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Evaluation of the Effect of Ginger Zingiber Officinale Extract on Liver of Albino Rat Administered with Graded Doses of Piroxicam

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A R T I C L E I N F O

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A B S T R A C T

This study aimed to evaluate the effects of Zingiber officinale (ginger) extract on the liver when administered with graded doses of piroxicam. Fifty albino rats were divided into five groups (A–E) of ten each. Group A served as the control, while Group B received 2.7 mg/kg of piroxicam, Group C was given 400 mg/kg of ginger, Group D received 2.7 mg/kg of piroxicam and 100 mg/kg of ginger, and Group E was administered 2.7 mg/kg of piroxicam along with 400 mg/kg of ginger. Substances were administered daily for 21 days, and the weights of both test and control animals were monitored. After treatment, the rats were anesthetized with chloroform, and their livers were harvested for immunohistochemistry processing. ANOVA was used for statistical analysis, with significance set at $P < 0.05$. Data were expressed as Mean ± SEM, with control group weight values recorded as 247.00 ± 3.35 at baseline, 219 ± 9.36 after acclimatization, and 219 ± 6.40 before sacrifice. No significant differences ($p < 0.05$) were found between the test groups and the control. Histological analysis revealed leukocyte infiltration in the liver of Group B (piroxicam 2.7 mg/kg) and leukocyte deposition in Group C (ginger 400 mg/kg). Group D (piroxicam 2.7 mg/kg + ginger 100 mg/kg) exhibited cellular changes and tissue damage, while Group E (piroxicam 2.7 mg/kg + ginger 400 mg/kg) showed neoplastic changes. Further research is recommended to accurately determine the effects of varying doses of Zingiber officinale on piroxicam-induced liver alterations

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INTRODUCTION

The current treatment approach, which relies on synthetic drugs, is costly and can cause genetic and metabolic changes. Therefore, a safer and more effective treatment is needed to manage disease development and progression. In this context, medicinal plants and their constituents play a crucial role in disease management through the modulation of biological activities (Goodman, 2017). Ginger, the rhizome of Zingiber officinale, has been recognized for its therapeutic benefits in health management since ancient times and is considered a promising chemopreventive agent. Several clinical trials and animal studies have demonstrated that ginger and its components play a significant role in disease prevention by modulating genetic and metabolic activities (Ahmad & Odin, 2017).

LITERATURE RIVIEW

In this study, we examined the therapeutic effects of ginger and its constituents in disease management, with a particular focus on their impact on genetic and metabolic activities. The liver plays a crucial role in maintaining and regulating the body's homeostasis, performing essential functions such as immunity, metabolism of carbohydrates, proteins, and fats, detoxification of exogenous (drugs) and endogenous substances, bile secretion, and vitamin storage. More than 900 drugs have been linked to liver injury, making it the leading cause for drug withdrawal from the market. Drug-Induced Liver Injury (DILI) has been increasing, and the general pathophysiological mechanisms involved in DILI have been outlined by Gonzalez et al. (2017).

a) Direct injury to hepatocytes, leading to membrane rupture (b) Disruption of bile flow through the blockage of transport proteins at the canalicular membrane (c) Apoptosis of hepatocytes (d) Immunologic response when a drug acts as an immunogen, potentially affecting the P450 system (e) Bile duct injury. Common drugs associated with Drug-Induced Liver Injury (DILI) include antibiotics, NSAIDs, anesthetic agents, antihyperlipidemics, antirheumatic drugs, TNF inhibitors, antiepileptics, antipsychotic drugs, acetylcholinesterase inhibitors, tricyclic antidepressants, and antihypertensive agents (Danan & Benichou, 2003; Lu et al., 2000).

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) characterized by low solubility and high permeability. It is commonly used as an analgesic and anti-inflammatory agent in clinical settings. Piroxicam is often preferred over other drugs for treating pain related to rheumatoid arthritis and osteoarthritis due to its long half-life (40 hours), allowing for once-daily dosing. It is also used to treat musculoskeletal diseases, dysmenorrhea, postoperative pain, and rheumatic diseases (Trivedi, 2015). However, like other NSAIDs, the use of piroxicam is associated with various side effects, including gastrointestinal issues, cerebrovascular problems, hypersensitivity reactions, respiratory complications, bone-related concerns, hepatotoxicity, and nephrotoxicity (Möller et al., 2015).

