Histological Assessment of the Ethanolic Extract of *Ficus platyphylla* on *N*-Nitroso-N-Methylurea Induced Toxicity in Female Albino Mice (*Mus musculus*).

[1]Love Emmanuel Adeboye ✉, Oloyede Adeola[2] and Olakunle Samuel Omotayo [3] Deborah Etooluwa Kumoye [4]

[1,3 & 4] Department of Science Laboratory Technology, Federal Polytechnic Ilaro, Nigeria
2 Department of Cell Biology and Genetics, University of Lagos, Akoka, Nigeria
✉: love.adeboye@federalpolyilaro.edu.ng

ABSTRACT

Ficus platyphylla Del. Holl (Moraceae) is used traditionally for treating stomach pain, infertility, and psychosis. The present study investigated the tissue repairing and protective potential of the ethanol extract of *Ficus platyhylla* bark in N-Nitoso-N-Methylurea-induced toxicity in female albino mice. Twenty-five (25) albino mice weighing 19-28g were grouped into five groups, with five mice in each group. Mice in all groups were injected intraperitoneally with Nitroso-Methyl Urea at a dose of 50mg/kg body weight. Mice were allowed to stay 7 days after the substance was induced to take effect before the commencement of the treatment. Mice in groups A, B, and C were treated orally with 1600mg/kg/day, 800mg/kg/day, and 400mg/kg/day of the plant extracts, respectively. Meanwhile, the mice in Group D received a standard dose of cisplatin through intraperitoneal injection, and the mice in Group E had access to water. Mice were sacrificed after 63 days of treatment. The liver, kidney, breast, heart, and lung tissues were harvested for histological studies. The histopathological examination showed that there is no presence of pathological changes in the heart and breast tissue. However, signs of tissue damage like features aligning with Renal Toxicity and Glomeruli toxicity are observed in the kidney, and mild hepatic toxicity in the liver of the treatment mice. The observed pathology and organ damage in the liver and kidneys are associated with the actions of NMU and cisplatin treatment. The treatments of the plant extract show signs of immune response and tissue rehabilitation. The extracts show possible tissue protection and rehabilitation.

Keywords: *Ficus platyphylla*, Albino Mice, ethanolic extract, histological assessment

1.0 INTRODUCTION

Plants have long been a source of potent medications and are extensively utilized for therapeutic purposes across various nations (Sumi et al., 2016). In Africa, the use of plants for medicinal purposes dates back to ancient times, and there has been a resurgence of interest in herbal therapy despite advancements in conventional medicine (Mahomoodally, 2013).

The role of indigenous populations in using traditional medicine for various treatments is significant; the World Health Organization reports that up to 80% of the global population depends on traditional medicine for their healthcare needs (WHO 20002). WHO estimates indicate that over 80% of the global population uses herbal medicine for treating numerous diseases, prompting impoverished nations, including Nigeria, to promote non-toxic herbal medicine (Kasilo & Nikiema, 2014). This has led to the National Agencies for Food, Pharmaceuticals, Administration, and Control (NAFDAC) and other similar regulatory bodies across the globe to enhance and standardizing herbal drug use. Historically, plants have been used medicinally long before the advent of recorded history. However, African societies have not exploited medicinal herbs as extensively as other cultures, such as those in China, India, and Greece. Recent research indicates that between 1999 and 2006, approximately 7500 species were screened for anti-cancer properties in South Africa, with 68% showing potent active compounds (Wyk, 2011).

Today, many plant species are employed in human and veterinary medicine (Sagbo & Otang-Mbeng, 2021). A medicinal plant is defined as one containing compounds that are of therapeutic purposes or as precursors for the semi-synthesis of chemo-pharmaceuticals. Such compounds include Tannins, Flavonoids, Saponins, Alkaloids, and Glycosides (Kumar & Tewari, 2018). The study investigated whether the ethanolic extract of *Ficus platyphylla* can prevent N-nitroso-methyl-urea (NMU)-induced toxicity in female albino mice and to also evaluate the toxicity of *Ficus platyphylla* on the internal organs of female albino mice.

2.0 MATERIALS & METHODS

EXPERIMENTAL PROCEDURE

Twenty-five pathogen-free female albino mice were used for this study and they were obtained from the National Agency for Food and Drug Administration and Control, Lagos, Nigeria (NAFDAC). The animals were regularly cleaned and housed in standard clean mice cages with sawdust as their cage bedding which were cleaned frequently during the research period. The cage with

animals is kept at room temperature in the Cell Biology and Genetics animal house at the University of Lagos. Normal mice pellet feed and water were provided throughout the experiment. The weight of the mice was also recorded using a sensitive weighing balance. the experimental process and design followed the ethical approval of:" CMUL/ACUREC/06/21/875".

