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Methanolic Leaf Extract of *Andrographis paniculata* Mitigates Aspirin Induced Ulcerogenic and Biochemical Changes in Wistar Rats

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Abstract **Original Research Article**

This study was aimed at evaluating the ameliorative effect of methanol extract of *Andrographis paniculata* by aspirin induced ulcerogenic and biochemical changes in wistar albino rats. This study was measured by the following parameters; Total protein, Total Bilirubin, Albumin and Superoxide Dismutase (SOD). Fifty rats (weighing about 150-250g) were evenly distributed into 5 groups of 10 rats each. Group 1 (Normal control) and group 2 (Positive control) received normal saline (10ml/kg), group 3 and 4 received 200mg/kg body weight and 400mg/kg body weight of the extract respectively and group 5 (standard) received 30mg/kg body weight omeprazole orally for 7 days. On day 7, groups 2,3,4 and 5 were fasted for 24 hours and on the 8th day the animal were induced with 200mg/kg body weight of aspirin orally. The animals were euthanized on the 9th day using chloroform anaesthesia. Blood was collected by puncturing the heart to perform a liver function assay. A portion of the liver and gastrointestinal tract of the rats were removed and preserved in 10% formalin for histological studies. The liver was also homogenised to conduct a lipid peroxidation assay. The study discovered that serum total protein, serum albumin and SOD activities in the positive control were significantly decreased ($p<0.05$) and total bilirubin was significantly increased when compared to normal control. However, pretreatment with *Andrographis paniculata* (200 and 400 mg/kg body weight) in groups 3 and 4 respectively, significantly increased the levels of SOD activities, serum total protein, albumin and significantly decreased the level of total bilirubin compared to the positive control group. Treatment with omeprazole at dose 30mg/kg body weight also caused a significant decrease ($p<0.05$) in total bilirubin level and an increase in total protein, albumin and SOD compared to the positive control. These findings are confirmed by the histopathological results obtained. The results of the present study indicate that methanolic extract of *Andrographis paniculata* may possess antioxidant phytochemicals that may confer hepatoprotective activities on aspirin induced albino rats.

Keywords: *Andrographis paniculata*, *O*meprazole, Ulcerogenic, Hepatoprotective, Aspirin.

INTRODUCTION

Medicinal plants are essential in traditional medicine, providing a natural approach to treating chronic conditions (Hosseinzadeh *et al*., 2015). According to Chaudhary *et al*., (2010), with over 80,000 plant species identified for their therapeutic properties, the bioactive phytochemicals found in these plants serve as primary or secondary metabolites, offering a diverse range of health benefits. Medicinal plants possess bioactive organic substances known as phytochemicals, which serve as a defence against various chronic diseases, including those caused by metabolic or genetic dysfunction as well as infectious disorders. The medicinal characteristics of plants can be acquired from various plant components, such as leaves, roots, bark, fruits, seeds, and flowers. Various components of plants can harbour distinct bioactive compounds within a single plant. Phytochemicals carry out intermediate metabolic processes and serve as primary metabolites, such as

lipids and sugars, which are present in all plants. On the other hand, secondary metabolites are found in a narrower range of plants and have specific roles (Olasehinde *et al*., 2012). Notably, Andrographis paniculata stands out for its pharmacological actions, including antidiarrheal, anti-inflammatory, and immune-stimulatory properties, making it a widely used medicinal herb across various regions (Nyakudya *et al*., 2020). Andrographis paniculata is a globally used and significant medicinal herb. It is a member of the Acanthaceae family. Andrographis paniculata is used as a traditional medicinal herb in Bangladesh, China, Hong Kong, India, Pakistan, the Philippines, Malaysia, Indonesia, and Thailand. It is commonly employed in ethnobotany for the treatment of snake bites, insect bites, diabetes, diarrhoea, fever, and malaria. This plant, Andrographis paniculata, has many medical uses. It can help with diarrhoea, hepatitis, high blood sugar, infections, malaria, cancer, the heart, HIV, cytotoxicity, protecting the liver, and boosting the immune system.