Therefore, the benefits of NSAIDs could be enhanced by controlling their adverse effects, which would create significant market potential. Drug withdrawals from the market are often due to two main causes: renal and hepatic

adverse events. Serum biochemistry measurements and histopathological tests are commonly used to assess hepatic and renal damage in preclinical animal models (Jiang et al., 2014). This study aims to evaluate the effects of ginger (Zingiber officinale) extracts on the liver when administered alongside graded doses of piroxicam.

METHODOLOGY

Research Design

Fifty albino rats were assigned to five groups (A–E) of ten each. Group A served as the control, while Groups B–E received varying doses of piroxicam and ginger for 21 days. Weight changes were tracked throughout the study. After the treatment period, the rats were euthanized, and their livers were collected for immunohistochemical analysis. Data were evaluated using ANOVA, with statistical significance set at $P < 0.05$.

Geographical Description of the Study Area

The study was conducted at Ambrose Alli University and Irrua Specialist Teaching Hospital in Edo State, Nigeria. Edo State, located in the South-South region of Nigeria, has a landmass of 17,450 sq.km and a population of 3.1 million people.

Experimental Animals/Housing Condition

Fifty adult albino rats (90g–130g) were procured and acclimatized for two weeks in wire mesh cages to prevent contamination. They were fed Growers' mash and water ad libitum, following standard laboratory animal care guidelines.

Animal Grouping and Study Duration

The rats were housed in five groups (A–E), with ten rats per group. Group A served as the control, while Groups B–E received different treatments of piroxicam and ginger. The entire study, including preliminary studies, acclimatization, drug procurement, experimentation, and data evaluation, lasted five months.

Substance Administration

Group A (Control) received normal feed and water. Group B was administered 2.7 mg/kg of piroxicam, while Group C received 400 mg/kg of ginger. Group D was given 2.7 mg/kg of piroxicam along with 100 mg/kg of ginger, and Group E received 2.7 mg/kg of piroxicam combined with 400 mg/kg of ginger.

Sample Collection and Analysis

Weight measurements were taken before, during, and after the experiment. The liver samples were collected under chloroform anesthesia, fixed in 10% formalin, and analyzed for growth performance and feed utilization.

Histological Processing and Staining Procedure

Liver tissues were processed using an automatic tissue processor at Irrua Specialist Teaching Hospital. The tissues were passed through graded alcohol solutions, xylene, and molten paraffin wax, then cooled and trimmed before being cut into 5nm sections for histological examination.

The prepared tissue sections underwent a hematoxylin and eosin (H&E) staining process to enhance microscopic visibility. The slides were deparaffinized, hydrated, stained, differentiated in acid alcohol, washed, dehydrated, and mounted before microscopic observation. Photomicrographs were taken for analysis

RESULT

Table 4.1 shows the baseline weight, weight after acclimatization and before sacrifice of control and test subjects in which the Mean±SEM of baseline weight, weight after acclimatization, weight before sacrifice were 247.00±3.35, 219±9.36 and 219±6.40 respectively for control subjects. None of the test groups were found statistically significant ($p<0.05$) when compared with their respective control.

Table 4.1: Comparison of Mean ± S.E of Different Stages of Weight Measurement in Groups and Control Group Using ANOVA.

