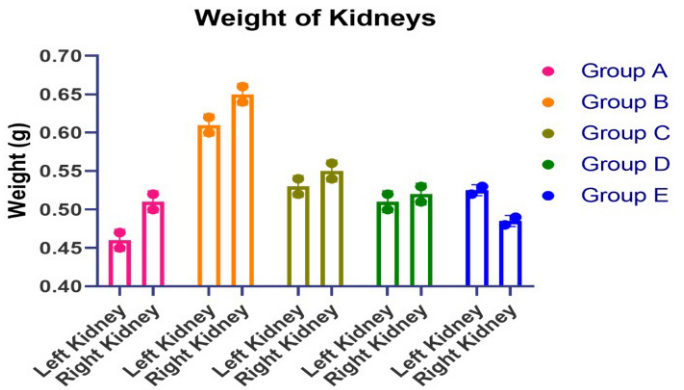

Figure 2. Showing the difference in the weigth of the left versus right kidney at the end of the experimental period.

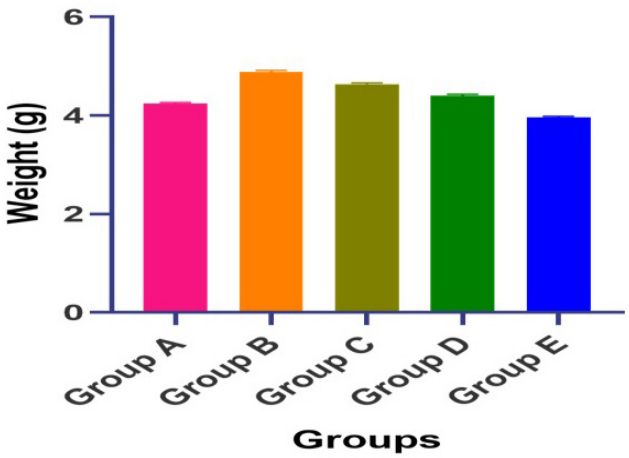

Figure 3. Depicting the weight of the liver in all groups at the end of the experimental period.

Histological Observations

Figure 4A depicts the micrograph of the animals in the Group A showing the histo-architecture of the liver with hepatocytes radiating towards the central vein which was intact and undisrupted, enclosing red blood cells. The sinusoids were located between hepatocyte cords and also contained red blood cells and lined by flattened endothelial cells as observed. The hepatocytes had a highly eosinophilic cytoplasm with darkly stained nucleus which had distinct nucleoli. Very few lymphocytes were found in the hepatic parenchyma and were recognizable by their rounded and condensed nuclei (Figure 4A).

Table 2. showing the weight of the left and right kidney and liver, average weight of the kidneys, liver and kidney indices.

Groups	Left Kidney (g)	Right Kidney (g)	Average Weight (g)	Weight of Kidney/ Total Body Weight	Kidney Index (%)	Weight of Liver (g)	Weight of Liver/ Total Body Weight	Liver Index (%)
Group A	0.46	0.51	0.49	0.0028	2.8	4.2	0.024	2.37
Group B	0.61	0.65	0.63	0.0041	4.1	4.9	0.032	3.20
Group C	0.53	0.55	0.54	0.0034	3.4	4.6	0.030	3.00
Group D	0.51	0.52	0.52	0.0033	3.3	4.4	0.029	2.90
Group E	0.52	0.48	0.50	0.0034	3.4	4.0	0.028	2.80

The liver of rats in Group B which had been treated with 50mg/kg of diclofenac showed hepatocytes that were shrunken when compared to Group A. the sinusoids were widened as a result of this shrinkage and the endothelial cells which lined the sinusoids were displaced into the sinusoidal spaces. The cytoplasm of the hepatocytes remained eosinophilic and the nucleus was also darkly staining with observable nucleolar blobs. Numerous lymphocytes were found close to the central vein which showed minimal disruption along the flattened endothelial cells which lined the veins (Figure 4B)

The micrograph of liver of rats in Group C showed lightly stained cells which were not as eosinophilic as observed in the other groups. The hepatocytes displayed a granular appearing cytoplasm and displayed cells that had clear nuclei. The central vein was interrupted and blood constituents were seen invading the hepatic parenchyma. The sinusoids were also widened and contained several lymphocytes (Figure 4C)

The micrograph of rats in Group D showed hepatocytes with eosinophilic cytoplasm and darkly stained nuclei which showed several nucleoli. The sinusoids were also widened and central vein was discontinuous which allowed the passage of lymphocytes into sinusoidal spaces along with blood constituents (Figure 4D).