On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin work by inhibiting prostaglandin synthesis through COX inhibition, effectively relieving pain and inflammation. As the inhibition of COX-1 by NSAIDs increases, so does its propensity to induce ulcers and facilitate bleeding. Nonsteroidal anti-inflammatory drugs (NSAIDs) lower blood flow to the kidneys, which makes diuretics less effective and lithium and methotrexate less likely to be flushed out of the body (Chikezie *et al*., 2015). Aspirin, a unique nonsteroidal anti-inflammatory medicine (NSAID), not only addresses fever and inflammation but also plays a crucial role in preventing blood clot formation over an extended period of time. Despite their effectiveness, NSAIDs can lead to side effects such as ulcers, bleeding, and reduced kidney function, affecting the efficacy of other medications like diuretics, lithium, and methotrexate. The reference is from Varga *et al*., (2017).

MATERIALS AND METHOD

Collection of Plants Material

Andrographis paniculata plant was collected in Benin Cityu, Edo state, Nigeria by Prof. Ching F. Poh, Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Amassoma, Bayelsa state. The plant was identified and authenticated by Professor Ayibesin Kolawale, Department of Pharmacognosy, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Amassoma, Bayelsa state.

Preparation of plant extract

After collecting the fresh plants of *Andrographis paniculata*, they were allowed to dry for 3 weeks under room temperature. The leaves were grinded to powder form using dry grinder then stored in a closed container for extraction.

Extraction Method

The grinded powder of *Andrograhis paniculata* leaves was weighed (604g) and was subjected to extraction with (3L) of methanol for 48 hours. The methanol extract was collected, filtered and evaporated under reduced pressure at 500C and 40rpm with Rotary vacuums evaporator, the residue was weighed (65.9g) and preserved in a refrigerator at 40C for further use.

Animal and Diet

Fifty healthy male Wistar rats weighing between (150-250g) were bought from the Animal house in the old Faculty of Pharmacy in University of Benin, Edo State. The animals were housed in ventilated polypropylene cages in the animal farm experimentation room of the Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, under room temperature with relative humidity of 45-55% and 24 hours and dark/light cycle (12:12). They were acclimatized for 2 weeks before the experiment and were fed with standard laboratory animal feed (pelletized feeds) and water throughout the experiments.

Equipment/ Apparatus

Test tubes, test tube rack, electronic balance, rotary evaporator, measuring cylinder, masking tape, beakers, diaphragm vacuum pump (model:GM-1,00), permanent marker, latex gloves, syringes, centrifuge, spectrophotometer (VIS-spectrophotometer S23A 18094), Amber bottles, universal sample bottles, foil, refrigerator, water bath. All equipment used where all analytical standard.

Chemicals/Reagents

Tween 80, Methanol, Randox Biochemical Kits of total Protein, Bilirubin, Albumin, Distilled Water. Chemicals and reagents used were of standard analytical grade.

Experimental Design

Fifty (50) healthy male albino rats were distributed into five (5) groups and were pretreated for 8 days as follows:

Group 1 (Normal Control): Feed + distilled water

Group 2 (Positive Control): Feed + distilled water + 200mg/kg body weight of aspirin

Group 3 (Test group 1): Feed+distilled water+200mg/kg body weight of methanolic extract of *Andrographis paniculata*+200mg/kg body weight of aspirin.

Group 4 (Test group 2): Feed+distilled water+400mg/kg body weight of methanolic extract of *Andrographis paniculata* +200 mg/kg body weight of aspirin.

Group 5 (Standard group): Feed+distilled water+ 30 mg/ body weight of Omeprazole+200 mg/kg body weight of aspirin.

On the 8th day of the study, animals in groups 2,3,4 and 5 were orally given 200 mg/kg body weight of aspirin and were sacrificed after 24hours.

Collection of Samples

On the 9th day of the study, animals were anaesthetized with chloroform and sacrificed. Using a 5ml syringes blood samples were collected from each rat via cardiac puncture. The blood was dispensed in plain samples bottle for coagulation. After coagulation the serum was separated from the whole blood by centrifuging at 4000rpm for 10minutes and was collected for biochemical analysis.

Biochemical Assays

Determination of Total Protein

Total proteins test kit is for the quantitative determination of total proteins concentration in human serum or plasma.

Principle

Alkaline

$$\text{Protein} + Cu^{++} \xrightarrow[pH]{} Cu^{-}\ \text{Protein Complete}$$

The presence of protein in serum results in the formation of a violet coloured complex when it reacts with cupric ions in an alkaline solution. The intensity of the colour violet is directly proportional to the quantity of protein present in relation to a solution with a known protein concentration. Pyrogallol red forms compounds with proteins in an acidic environment that contains molybdate ions. The resultant complex with a blue colour exhibits maximum absorption at a wavelength of 600 nm.