Weight	**Group A**	**Test group**				**F**	**P**
	(Control) (N=10)	**Group B (N=10)**	**Group C (N=10)**	**Group D (N=10)**	**Group E (N=10)**	**Valu**	**value**
Baseline Weight(gram)	247.00 ±3.35	244.00 ±1.63	244.00 ±1.63	241.00 ±1.80	241.00 ±1.80	1.370	0.2596
After Acclimatization(gram)	219.00 ±9.36	236.70 ±4.41	226.70 ±8.03	240.00 ±4.47	241.00 ±2.33	2.300	0.0782
Before Sacrifice(gram)	219.00 ±6.40	221.10 ±10.20	221.70 ±10.14	240.00 ±4.47	205.00 ±13.76	1.172	0.3399

**Means Statistically Significant (P<0.05)*

Table 4.2: General Tissue Appearance of H & E Staining

Pathological Conditions	Group A (N=10)	Group B (N=10)	Group C (N=10)	Group D (N=10)	Group E (N=10)
leucycocytes infiltrates	--	+	--	--	--

Neoplastic changes	--	+	+	--	--
malignant changes	--	+	+	--	+
hepatocellular carcinoma	--	+	+	--	+
Adenocarcinoma	--	--	+	--	--
Inflammatory infiltrate	--	--	--	++	--

Key
+denote present
-denotes absent

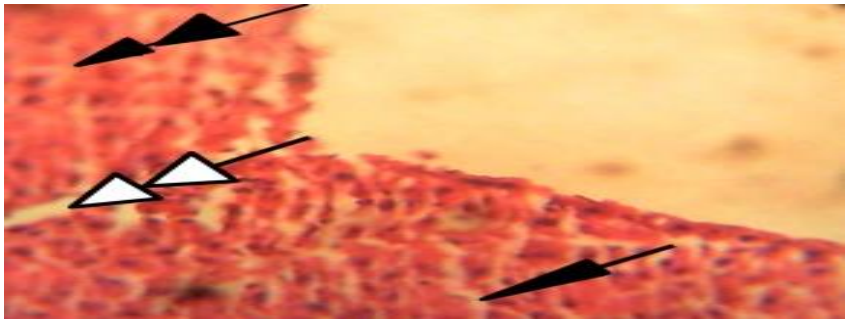

Fig 1. Group A (Control 1): The Photomicrograph 1 and 2 are Rats Liver Tissue has a Central Vein (Double thin Arrow) and Nucleated Liver Plates (Hepatocytes) (thin Arrow)

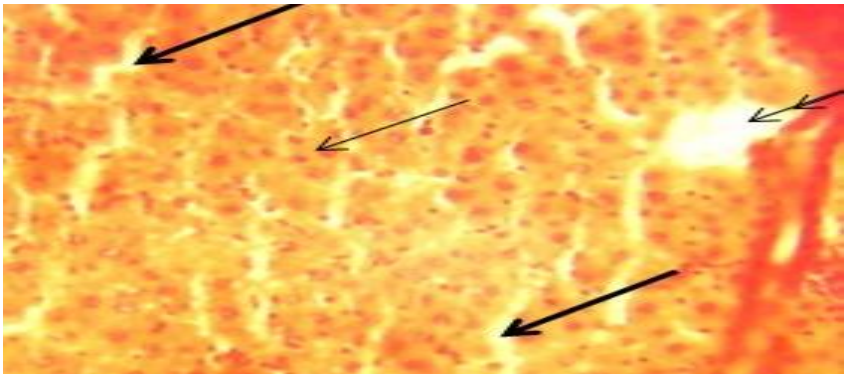

Fig 2. Group A (Control 2): on the Slides, There is no Evidence of Kupffer Cell, This May be as a Result of Staining Reation no Evidence of Fibrosis Therefore the Slide Can be Passed as a Normal Slide.