PLANT COLLECTION AND IDENTIFICATION

Bark of *Ficus platyphylla* was collected in March 2021, from traditional merchants in Bariga market, Bariga, Lagos. The plant was identified and confirmed taxonomically in the Department of Botany, University of Lagos, Lagos, Nigeria, with voucher number LUH8746 of the plants deposited in the herbarium.

PLANT PREPARATION AND EXTRACTION

The bark of *Ficus platyphylla* was cut in smaller bits and air dried in a clean and good air circulated space. After air drying for one week, plant samples were again dehydrated at 35 °C in a food dehydrator with air circulation for 60 minutes, for total removal of any present water molecules. The dehydrated bark of *F. platyphylla* was ground in a stainless-steel grinder machine to achieve a fine powdered form of the plant.

The Bark extract was obtained by using a crude extraction protocol, using a ratio of 1:3 solute to solvent, i.e., 2500g of powdered form of *Ficus platyphylla* to be soaked in 7500ml of ethanol to achieve a properly soaked plant powder. The prepared solution was allowed to stand for 72hours and rocked intermittently during the period, for proper extraction of the active constituents of the plant. This was later filtered using a funnel and cotton wool. The filtrate was then poured into a beaker and concentrated using a hot plate at 40±10C. The recovered extracts obtained were weighed and used to prepare the different concentrations to be used for the experiment.

PREPARATION OF NMU

1g of Nitroso-methyl Urea (NMU) was measured and diluted with 20ml saline to give 50mg/ml of NMU which was then dispensed into a universal bottle. After five days of acclimatization, the NMU was administered to the mice at 50mg/kg body weight. The NMU solution was injected intra-peritoneally in the ventral midline of the animal (between the third and fourth pair of the mammary gland) following a process described by (Rajmani*et al*, 2011). Mice were allowed to stay 7 days after the substance is induced so as to take effect before the commencement of the treatment.

PROCEDURE

Twenty-five albino mice were weighed and divided into five treatments and one control (negative) group with five (5) mice each, and distributed into the cages. Before induction and treatment, the mice were allowed to acclimatise for 14 days. After acclimatization, all grouped mice were induced with the prepared Nitroso-methyl Urea and then allowed to rest for two days. The positive control group mice were treated with cisplatin, which was injected intraperitoneally; the negative control group was treated with normal saline, injected intraperitoneally, same time as the positive control. The treatment group was dosed with 400, 800 and 1600mg/kg of plant extracts orally. During the duration of treatments, the mice were weighed and inspected for any irregularities especially around the mammary glands. The mice were sacrificed at the end of the tenth week of treatment. Jugular puncture was carried out on each mouse and the blood was taken in EDTA bottles. The breast, liver, heart, lungs left kidney from each mouse were sliced off using a sterile surgical blade. The organs were preserved in 10% buffered formalin for histopathological examinations. The tissue biopsies was dehydrated and embedded in paraffin, cut into 4- 5 µm sections with rotary microtome (LEICA RM 2235 Rotary Microtome), and stained with hematoxylin-eosin for photomicroscopic examination.

RELATIVE ORGAN WEIGHT

Relative organ weight was calculated with the method of Oloyede *et al*., 2011.

STATISTICS ANALYSIS

The statistical analyses were performed using Microsoft Excel. The data were expressed as the Mean ± SEM. The data was subjected to a sample t-test, evaluating the statistical significance of the difference between two means of various parameters between the control and experimental group. The p-value was found by means of Microsoft Excel.

HISTOPATHOLOGICAL PREPARATION

Vital organs collected in from each animal were fixed in 10% formalin and processed for hematoxylin-eosin staining. Photographs of the prepared slides were taken with a camera attached to the compound light microscope in the department of Morbid Anatomy Lagos State University Teaching Hospital. The Microtone model that was used for the preparation is LEICA.

3.0 RESULTS and DISCUSSION

Weight of animal

The twenty-five albino mice were weighed and divided into five treatments and one control (negative) group with five mice (5) each distributed into cages while ensuring that each group has the approximate average mean weight. The table below shows the weight gotten from each mouse in each group:

Table 1: weight of mice during the experiment in the treatment groups and the control

Weeks	Control	A	B	C	D
1	20.38±0.33	25.92±0.63	23.62±0.23	22.42±0.09	21.22±0.35
2	20.72±0.52	25.82±1.03	25.37±0.88	24.44±1.43	23.04±0.52
3	21.58±0.77	26.42±1.31	25.92±0.85	25.43±1.72	24.45±0.30
4	22.73±0.58	28.13±1.27	26.78±0.82	27.13±1.59	25.4±0.41
5	23.65±0.75	28.42±0.46	27.72±0.63	27.27±0.96	26.45±0.36
6	23.86±0.80	28.57±0.43	27.82±0.62	27.47±0.95	26.62±0.34
7	24.05±0.8	25.47±0.67	24.97±1.62	24.4±0.98	23.95±1.35
8	24.15±0.73	27.13±2.32	27.65±0.82	26.83±0.82	23.63±1.26
9	24.35±0.75	27.33±2.31	27.82±2.62	27.13±0.87	23.05±1.55
10	24.83±0.85	27.92±2.32	28.25±2.55	27.57±0.79	23.7±1.42