Determination of Bilirubin

The procedure for determining the amount of total bilirubin involves the use of caffeine, which causes the release of bilirubin bound to albumin. This released bilirubin then reacts with diazotised sulphanilic acid.

Principle of Bilirubin

Total bilirubin is determined in the presence of caffeine, which releases albumin bound bilirubin, by the reaction with diazotised sulphanilic acid.

Determination of Albumin

The binding of albumin with Bromcresol Green (BCG) results in a shift in the absorbance peak of BCG. The change can be quantified using spectrophotometry and utilised to ascertain the concentration of albumin.

Principle of Albumin

Albumin is specifically bound to bromcresol green, resulting in the formation of a coloured complex that can be detected using photometric techniques.

Determination of Superoxide Dismutase (SOD)

Superoxide dismutase (SOD) catalyses the dismutation of superoxide radical (O_2) to yield Hydrogen peroxide and oxygen.

$$2O_2 + 2H^{+} \xrightarrow{SOD} O_2 + H_2O$$

The method of Marklund (1974) with some modification, which is an assay based on the ability of SOD to inhibit autoxidation of pyrogallol was used for the determination of the activity of this enzyme.

Principle

$$\text{Pyrogallol} + O_2 \underset{\text{Inhibition of SOD}}{\overset{\text{Autoxidation}}{\longleftrightarrow}} O_2 + \text{Oxidation product}$$

RESULT

Effects of aspirin and *Andrographis paniculata* on the Mean Body Weight(g) of the Male Wistar Albino Rats

Decrease in mean body weight, in *Andrographis paniculata*treated rat, at the end of the study. Extract of andrographis paniculata at 200 and 400 mg/kg of body weight, ($p < 0.05$) (Table 1).

Effect of *Andrographis paniculata*on Aspirin-induced hepatic changes in wistar rats

Administration caused a significant decrease ($p<0.05$) in serum Total Protein (2.26±0.39), Albumin (1.94±2.02) and GIT tissue SOD (4.83+1.15) in comparison with the normal group. It also caused a significant increase in total bilirubin (4.39±0.35) in relation to normal rats. Treatment with *Andrographis paniculata* extract at dose 200mg/kg and 400mg/kg respectively significantly increased Total protein (4.41±0.15and 5.96±0.49), albumin (3.44±0.17and 4.51±0.06) and SOD (6.86+0.07 and 7.82+0.062) compared to the positive control group. It also caused a significant decrease in total bilirubin (3.22±0.26and 3.03±0.35) compared to the positive control group. Similarly, the administration of Omeprazole significantly increased activity of total protein (6.05±1.82), Albumin (4.57±0.03) and SOD (8.04±0.24).) and also decreased the level of total bilirubin compared to the positive control group.

Ulcer index for each of the group and the protection percentage

Administration of aspirin 200mg/kg caused ulceration of GIT lining which was used as an index to evaluate the percentage of inhibition by the extract. Result obtained showed that administration of the extract (200 and 400mg/kg) gave a percentage inhibition of 13.85% and 22.29% respectively while the Omeprazole group (standard) gave a percentage inhibition of 26.20% compared to positive control.

Table 1: Effect of ethanol extract of *Andrographis paniculata* leaf on body weight of wistar albino rats

	WEIGHT (MEAN ± STANDARD DEVIATION)	
	BEFORE PRETREATMENT	**AFTER PRETREATMENT**
GROUP 1 Normal control	236.77 ± 21.302[a]	223.44 ± 22.979 [a]
GROUP 2 Positive control	155.185 ± 19.183 [a]	151.616 ± 17.406 [a]
GROUP 3 Test group 1 with 200mg/kg body weightof extract	223.239 ± 34.209 [b]	204.404 ± 30.366 [b]
GROUP 4 Test group 2 with 400mg/kg body weight of extract	199.511 ± 28.281 [c]	182.846 ± 27.330 [c]
GROUP 5 Standard group with 30mg/kg body weight of Omeprazole	206.056 ± 33.681 [d]	185.113 ± 31.966 [d]

Data are expressed as the MEAN ± SD (n= 10). Means with the same superscript letters on the same row are not significantly different ($p \leq 0.05$)