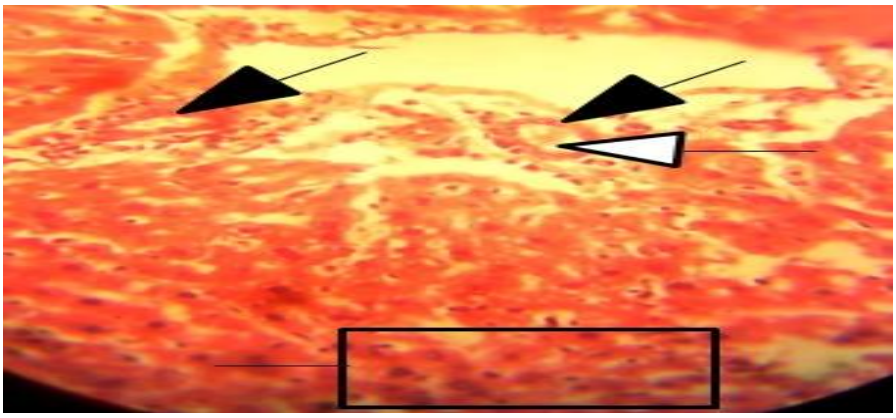

Fig 3. Group B (Peroxicam 2.7mg/Kg) 1. on the Photomicrograph, Hepatocellular Carcinoma is Eveident with Basophilic and Pleomorphic Nuclei (Malignant Cells)(Black Arrow) Forming Acini (White Arrow).

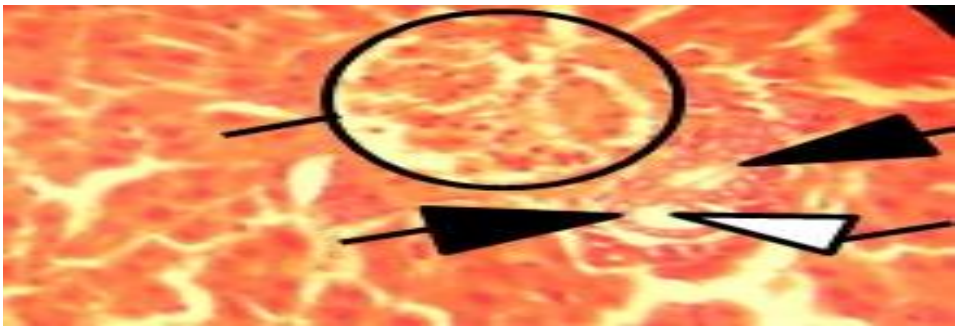

Fig 4. Group B (Peroxicam 2.7mg/Kg) 2: There is Tumor Infiltration to a Supposedly Bile Duct Whose Cells are Columnal Cells, Consequently Denoting Adenocarcinoma (Circle Arrow).

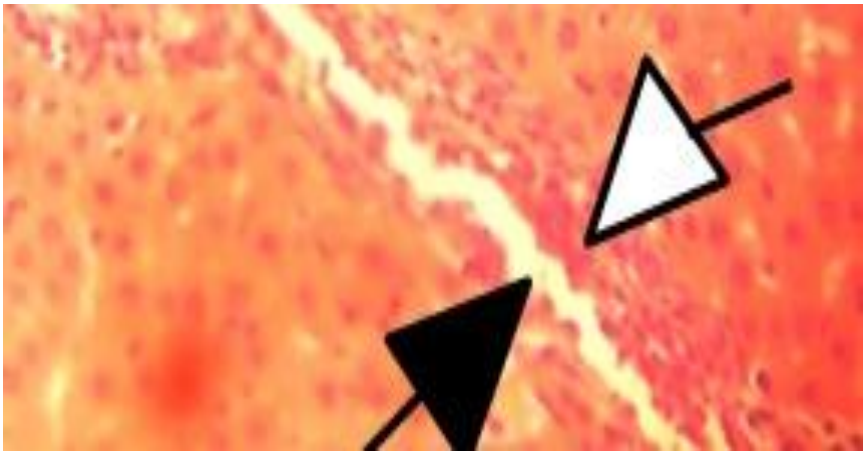

Fig 5- Group C (Ginger 400mg/Kg) 1: There is Deposition of Leucocyte Infiltrates (White Arrow), Along the Boundaries of Sinusoids (Black Arrow), Inflammatory Response, to the Liver Tissues with the Eveidnece of Leucocytes Infiltration as Shown Above (White Arrow).