Values are mean ± Standard error of the mean (SEM) $p>0.05$
A: Animals treated with 1600mg/kg of *Ficus platyphylla* after being injected with NMU.
B: Animals treated with 800mg/kg of *Ficus platyphylla* after being injected with NMU.
C: Animals treated with 400mg/kg of *Ficus platyphylla* after being injected with NMU.
D: Animals treated with Cisplatin after being injected with NMU.

THE RELATIVE ORGAN WEIGHT.
The relative organ weight observed after the treatment of experimental mice is shown on Table 1 above. Mice treated with 800mg/kg of plant extract showed a significant change in the relative lung and heart weight when compared with the control group. While mice treated with 400mg/kg of plant extract showed a significant reduction in the weight of the liver when compared to the control. Mice treated with the highest dose of plant extract used in this study and mice treated with cisplatin showed no significant changes when compared with the control group.

TABLE 2: Relative Organ weight of experimental mice after 63 days of treatment

Value a= <0.05, b= <0.01, c=0.001.
A: Animals treated with 1600mg/kg of *Ficus platyphylla* after being injected with NMU.
B: Animals treated with 800mg/kg of *Ficus platyphylla* after being injected with NMU.
C: Animals treated with 400mg/kg of *Ficus platyphylla* after being injected with NMU.
D: Animals treated with Cisplatin after being injected with NMU.
E: The animal had access to feed and water only after injection of NMU

HISTOLOGY REPORT

The histopathology test was carried out on the breast, lungs, kidney, liver, and heart of the animals in each group. This was used to evaluate the anti-hepatotoxic activity of the ethanolic extract of *ficus platyphylla* on the tissues and organs of infected mice. The micrograph below shows the photomicrograph of the organs listed above:

HISTOLOGICAL ASSESSMENT OF THE BREAST

GROUP	KIDNEY	LUNGS	HEART	LIVER
A	0.89±0.10	0.89±0.15	0.56±0.22	4.74±1.22
B	0.72±0.07	0.71±0.09[a]	0.36±0.04[a]	5.19±0.65
C	0.37±0.01	0.54±0.23	0.365±0.01	4.96±0.05[a]
D	0.65±0.25	1.09±0.98	0.875±0.48	4.71±1.12
E	0.63±0.25	0.82±0.09	0.82±0.06	5.74±0.01