Table 2: The protective effect of *Andrographis paniculata*on Aspirin-induced hepatic changes in wistar rats

Groups	Total Protein (g/dl)	Bilirubin (µmol/l)	Albumin (g/l)	SOD (GIT) (ml)
Group 1 (feed and water)	6.76±0.30[a]	1.48±0.39[a]	4.54±0.23[a]	8.81±1.04[a]
Group 2 (200mg/kg aspirin)	2.26±0.39[b]	4.39±0.35[b]	1.94±2.02[b]	4.83±1.15[b]
Group 3 (200mg/kg extract 200mg/kg aspirin)	4.41±0.15[b]	3.22±0.26[c]	3.44±0.17[c]	6.86±0.07[c]
Group 4 (400mg/kg extract + 200mg/kg aspirin)	5.96±0.49[d]	3.03±0.35[c]	4.51±0.06[a]	7.82±0.062[a]
Group 5 (30mg/kg Omeprazole + 200mg/kg aspirin)	6.05±1.82[e]	1.94±0.54[a]	4.57±0.03[a]	8.04±0.24[a]

Values are expressed as MEAN ± SD (Standard deviation), values with different superscript from control are statistically different at ($p<0.05$).

Table 3: Ulcer index and protection percentage

GROUP	PERCENTAGE PROTECTION
GROUP 1 Normal control	**100%**
GROUP 2 Positive control	**0%**
GROUP 3 Test group 1 with 200mg/kg extract	**13.85%**
GROUP 4 Test group 2 with 400mg/kg extract	**22.29%**
GROUP 5 Standard group with 30mg/kg of Omeprazole	**26.20%**

HISTOPATHOLOGY OF THE GASTROINTESTINAL TRACT

Photomicrographs of GIT tissue of an adult Wistar albino rat stained with haematoxylin and Eosin technique Transverse section of haematoxylin and Eosin stained slides X400 magnification.

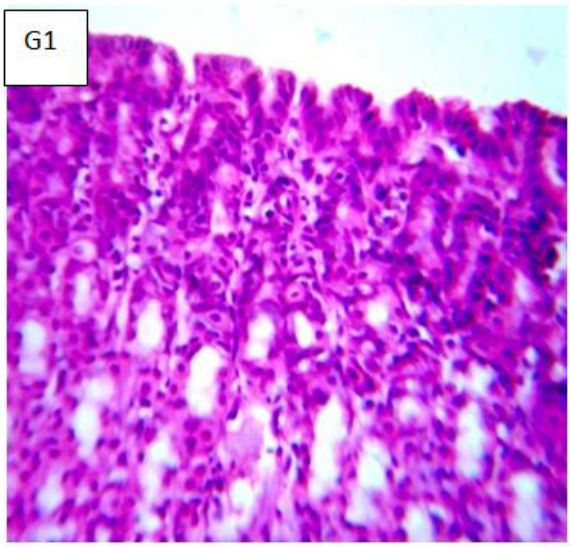

Plate 1A: (Normal Control Group 1): Shows transverse section of the GIT with normal gastric pits, mucosa and abundant gastric glands consistent with histology of the GIT X400magnification

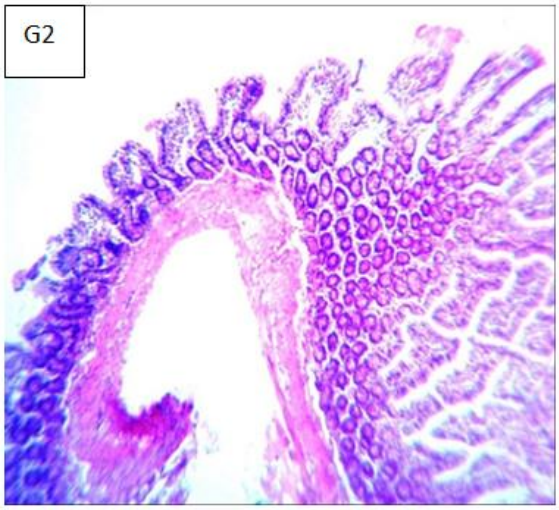

Plate 2A: (Positive Control Group 2): Sections shows area of ulcerated epithelium with atrophic gastric glands