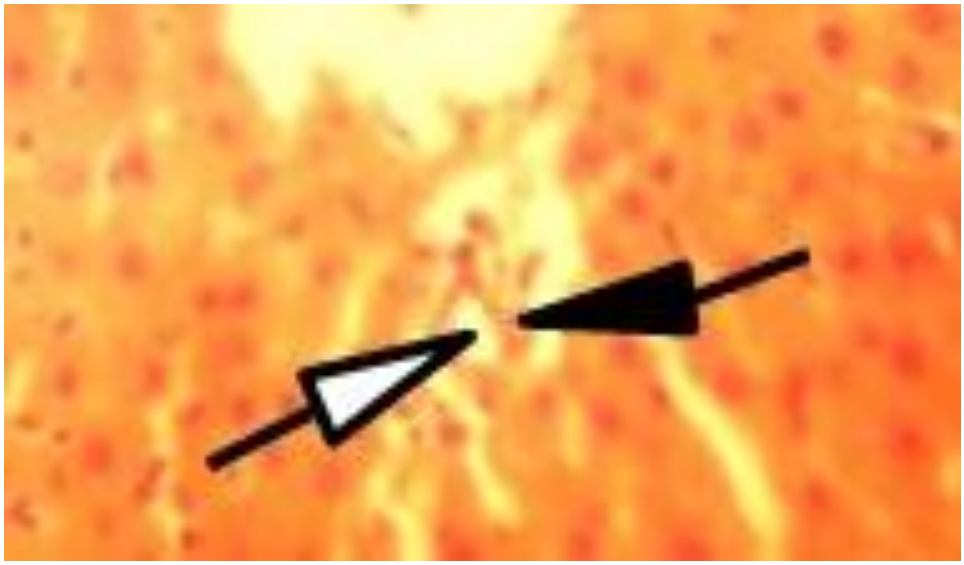

Fig 6. Group C (Ginger 400mg/Kg) 2:, Hepatocellular Carcinoma is Evident with Basophilic and Pleomorphic Nuclei (Malignant Cells)(Black Arrow) Forming Acini (White Arrow).

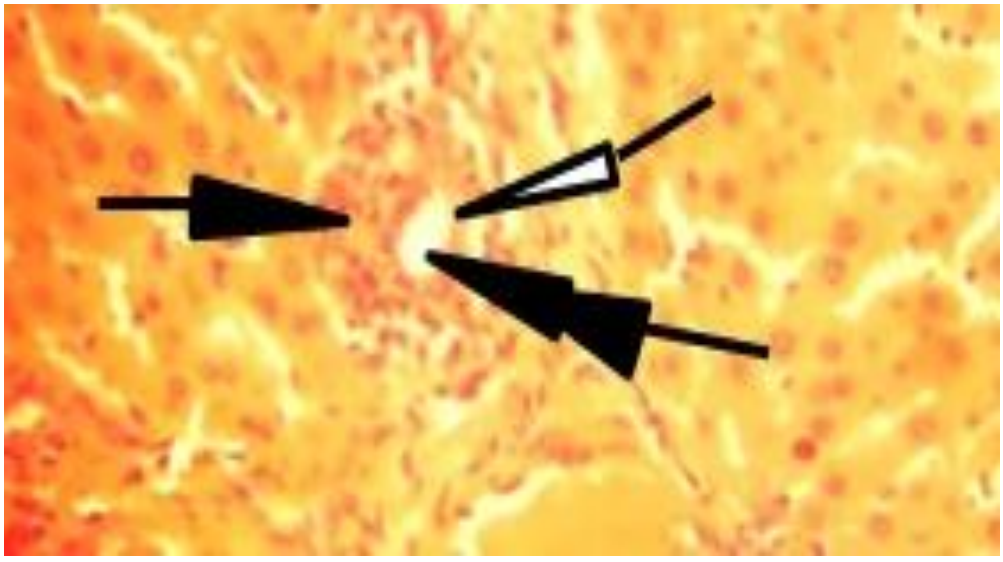

Fig 7. Group D (Piroxicam 2.7mg and 100mg Ginger) 1: Cellular Changes and Damage to the Tissue. on Parts of the Tissue, There are Pockets of Inflammatory Infiltrates (Single Black Arrow) Surrounding Malignant Basophilic Pleomorphic Cells (White Arrow) Appearing in form of a Dull Circle With a Clear Acini (Double Black Arrow).