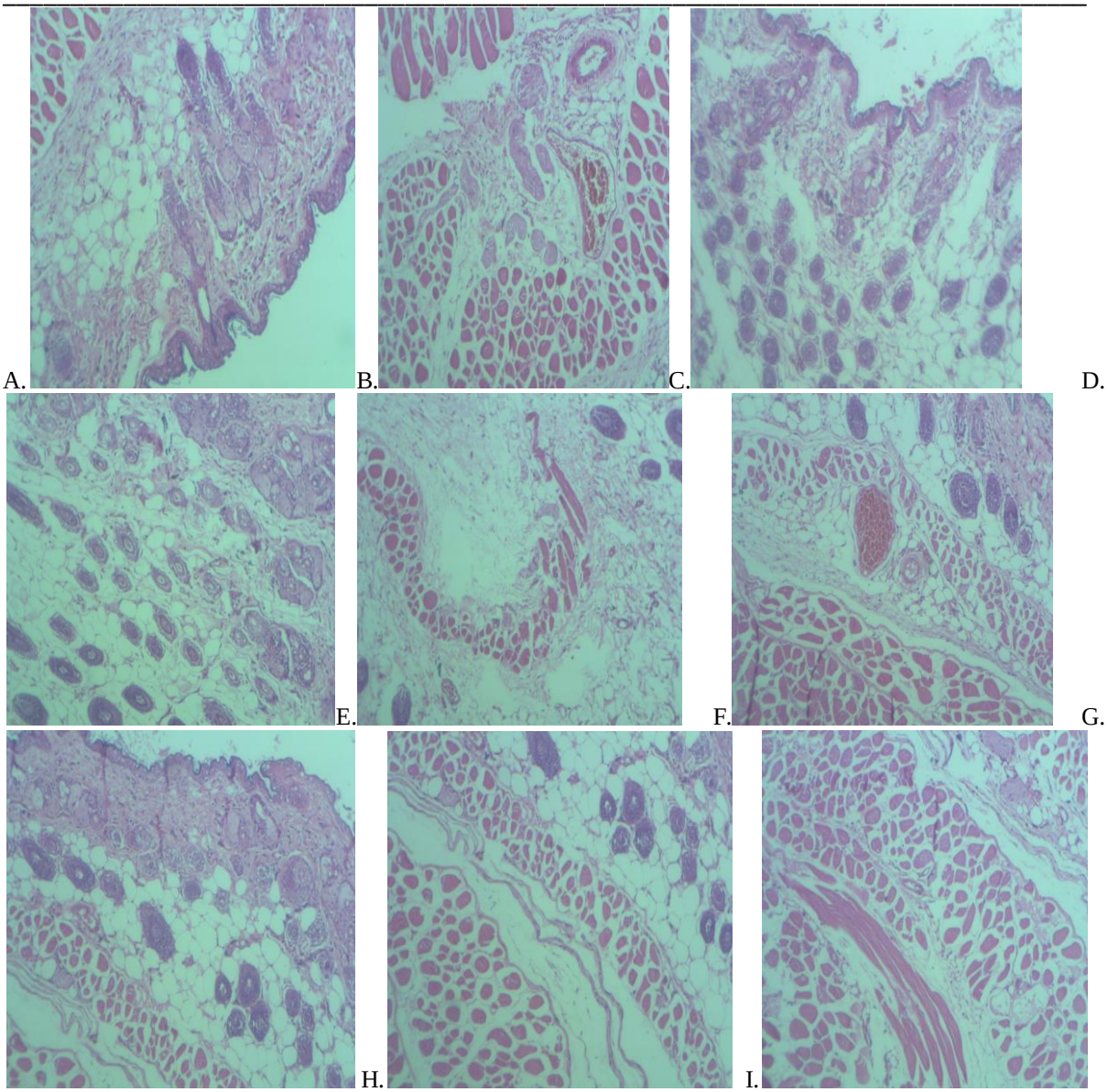
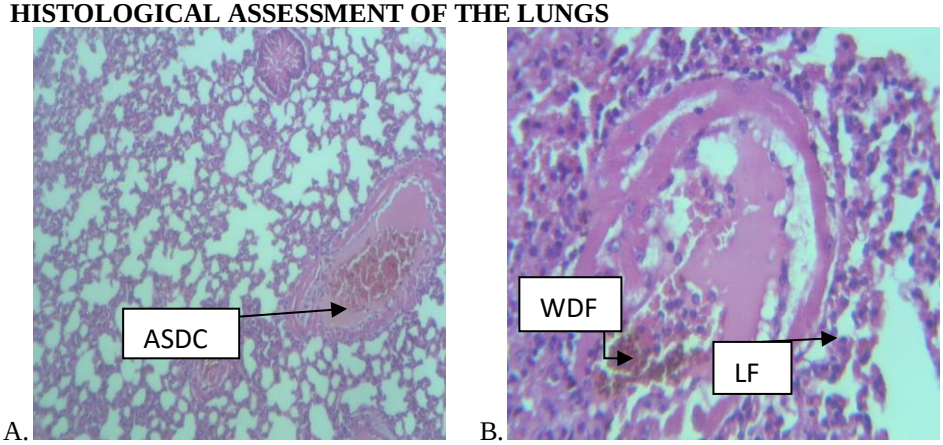


Plate 1:The photomicrographs above shows the micrograph of the breast tissue of group A(1600mg/kg),B(800mg/kg),C(400mg/kg), Cisplatin and with Saline water (negative control) with Mgx40. No pathology was observed in any of the groups**.**