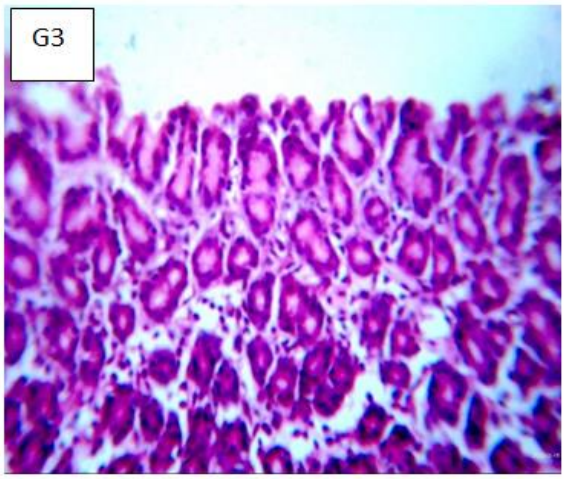

Plate 3A: (*AndrographisPaniculata* 200mg/kg + aspirin) Group 3: Section shows gastric mucosa with disappearance of the original gastric glands with replacement of order epithelium

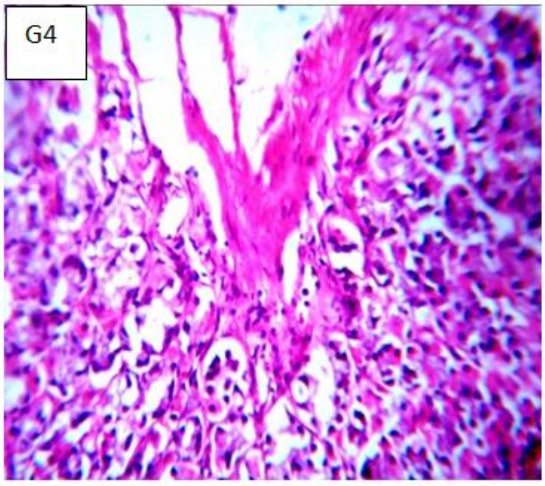

Plate 4A: (*AndrographisPaniculata* 400mg/kg + aspirin) Group 4: Section shows healing by fibrous

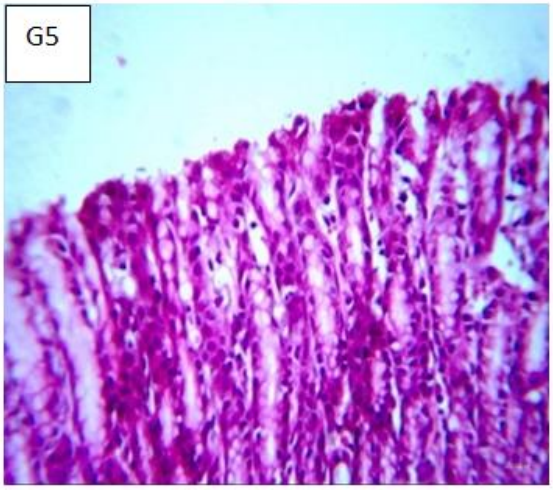

Plate 5A: (30mg/kg Omeprazole + Aspirin) Standard Control Group 5: Section shows regenerating epithelium with tall gastric glands displaying normal columnar epithelium

HISTOPATHOLOGY OF THE LIVER

Transverse Section of the liver Stained with haematoxylin and eosin X400magnification.

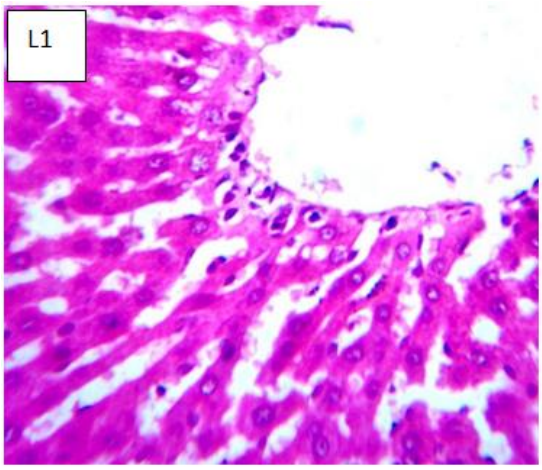

Plate 1: (Liver Section of Group 1): Normal control rats show liver with normal central vein, sinusoids and hepatocytes consistent with histology of the liver