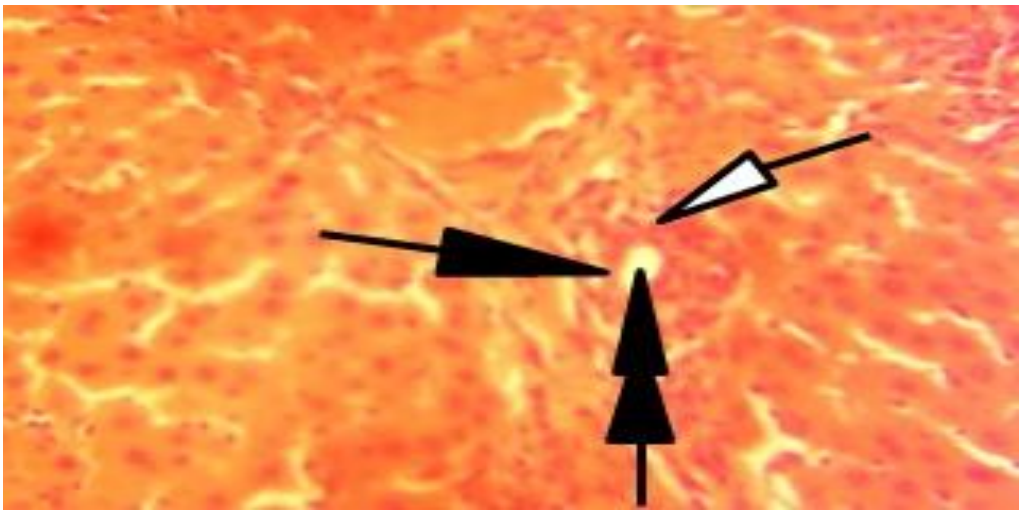

Fig 8. Group D (Piroxicam 2.7mg and 100mg Ginger) 2: on Parts of the Tissue, There are Pockets of Inflammatory Infiltrates (Single Black Arrow) Surrounding Malignant Basophilic Pleomorphic Cells (White Arrow) Appearing in form of a Dull Circle with a Clear Acini(Double Black Arrow).

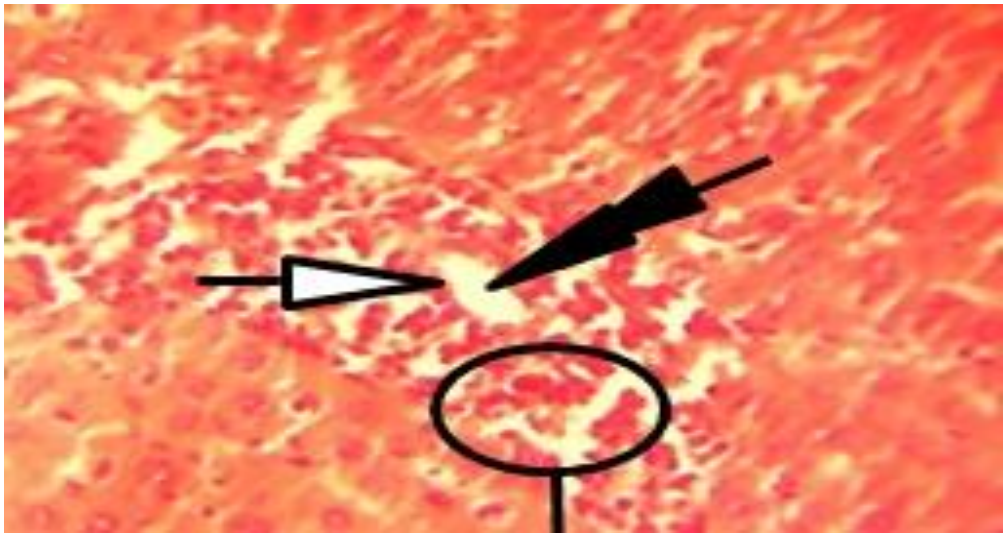

Fig 9- Group E (Piroxicam 27mg and 400mg Ginger) 1: The Underlining Features are the Cellular Reaction Observed. Inside a Large Sinusoid (Blood Vessel) are Red Blood Cells (Circle Arrow) Surrounding Malignant Basophilic Pleomorphic Cells (White Arrow) within the Sinusoid. the Pleomorphic Cells, Demonstrate Highly Visible Acini (Double Black Arrow).