HISTOLOGICAL ASSESSMENT OF THE LUNGS



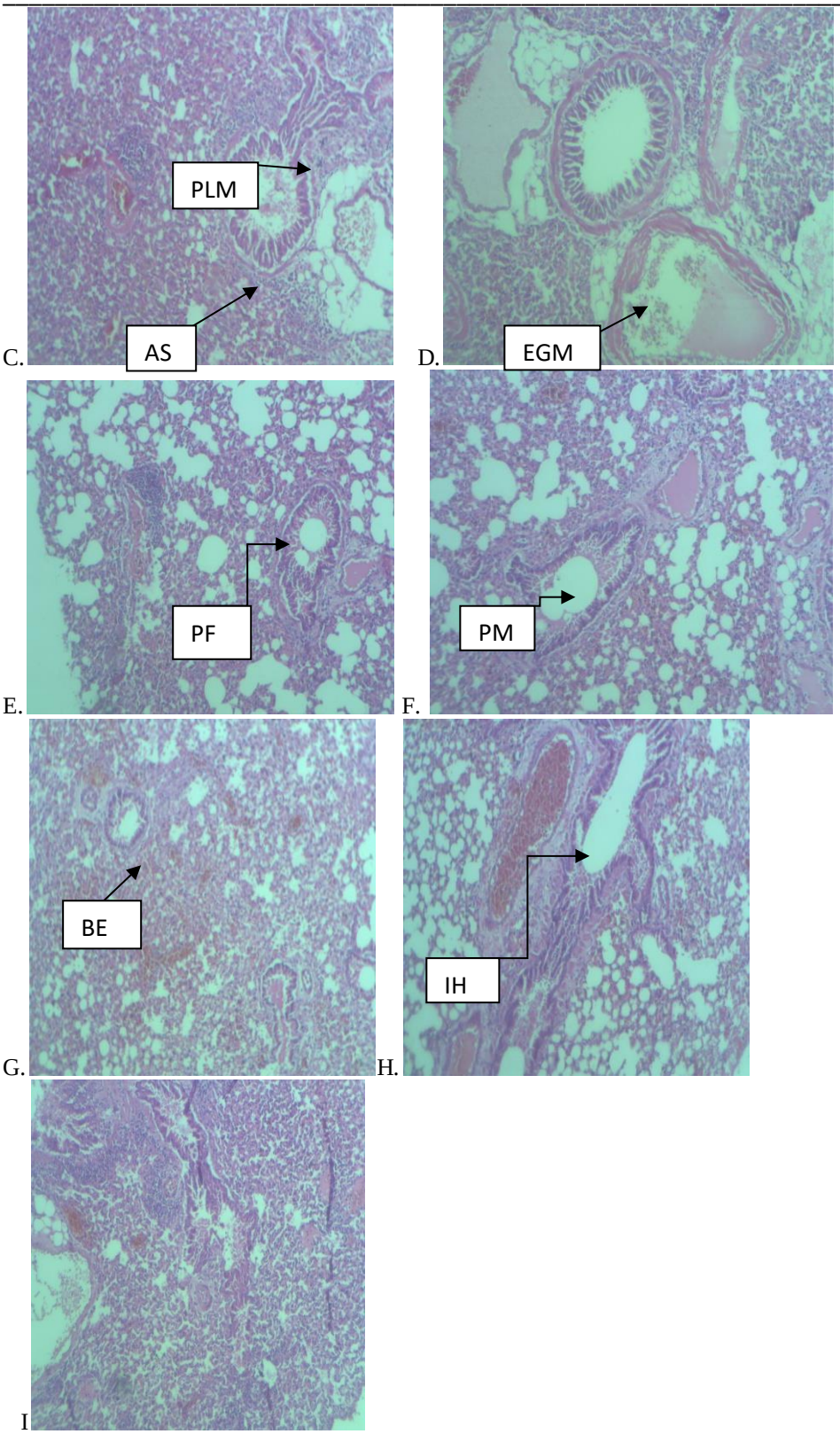


Plate 2: The photomicrographs above show the micrograph of the lung tissue of the group treated with *ficus platyphylla* of concentration of 1600, 800, and 400mg/kg, cisplatin and control (saline water) with Mgx40 with (ASDC) alveoli sac dilation and constriction (WDF) wall distortion and fibrinization. (LF) lymphoid follicle (EGM) eosinophilic globules and macrophages (AS) alveoli sacs (PLM) pneumocytes and lumen fill macrophages (PMC) pneumocytes and macrophages cells (PF) Perivascular fibrosis (BE) bronchi expansion (IH) interstitial hemorrhage