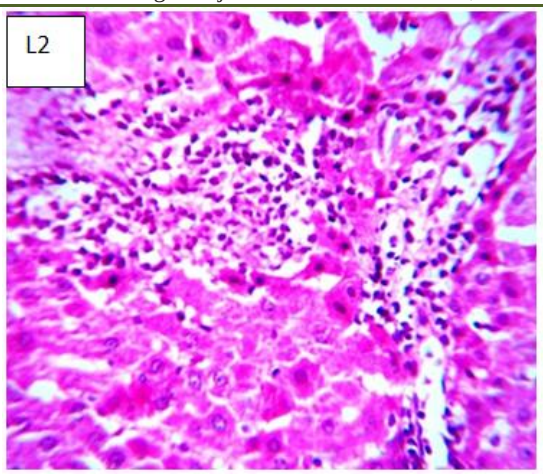

Plate 2: (Liver Section of Positive Control Group 2): Section shows total obliteration of the central (right) and infiltration, inflammatory into the liver parenchyma with island abnormal cells

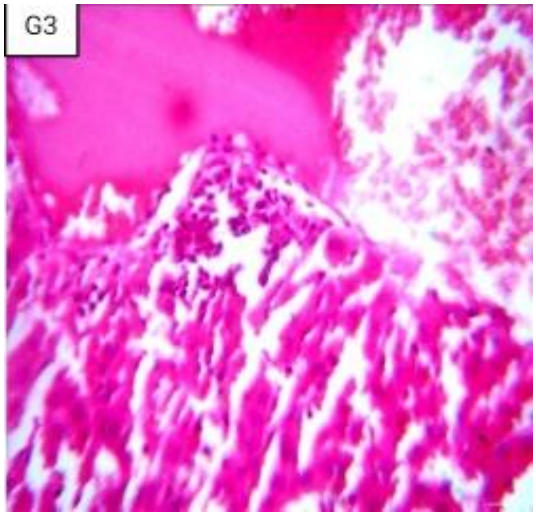

Plate 3: (Liver section of aspirin + *Andrographis Paniculata* 200mg/kg Group 3): Section shows abnormal liver with inflammation of the blood vessel and congestion of the central vein.

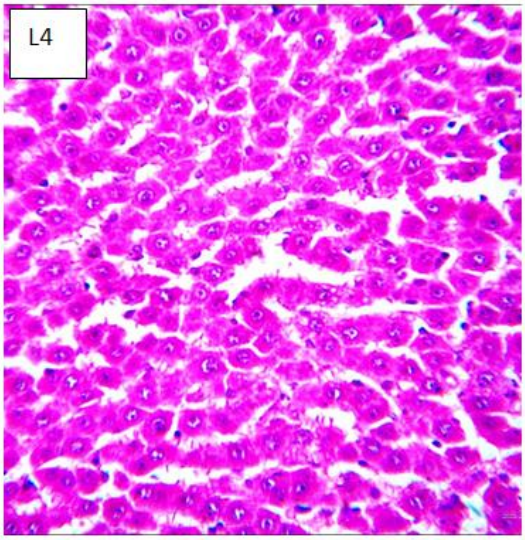

Plate 4: (Liver section of aspirin + *Andr*ographis *paniculata* 400mg/kg Group 4): Section shows normal histology of the liver

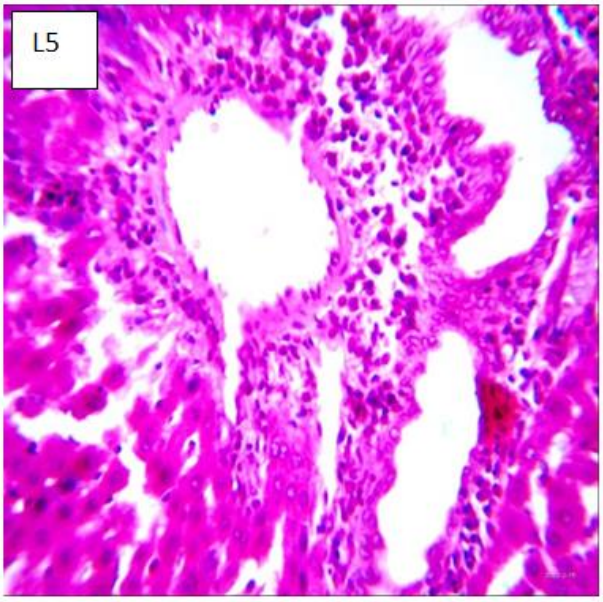

Fig 5: (Liver section of aspirin + 30mg/kg Omeprazole Group 5): Section shows central necrosis and hypertrophic sinusoids at different zones while the right section shows a central vein with normal radiating sinusoids