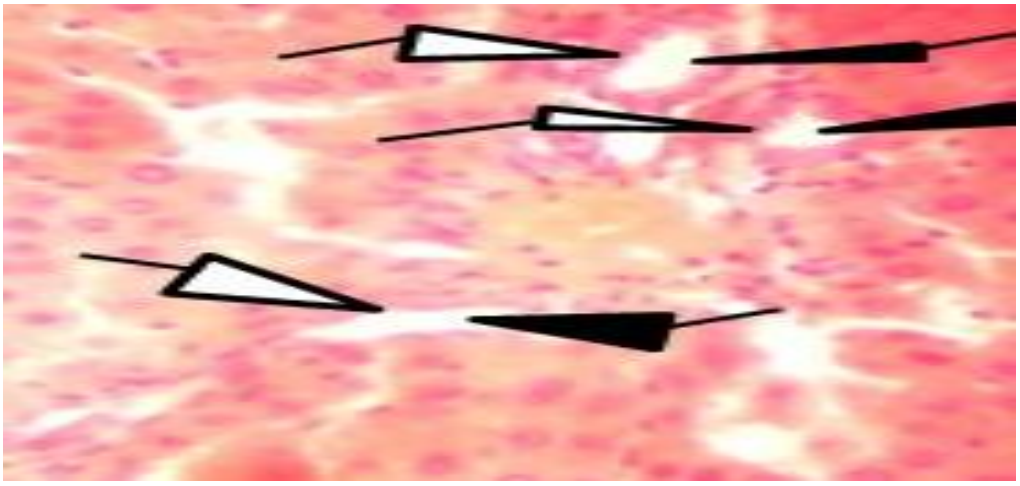

Fig 10- Group E (Piroxicam 27mg and 400mg Ginger) 2: There Were Notable Cellular Changes Such as Neoplastic Changes and Inflammatory Response. Neoplastic Cells Arising from Hepatocytes, are Seen to Be Basophilic and Pleomorphic (White Arrow) With a Well and Clear Acini (Black Arrow).

Pictorially, The Parenchymal Cells (Hepatocytes) are the Primary Cells Affected Suggesting Therefore the Condition of Hepatocellular Carcinoma in-Situ.

DISCUSSION

The liver, along with other organs, collaborates to digest, absorb, and process food. Its primary role is to filter blood coming from the digestive tract before passing it to the rest of the body. Additionally, the liver detoxifies chemicals, metabolizes drugs, and secretes bile that is reintroduced into the intestines. The liver also produces proteins essential for blood clotting and other vital functions (Ozougwu, 2017). Piroxicam, a nonsteroidal anti-inflammatory drug (NSAID) from the oxicam class, is used to alleviate the symptoms of painful inflammatory conditions such as arthritis (Xu et al., 2014). Zingiber officinale, commonly known as ginger, is one of the most widely used spices worldwide. Ginger oil is known for its antibacterial and antifungal properties, especially in food preparation. These effects are attributed to the variety of biologically active compounds found in both fresh and dried ginger oil, as mentioned by Ramakrishna et al. (2016). This study aims to evaluate the effect of Zingiber officinale (ginger) on the liver of Wistar rats induced with graded doses of piroxicam.

Liver group A in the photomicrograph represents the control group showing a normal slide and its histology can be said to be exactly that of an healthy rat.