HISTOLOGICAL ASSESSMENTS OF THE KIDNEY

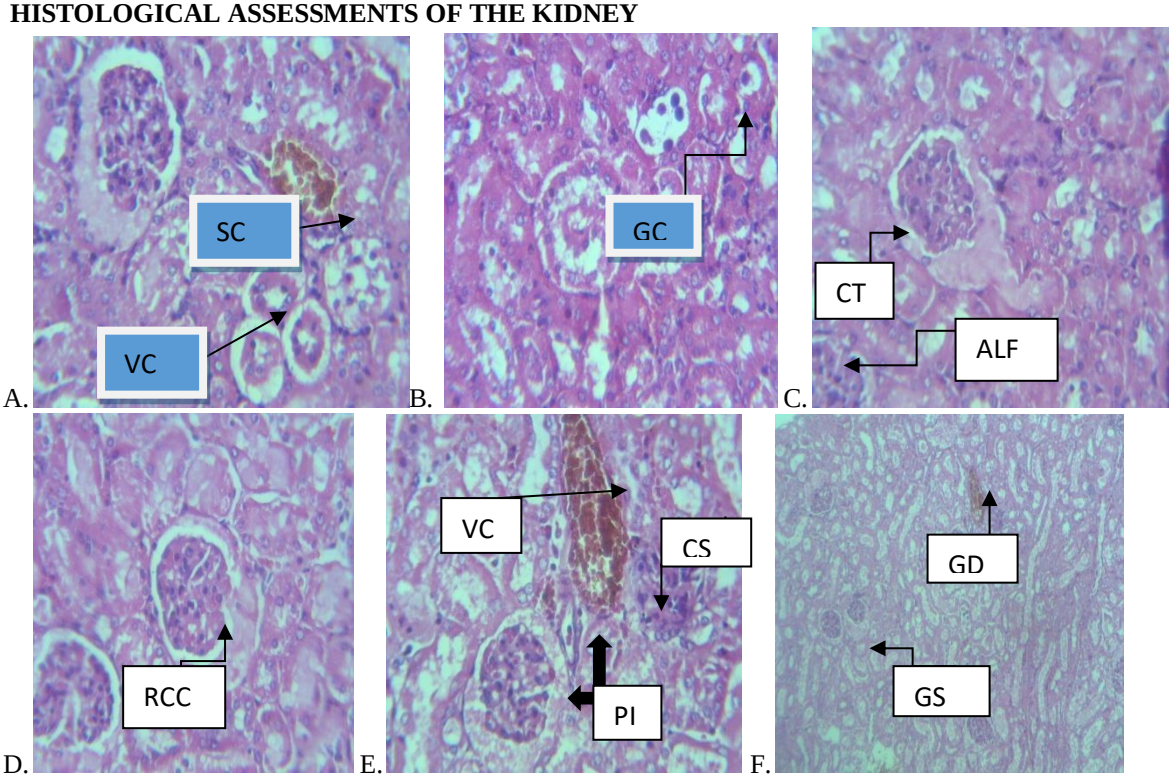
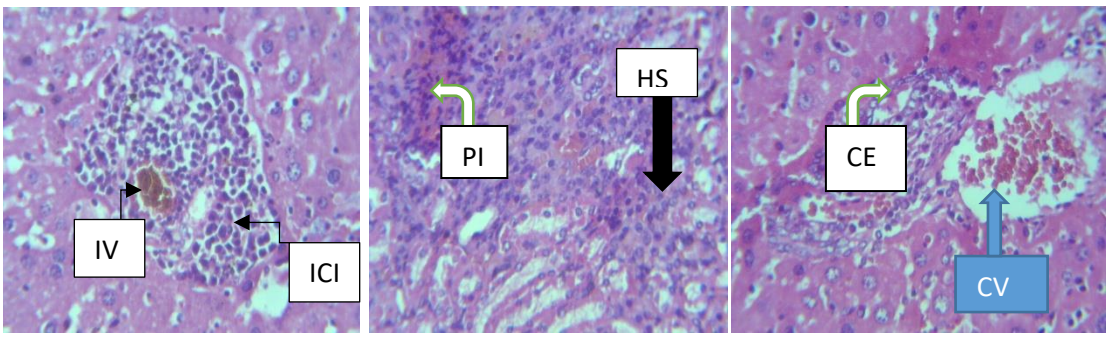


Plate 3: The photomicrographs above show the micrograph of the Kidney tissue of the group treated with *ficus platyphylla* of concentration of 1600, 800, and 400mg/kg, cisplatin and control (saline water) with Mg x 40 with (SC) showing The subcapsular tubules (GC) shows an increase in glomeruli capsular space. (VC) showing the Areas of vascular congestion and perivascular inflammatory cells infiltrate (CT) showing the cortex seen convoluted tubules and variable sizes of renal corpuscles. (RCC) showing. The renal corpuscle's capsule space is increased and contains eosinophilic material within it. (ALF) showing Areas of congested blood vessels and adjacent lymphoid follicle aggregates are seen. (PI) periglomeruli and perivascular inflammatory cells infiltrate. (GD) shows Areas of vascular channel congestion and glomeruli degeneration.