The hepatocytes in the micrograph of the rats in group E showed a restoration in the cord-like arrangement with the cells radiating towards the central vein as observed in Group A. The endothelial cells lining the central vein were continuous and the sinusoids were clear and evenly spaced. Numerous lymphocytes were aggregated towards the space between the central vein and the hepatocytes close to the vein (Figure 4E)

Figure 5A represents the micrograph of the kidney in Group A showing normal histological features of the kidney. The renal corpuscle was depicted the glomerulus suspended in Bowman's space with Bowman's capsule remaining intact. The renal tubules were intact and the lumen was easy to visualize in both proximal and distal convoluted tubules (Figure 5A).

Figure 5B shows the renal corpuscle in the rats in Group B showing a glomerulus that is suffused with blood and dilated. Bowman's space was reduced and the capsule was discontinuous leading to areas where the glomerulus was in contact with renal tubules. The renal tubules were also disorganized and harder to differentiate (Figure 5B)

Group C micrographs showed the kidney in the extract-treated group showing a restoration of Bowman's capsule. The glomerulus was still blood-filled and Bowman's space also reduced when compared with the rats in the control group (Figure 5C)

The rats in Group D also had reduced blood constituents in the glomerulus but Bowman's space and capsule were intact. The renal tubules appeared distorted and disorganized (Figure 5D).

Figure 5E demonstrated the kidney in Group E rats showing discontinuous Bowman's capsule, continuous Bowman's space and bleeding in the renal parenchyma just below Bowman's capsule. The renal tubules were more organized than in the arrangement observed in rats in Group D.

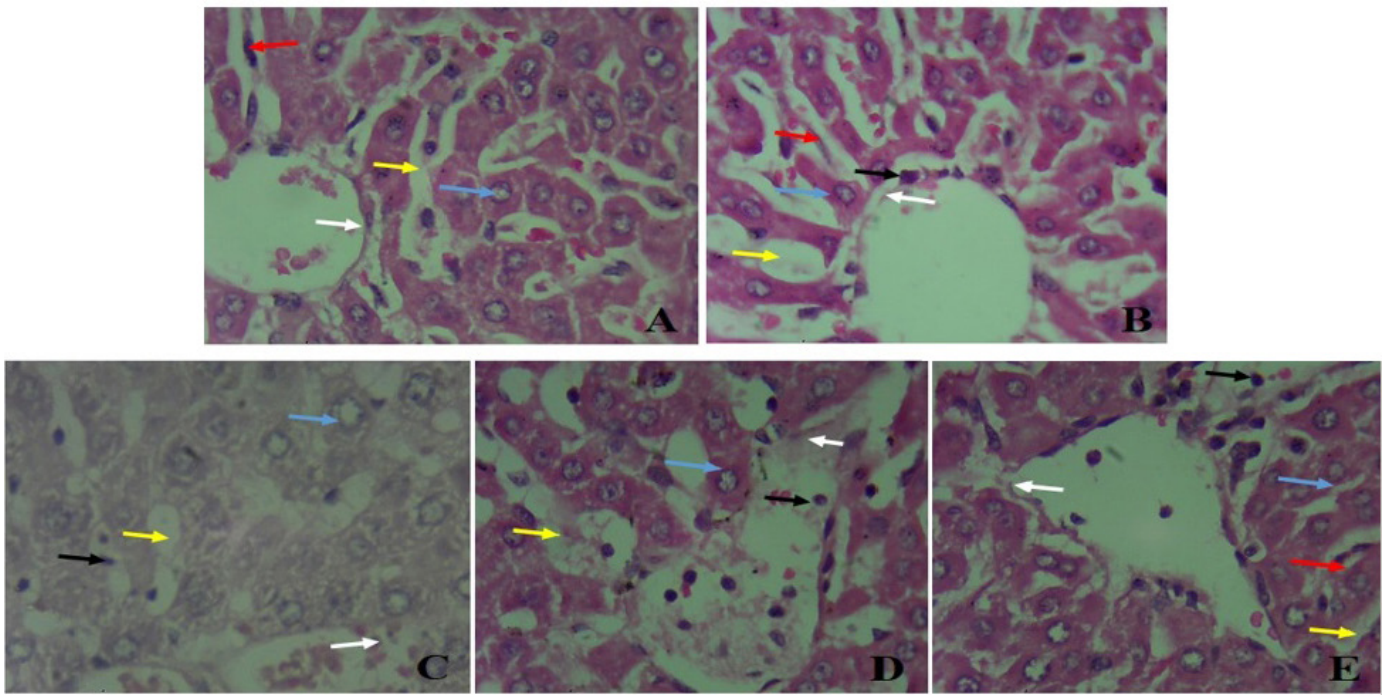

Figure 4. Showing the liver in Groups A-E showing hepacytes (blue arrow) sinusoids (yellow arrow), central vein (white arrow), endothelial cell (red arrow) and lymphocytes (black arrow). H and E X 400.