Liver group B (2.7mg of Piroxicam) in the photomicrograph showed the liver tissue from rat previously exposed to 2.7mg/kg piroxicam for a period of 14 days. The tissue evidently shows leucycocytes infiltrates (rectangles arrow). The exposure to the piroxicam causes cellular changes (neoplastic) changes on the liver parachymal cells. The parachymal cells (hepatocytes) are seriously

affected to the level of malignant changes. On the photomicrograph, hepatocellular carcinoma is eveident with basophilic and pleomorphic nuclei (malignant cells) forming acini. The finding of this study was in similarity with the findings of Forner et al., (2012) who identified the presence of Hepatocellular carcinoma (HCC) in subjects exposed to piroxicam overdose , which is the currently the most common cause of death in people with cirrhosis (Forner et al., 2012). This cause of this cellular neoplasmic changes in this group could have been due to the fact that piroxicam caused metabolic syndrome and NAS1Z` z`H which are risk factors for HCC (Kumar et al. 2005). Therefore, the administration of 2.7mg/kg piroxicam, had evidently shown that it can cause malignant changes on the rats liver cells.

Liver group C (400mg of Zingiber officinale) in the photomicrograph showed a the liver tissue from a rat previously exposed to ginger for a period of 14days and leucocytes infiltration as shown above (white arrow) was seen. This inflammatory response could have been due to injured tissues, often caused by, trauma, toxins, heat or any other cause as a result of its exposure to Zingiber officinale. Injured cells can release a range of chemicals, including histamine, bradykinin, and prostaglandins. These substances make blood vessels more permeable, causing fluid to seep into the surrounding tissues and leading to swelling. This reaction helps isolate the foreign material and limits its interaction with the body's tissues. Furthermore, these chemicals draw white blood cells called phagocytes, which consume bacteria, as well as dead or damaged cells. The result of this study was in similarity with Zakhari, (2006). Who observed similar inflammatory changes due to Zingiber officinale overdose

Liver group D (2.7mg of Piroxicam and 100mg of Zingiber officinale) showed pockets of inflammatory infiltrates (single black arrow) surrounding malignant basophilic pleomorphic cells (white arrow) appearing in form of a dull circle with a clear acini(double black arrow). These changes could occur when inflammatory cells, including neutrophils, eosinophils, lymphocytes, plasmacytes, macrophages, and mast cells, infiltrate around the blood vessels, a process known as perivascular infiltration. It could also be caused as a result of exposure to pathogens, toxins, pollutants, irritants and allergens as seen in closely related studies by Yemitan & Izegbu, (2006).

Liver group E (2.7mg of Piroxicam and 400mg of Zingiber officinale) in the photomicrograph shows the liver tissue extracted from a rat previously exposed to 27mg proixicam and 400mg ginger for a period of 14days. The underlining features are the cellular reaction observed. Inside a large sinusoid (blood vessel) are red blood cells (Circle arrow) surrounding malignant basophilic pleomorphic cells (white arrow) within the sinusoid. There were notable cellular changes such as neoplastic changes and inflammatory response. This Neoplastic change occurs when an abnormal mass of tissue forms as a result of cells growing and dividing excessively or failing to die as they should. It could also be sometimes caused or triggered by DNA mutations within the cells as seen in Habib et al., 2008; Mansour et al., 2010).

CONCLUSIONS

There was no significant changes in the body weight, Liver group B (2.7mg of Piroxicam) had evidently shows leucycocytes infiltrates (rectangles arrow), Liver group C (400mg of Zingiber officinale) had deposition of leucocyte infiltrates, Liver group D (2.7mg of Piroxicam and 100mg of Zingiber officinale) had cellular changes and damage to the tissue and Liver group E (2.7mg of Piroxicam and 400mg of Zingiber officinale) had Neoplastic changes

RECOMMENDATION

Based on the histological observations acknowledged in this present study, it may be concluded that;

- There is need for further study to determine accurately the effect of introduction of mild, moderate and high dosage of Zingiber officinale (ginger) on liver already induced with varying doses of Piroxicam.
- Although Zingiber officinale (ginger) is of great medical importance, its use should also be regulated to prevent adverse side effects.
- People who take this medication should be exceedingly careful and cautious especially in the dosage.

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