HISTOLOGICAL ASSESSMENT OF THE LIVER



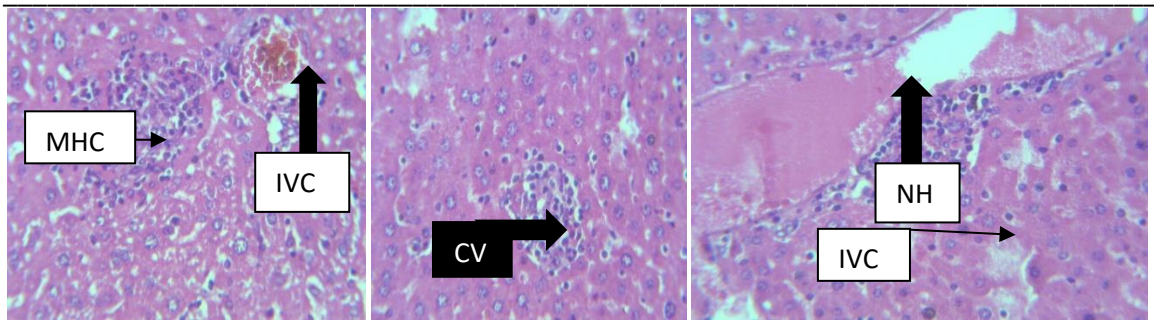


Plate 4:The photomicrographs above shows the micrograph of the liver tissue of group treated with *ficus platyphylla* of concentration of 1600, 800, and 400mg/kg, cisplatin and control (saline water) with Mgx40 with (HS) hepatic sinusoids space compression. (ICI) perivascular inflammatory cells infiltrates and periductal inflammatory cells infiltrates. (IVC) Interlobular vessels are congested and dilated. (CV) congested central veins with it hepatic plate cells and increase hepatic sinusoids spaces. (MHC) mild hepatic cytoplasmic destruction and central veins dilation and congestion with eosinophilic material. Within the portal area are seen (PI) periductal inflammatory cells infiltrate. Areas show scattered aggregates of lymphoid cells within the hepatic parenchyma. Most of the inflammatory cells aggregate are seen adjacent to the vascular channels.

HISTOLOGICAL ASSESSMENT OF THE HEART

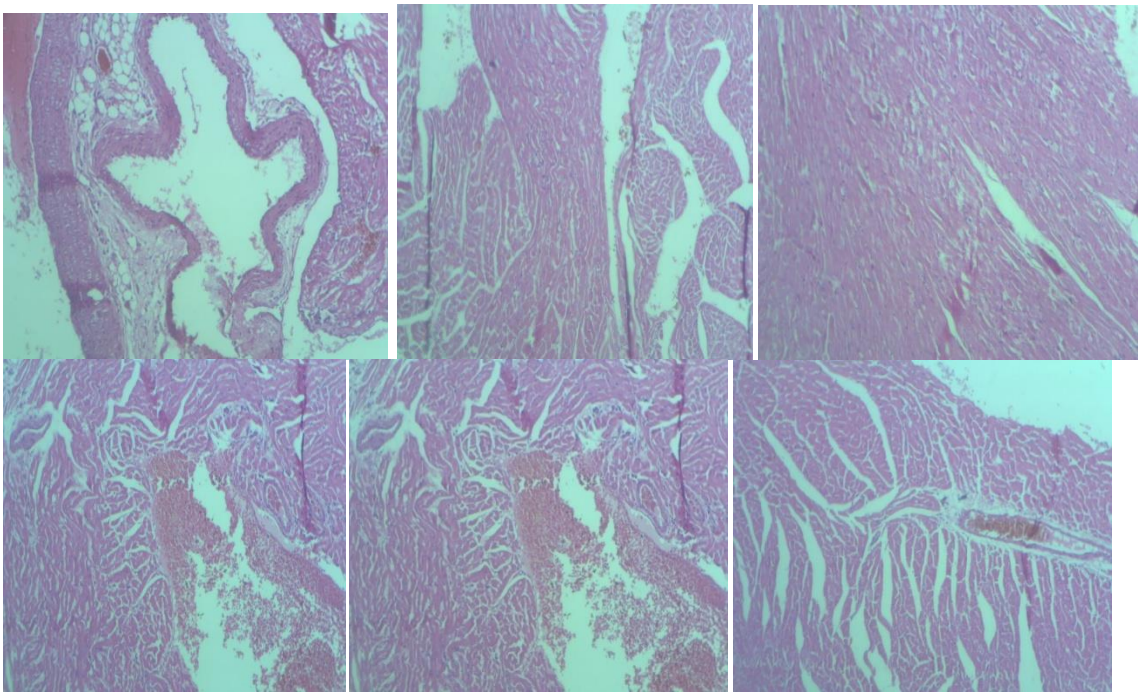


Plate 5: The photomicrographs above show the micrograph of the heart tissue of the group treated with *ficus platyphylla* at concentrations of 1600, 800, 400mg/kg, cisplatin and control (saline water) with Mgx40. The hearts of all groups were unaffected. A section of the heart tissue for all groups showed cardiac muscle bundles in longitudinal and transverse sections. Within it are seen red blood cells filling the lumen of vascular channels both small and large ones and intermuscular spaces are within normal limits. These features are unremarkable indicating no pathology.

3b DISCUSSION

Body Mass Index (BMI) is a well-documented factor influencing both cancer development and treatment-related toxicity, particularly in breast cancer among females (Yumuk et al., 2008). In this study, the absence of statistically significant weight gain across the treatment groups particularly in the group treated with the highest dose of *Ficus platyphylla* could be indicative of a better prognosis. This observation aligns with findings by Chlebowski et al. (2002), who noted that weight gain during or after breast cancer treatment correlates with higher recurrence and mortality, while stable or reduced weight suggests more

favorable treatment outcomes. Therefore, the stable weight profiles observed in this experiment may reflect a protective role of the extract against treatment-induced metabolic disruptions.