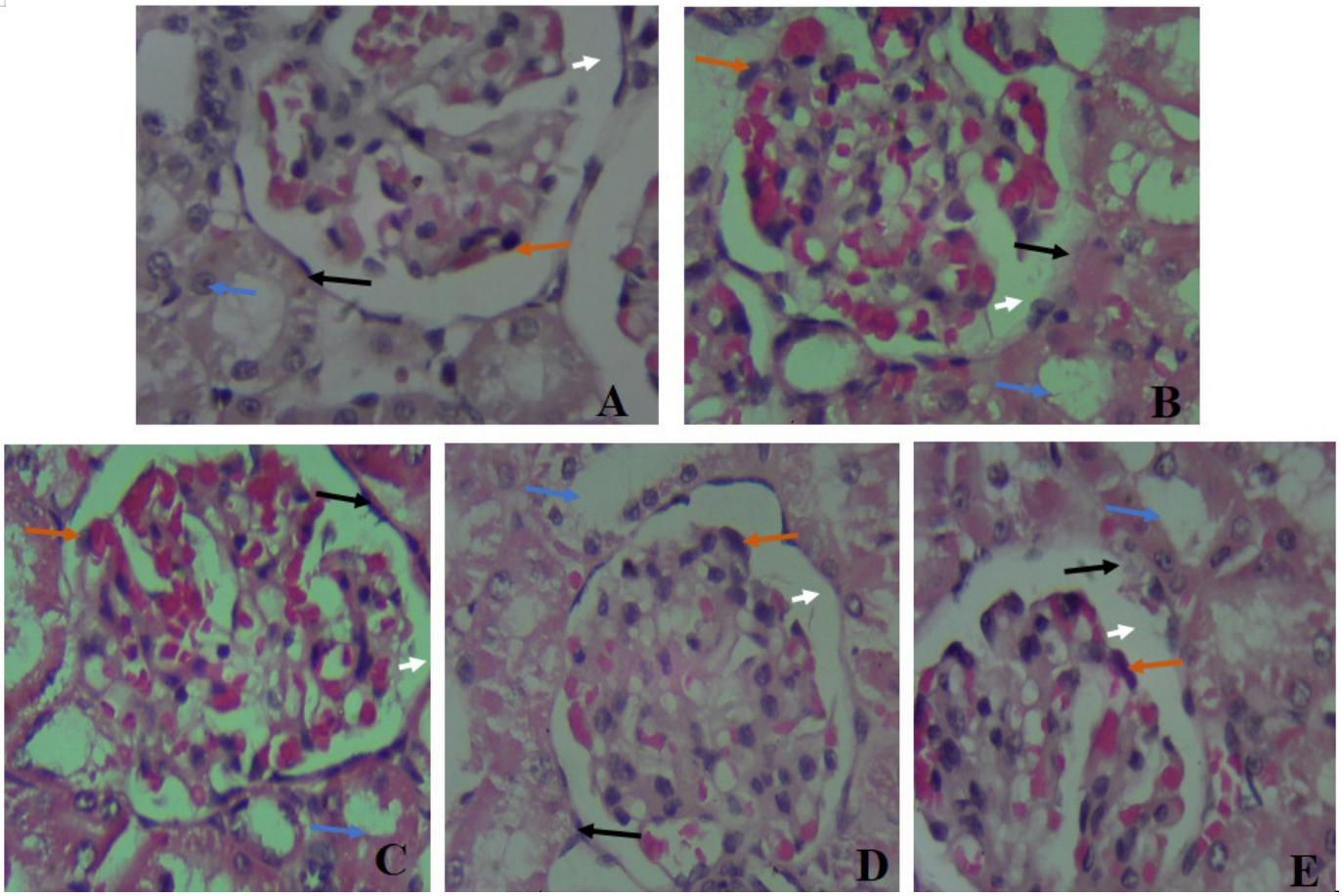

Figure 5. Showing the renal corpuscle in Groups A - E Showing the glomerular basement (black arrow) which is discontinuous in Groups B and E. Bowman´s space (white arrow) is reduced in Groups B, C and D. Podocytes (orange arrows) are also found lining the glomeruli within the renal corpuscle H and E x400.