DISCUSSION

Aspirin is classified as a nonsteroidal anti-inflammatory medication (NSAID). It was the first drug in this category to be found. It functions in a comparable manner to other NSAIDs but further inhibits the regular activity of platelets. Aspirin, commonly used as a pain reliever, fever reducer, and non-steroidal anti-inflammatory drug (NSAID), can inhibit the activity of COX in platelets. This prevents the production of thromboxane A2, which is responsible for binding platelets together during blood clotting and causing narrowing of blood vessels and airways. Aspirin, a nonsteroidal anti-inflammatory medicine (NSAID), hinders the action of COX in platelets, hence limiting the synthesis of thromboxane A2. This compound is essential for the aggregation of platelets and the constriction of blood vessels (Cameron, 1975; O'Laughlin, 1981; Gilroy, 2005).

High doses of aspirin are administered to experimental rats in order to develop ulcers. Prior studies have indicated that non-steroidal anti-inflammatory medicines (NSAIDs) like aspirin reduce the activity of antioxidant enzymes in the stomach of rats, leading to the development of gastric ulcers. This is caused by the excessive influence of free radicals on the cellular antioxidant defence systems, leading to oxidative harm in the stomach. High-dose therapy with aspirin is often linked to mild antinotrand, which can result in severe apparent, acute, or chronic liver damage (Durak *et al*., 2011).

Andrographis paniculata is a potential herb used for the treatment of liver complaints, fever, and as an anti-inflammatory and immunostimulant. *Andrographis paniculata* was reported to contain andrographolide, which contributes to antioxidant defences (Roy 2010). Arhoghro *et al*., 2023 also reported the cardioprotective effect.

Results obtained from the ulcer index of the GIT showed that administration of aspirin at 200 mg/kg caused ulceration in the GIT of the rats when compared with the normal control. Administration of the extract (200 and 400 mg/kg) significantly protected the rats from aspirin-induced ulceration of the GIT. It gave a percentage inhibition of 13.85% and 22.29%, respectively, while the Omeprazole group (standard) gave a percentage inhibition of 26.29% compared to the positive control.

The present study investigated the hepatic protective property and biochemical changes of *Andrographis paniculata caused* by aspirin-induced hepatic damage in Wistar rats by assaying the serum activities of total protein, albumin, bilirubin, and SOD in the GIT tissues of the rats. Results obtained revealed that aspirin administration significantly ($p<0.05$) decreased serum total protein, albumin, and GIT tissue SOD in comparison with the normal group. It also caused a significant increase in total bilirubin in relation to normal rats. However, treatment with *Andrographis paniculata* extract at doses of 200 mg/kg and 400 mg/kg, respectively, significantly increased total protein, albumin, and SOD compared to the positive control group. It also caused a significant decrease in total bilirubin compared to the positive control group. Similarly, the administration of Omeprazole (30 mg/kg body weight) significantly increased the activities of total protein, albumin, and SOD compared to the positive control group. It also decreased the level of total bilirubin compared to the positive control group. The significantly increased levels of serum total protein, albumin, and GIT

tissue SOD, coupled with the marked decrease in serum total bilirubin, are indicative of the anti-oxidative potentials of *Andrographis paniculata*. This finding is consistent with previous findings, which revealed that the methanol extract of *Andrographis panicuilata* possesses hepatoprotective activity in animal studies (Abu-Ghefreh *et al.*, 2008).

Also supporting our results, *Andrographis paniculata's* hepatoprotective properties and ability to increase serum total protein, albumin levels, and SOD activity while decreasing total bilirubin levels have been demonstrated in studies, highlighting its potential in protecting against aspirin-induced hepatic damage (Kawamura *et al*., 2013).

Studies have revealed that *Andrographis paniculata* leaf contains andrographolides, which are diterpines, lactones, and flavonoids. These phytochemicals may confer on the extract the potential to prevent gastric mucosal lesions. Flavonoids can get rid of harmful free radicals, stop lipids from oxidising, and raise the levels of prostaglandins and mucosal content in the stomach. This demonstrates their protective effects on the cells (Okhuarobo *et al*., 2014).