Changes in internal organ weights, such as those seen in the liver, lung, and heart, are sensitive biomarkers for systemic toxicity (Oloyede et al., 2018). A comparison between the control and treatment groups revealed statistically significant reductions in the relative weights of the liver and heart, particularly in mice treated with lower doses (400 mg/kg and 800 mg/kg) of *Ficus platyphylla* extract. This suggests that these lower doses may be insufficient to fully counteract the toxic effects of NMU. In contrast, the group treated with the highest dose of 1600 mg/kg showed relatively stable organ weights, indicating a stronger protective effect at this dosage. Reductions in organ weight, as seen in the lower dose groups, can reflect toxicological impacts such as hepatocellular or myocardial hypertrophy (Greaves, 2000), which may be either adaptive or degenerative responses to chemical insult.

Histopathological examination remains the gold standard for assessing tissue integrity, inflammation, and pathological progression (Gonzalez-Sánchez et al., 2017). In the pre-treatment (NMU-induced) groups, liver sections showed notable cytoplasmic disruption, consistent with apoptotic hepatocytes and toxic-induced injury. However, post-treatment analysis revealed dose-dependent tissue responses. Mice treated with the highest dose (1600 mg/kg) of *F. platyphylla* exhibited only mild inflammatory infiltration and largely preserved liver structure, indicating significant attenuation of NMU toxicity and possible activation of immune-mediated tissue repair mechanisms. Lower-dose treatment groups showed partial structural improvement but with more evident inflammatory markers, suggesting a less pronounced protective effect (Sheidu et al., 2020; Kruk et al., 2021).

In the kidney, histopathological differences were prominent. Cisplatin-treated mice displayed renal damage markers such as tubular necrosis, vascular congestion, and glomerular degeneration, consistent with Acute Kidney Injury (AKI) (Ozkok & Edelstein, 2014). Mice treated with *Ficus platyphylla* showed fewer pathological alterations compared to the cisplatin group, indicating a dose-dependent nephroprotective trend. Notably, the group treated with the highest dose of 1600 mg/kg exhibited the most pronounced protective effects, with the least evidence of renal damage. This suggests that higher doses of the extract may attenuate nephrotoxicity more effectively, possibly through antioxidative or anti-inflammatory mechanisms, although they do not entirely reverse cisplatin's effects.

The breast tissue of control and NMU-only groups showed no pathological or neoplastic changes, and similarly, no tumour initiation was observed in the treated groups. This absence of malignancy aligns with previous studies, such as Perše et al. (2009), where tumour development using NMU induction can be variable depending on dosage, duration, and host susceptibility. The findings here suggest that either the NMU dose was insufficient to initiate mammary tumours or, more plausibly, that *Ficus platyphylla*—particularly at the 1600 mg/kg dose—exerted a chemopreventive effect by inhibiting early oncogenic pathways and cellular transformation events associated with NMU.

Similarly, no observable cardiac pathology was found across all groups. Heart tissue retained normal architecture with no signs of muscle degeneration or inflammatory infiltration, in agreement with existing literature suggesting that NMU does not directly induce cardiotoxic effects (Singh, 2011).

Lung tissues from untreated and cisplatin-treated mice showed alveolar distortion, wall thickening, and infiltration of immune cells, indicating pulmonary toxicity. In contrast, mice treated with *F. platyphylla* showed milder alterations and partial preservation of alveolar structure. This further supports the extract's potential for organ protection and mitigation of inflammatory damage.

Collectively, a comparison of the histopathological profiles between treatment and control groups reinforces the therapeutic promise of *Ficus platyphylla*, with the 1600 mg/kg dosage exhibiting the most pronounced protective effects. This dose consistently resulted in reduced histopathological alterations and better preservation of tissue structure across multiple organs, including the liver, kidneys, and lungs. Although the extract was not entirely curative, it demonstrated significant anti-inflammatory activity, tissue preservation, and potential immune modulation. These results underscore the importance of further exploring dose-response relationships, isolating the bioactive compounds responsible for these therapeutic outcomes, and clarifying the underlying molecular pathways.

4.0 CONCLUSION

The research on the ethanol extract of Ficus platyphylla bark presents promising initial results in the prevention of NMU-induced mammary cancer and toxicity. The ability of the extract to inhibit the initiation phase of cancer development suggests its potential as a prophylactic agent against this type of toxicity. Nonetheless, the precise mechanisms

through which the extract affects tumour cells remain unclear, and understanding these mechanisms is crucial for advancing its application in toxicity and cancer prevention. While the initial findings regarding Ficus platyphylla bark extract are encouraging, extensive research is required to fully understand its potential as a cancer-preventive agent. Unlocking this potential could lead to the development of novel preventive treatments for mammary and possibly other types of cancer.

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