Discussion

Gum arabic is a complex polysaccharide that is often used as a suspending agent. It also has varied uses in traditional folklore as a restorative agent useful for its curative purposes for renal failure patients and for individuals with liver disorders[24-26].

In the present study, the weight of the rats in the control group increased at the end if the study compared to the groups that were treated with diclofenac and this could be attributed to decreased feeding which led to a consequent weight loss. Gum arabic was found to significantly increase the weight of the kidney in the groups that were treated with diclofenac alone.

In agreement with the result obtained above, a study conducted by[27], showed that rats treated with diclofenac exhibited a significant decrease in body weight as a result of a reduction in food and water intake during the period of the study. There was also a reduction on the weight of the kidney and liver tissue, however, there was no observable histological changes neither were there changes in haematological parameters in the rats. Another study[28] and[29] concluded that healthy rats administered Gum arabic at doses of 200 mg/kg or 400 mg/kg or 600 mg/kg orally for 2 weeks had distorted normal body chemistry reflected in body weight reduction due to uremia. Weight reduction in groups treated with gum arabic was also attributed to slowed intestinal glucose transport[29].

The micrograph of the rats treated with diclofenac showed characteristics of liver damage with the atrophied hepatocytes, presence of inflammatory cells and widened sinusoids. The renal tissue also showed signs of degeneration with the renal tubules and reduced Bowman's space and interrupted Bowman's capsule. This observation is similar to the result observed in studies conducted by other researchers where the micrograph of rats treated with diclofenac showed distorted central vein, significant infiltration with inflammatory cells, normal and dead hepatocytes, and marked degeneration of hepatic tissue[13,30]. [12]and[31] reported mild necrosis observed in the liver of rats administered with diclofenac and there was also observable infiltration of lymphocytic and neutrophilic infiltration around the hepatic portal vein. Observed also was mild disruption of the portal vein, enlarged portal tract, mild fibrous tissue proliferation, interstitial and portal tract inflammation. This was attributed to formation of reactive metabolites around the portal vein leading to apoptosis. [32] reported aggregation of Kupffer cells and nuclear degeneration.

The present study presented histological features as observed in the study conducted by[29] where gum arabic was administered in several concentrations. The liver tissue treated with gum arabic showed focal haemorrhage in the hepatic tissue and coagulative necrosis of hepatocytes. The kidney of rats that were treated with gum arabic showed congestion of the renal glomeruli with degenerative changes in Bowman's capsule in the lower concentration. [29] observed necrotic changes in the renal tubules and glomerulus which was not observed in the current study. [33] also observed that gum arabic did not protect or repair hepatocyte deterioration induced by diethylnitrosamine/tetracycline and did not induce cellular apoptosis. [34] also revealed that liver histology of healthy mice treated with gum arabic alone in showed many pathological changes in hepatic architecture. However, contrary to these findings, [35] concluded that pre-treatment with gum arabic was able to protect mice against acetaminophen-induced liver damage.

Vitamin C treatment slightly protected the histological features in the liver and kidney tissues, restoring the integrity of the glomerular cells and re-establishing Bowman's space. In the liver tissue however, the inflammatory cells were increased around the central vein with observed distortion of the hepatocytes and sinusoidal spaces. The reason for this was not known but in similar studies, other researchers have found out that vitamin C restored histological damage associated with hepatic damage and their effect was attributed to the inhibition of free radical generation and free radical scavenging activity[36].

Conclusion

In the current study, Gum Arabic was administered in rats to treat diclofenac-induced renal and hepatotoxicity. Contrary to folkloric belief, gum Arabic did not protect the histo-architecture of the hepatic and renal tissue. In the groups treated with vitamin C with the hope of ameliorating the effect of diclofenac, there was little preservation of the histology of the tissue in these groups.

Recommendation for Further Studies

It is recommended that the effect of the extract be carried out on biochemical and oxidative stress parameters and also cellular death should be determined by TUNEL assay to identify and qualify apoptotic cells and determine DNA damage in individual cells in the kidney and liver tissue.

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