Studies have also indicated that *Andrographis paniculata's* phytochemicals, like flavonoids, can scavenge free radicals, inhibit lipid peroxidation, and increase prostaglandins, contributing to cytoprotective effects on the gastric mucosa (Kawamura *et al*., 2013).

The findings of this study are corroborated by the histopathological report shown in the photomicrographs above. The positive control group (Plate. 2A) shows ulcerated epithelium with atrophic gastric glands. This report indicates wasting of the inner lining of the GIT wall and loss of gland cells in the lining responsible for digestion induced by aspirin, compared to the histology reported in Plate. 1A (normal control), which shows normal gastric pits, mucosa, and abundant gastric glands consistent with the histology of the GIT. Administration of a methanol extract of *Andrographis paniculata* at a concentration of 200 mg/kg in Plate. 3A (Group 3) indicated gastric mucosa with the disappearance of the original gastric glands and the replacement of epithelium. However, the histopathology report in Plate. 4A (Group 4), which was administered at 400 mg/kg of methanol extract, shows healing by fibrous tissue, which indicates the replacement of ulcerated tissues. Administration of omeprazole at 30 mg/kg shows regenerating epithelium with tall gastric glands displaying normal coloumnar epithelium. The level of cell damage was reduced compared to Plate. 2A (positive control Group 2), thereby approaching normal levels compared to Group 1.

The histology report of the albino rats, as shown in Plate. 2 (positive control Group 2), shows total obliteration of the central (right), inflammation, and infiltration of the liver with liver parenchyma and abnormal cells.

This report has indicated cellular damage to the liver tissues due to oxidative stress induced by aspirin, as indicated by the histopathology reported in Plate. 1 (Normal Control Group 1), which shows the liver with a normal central vein, sinusoids, and hepatocytes consistent with the histology of the liver. Administration of a methanol extract of *Andrographis paniculata* at a concentration of 200 mg/kg in Plate. 3 (Group 3) indicated an abnormal liver with inflammation of the blood vessels and congestion of the central vein. Furthermore, the histopathology report in Plate 4 (Group 4) shows normal liver histology after being administered 400mg/kg of methanol extract. The level of cell damage was reduced compared to Plate. 2 (positive control Group 2), and that of Fig 5 (Group 5) shows central necrosis and hypertrophic sinusoids at different zones, while the right section shows the central vein with normal radiating sinusoids.

In conclusion, the study has demonstrated the potential of *Andrographis paniculata* extract in protecting the liver from aspirin-induced damage in experimental rats. The findings show that the extract was able to increase serum levels of total protein, albumin, and superoxide dismutase (SOD) activity in the gastrointestinal tissues while also reducing levels of total bilirubin. These results suggest that *Andrographis paniculata* may possess hepatoprotective and antioxidant properties that can mitigate the harmful effects of aspirin on the liver.

Moreover, the histopathological analysis backed up the biochemical results, showing that giving the extract to the rats reduced cellular damage in both their stomach and liver tissues. The fact that the treated groups' histology returned to normal suggests that *Andrographis paniculata* could be used as a medicine to protect the liver.

This study contributes to the growing body of knowledge on the potential medicinal properties of *Andrographis paniculata* and its role in liver protection. The findings suggest that the extract may have promising applications in the treatment of liver disorders induced by oxidative stress, such as those caused by high-dose aspirin therapy. Further research is warranted to elucidate the underlying mechanisms of action and to explore the potential clinical implications of these findings.

In conclusion, the study gives us useful information about how *Andrographis paniculata* extract can help protect the liver from damage caused by aspirin. The results highlight the potential of this herbal remedy as a natural alternative for liver protection and support its further investigation as a therapeutic agent for liver disorders.

Compliance with ethical standards

Acknowledgments

The authors are grateful to the Technical laboratory staff of the Department of Biochemistry Niger Delta University, Amassoma.

Disclosure of conflict of interest: The authors declare that there is no conflict of interest.

Statement of ethical approval

The study protocol was approved by the Ethical and Research Committee of Niger Delta University, Bayelsa State, Nigeria. The ethical principles for medical research involving animal subjects as outlined in the Helsinki declaration in 1975 and subsequent revisions were strictly followed in the course of this study

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