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Original Article

Effect of Aqueous Extracts of *Kigelia africana* and *Acacia nilotica* on Selected Tumour Markers in Diethylnitrosamine-Induced Liver Cell Dysplasia in Wistar Rats

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ABSTRACT

Background: Diethylnitrosamine (DEN) is a nitrosamine derivative with alkylating, carcinogenic, and mutagenic properties that causes major liver damage and acts as a hepatocarcinogen in rodents. *Acacia nilotica* and *Kigelia africana* are plants used in local communities to treat wounds and ulcers.

Objective: This study investigated the effect of aqueous extracts of *Kigelia africana* and *Acacia nilotica* on alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and cancer antigen 125 (CA-125) levels in DEN-induced liver cell dysplasia in Wistar rats.

Methods: Forty (40) male Wistar rats, aged 6–8 weeks, were divided into eight (8) groups of five (5) animals each. Liver cell dysplasia was induced with a single intraperitoneal dose of DEN (100 mg/kg) and promoted with oral phenobarbitone (0.25 mg/kg) twice weekly, beginning one week after induction. Group I received clean drinking water; group II received DEN only; group III received DEN + phenobarbitone; groups IV and V received DEN + phenobarbitone + 250 mg/kg and 500 mg/kg of *Acacia nilotica* respectively; groups VI and VII received DEN + phenobarbitone + 250 mg/kg and 500 mg/kg of *Kigelia africana* respectively; and group VIII received DEN + phenobarbitone + 10 mg/kg of sorafenib. Blood samples were collected on day 120 for biomarker evaluation, and liver tissue was processed for histopathology.

Results: CEA and CA-125 differed significantly among groups ($p < 0.001$), although group means largely remained within the physiological reference range; AFP showed no significant difference ($p = 0.580$). The highest CEA values occurred in the DEN-only and DEN + phenobarbitone groups, while CA-125 was highest in the DEN-only and sorafenib-treated groups. Animals treated with the plant extracts, particularly at the higher dose (500 mg/kg), maintained CEA and CA-125 values close to those of the negative control. Histopathology showed dose-dependent attenuation of DEN-induced changes by both extracts, with the higher dose of *Kigelia africana* producing near-normal liver architecture.

Conclusion: Both extracts, especially at higher doses, appeared chemoprotective against DEN-induced hepatic changes, supporting further investigation of their underlying mechanisms.

Keywords: Liver Dysplasia; Carcinoembryonic Antigen; Alpha-Fetoprotein; Cancer Antigen 125; Diethylnitrosamine

Introduction

Liver cell dysplasia (LCD) is characterised by cellular enlargement, nuclear pleomorphism, and multinucleation of liver cells occurring in groups or within cirrhotic nodules [1,2]. The term dysplasia denotes an ongoing process of malignant transformation, as it histologically indicates a recognisable alteration in cell proliferation and differentiation [3]. Anthony and colleagues coined the term "liver cell dysplasia" to describe a complex of hepatocellular cytological abnormalities found to be significantly prevalent in cirrhotic livers harbouring hepatocellular carcinoma (HCC) [1].

Diseases of the liver can be devastating because no other organ in the body can compensate for its functions [4]. Alcohol, drugs, xenobiotics, and many other agents and metabolites can damage liver cells. Diagnostic indicators of liver disease and injury include rising serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), abnormal liver biomarkers, jaundice, prolonged clotting times, oedema, and hepatic encephalopathy. Many liver diseases impair hepatic metabolic function and progress to non-alcoholic fatty liver disease (NAFLD), hepatic fibrosis, cirrhosis, and malignant transformation [4,5].

There are more similarities than differences between rodent and human livers [6]. The lobated liver of the rat and the non-lobated liver of humans share the same physiology and internal cytoarchitecture; the larger liver consists of more rather than larger lobules, and larger livers are perfused by proportionally more arterial and less portal blood. However, the rat liver lacks a gall bladder, which does not confer any selective disadvantage [6]. The liver is essential for life, being responsible for many biochemical and metabolic functions, including ridding the body of substances that would otherwise accumulate to injurious levels. It is also the first port of call for most nutrients absorbed across the gut wall, supplies most plasma proteins, and synthesises the bile that optimises fat absorption and serves as an excretory fluid for many drug metabolites [7,8].

Alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) are among the most useful biomarkers for the evaluation of liver cell damage and neoplasia, and are commonly found in the serum of patients with chronic liver damage and hepatic neoplasia [9]. AFP is a glycoprotein normally produced during foetal and neonatal development by the liver, yolk sac, and, in small concentrations, the gastrointestinal tract [10]. Serum AFP reaches a maximal concentration of approximately 3 g/L between weeks 12 and 16 of foetal life, after which levels decline rapidly, with only trace amounts normally detected in serum thereafter. Abnormally high serum AFP levels correlate with the development of several malignancies, most notably HCC [11].

Cancer antigen 125 (CA-125), although classically associated with epithelial ovarian malignancy, is increasingly recognised as a non-specific marker of serosal and mesothelial irritation and is frequently elevated in chronic liver disease, cirrhosis, and HCC, where it is thought to reflect peritoneal and hepatic inflammation rather than gynaecological pathology [12]. It was therefore included in the present study, alongside AFP and CEA, as an additional marker of epithelial injury and inflammation accompanying DEN-induced hepatic damage.

This study aimed to evaluate the effect of aqueous extracts of *Kigelia africana* and *Acacia nilotica* on selected tumour markers in diethylnitrosamine-induced liver cell dysplasia in Wistar rats.

Materials and Methods

Equipment and Reagents

Equipment used included animal cages, a microtome for tissue sectioning, a light microscope, syringes and needles for drug administration, a freeze-dryer, a water bath, and a calibrated microplate reader. Reagents and chemicals included diethylnitrosamine (DEN; Sigma-Aldrich, Germany; N0756), phenobarbitone tablets, sorafenib tablets, 10% formalin, graded alcohols, xylene, paraffin wax, haematoxylin and eosin, sodium hypochlorite, the AFP ELISA test kit, the CEA enzyme immunoassay kit (Cat. No. 10106), and the CA-125 enzyme immunoassay kit.

Preparation of Aqueous Extracts of *Acacia nilotica* and *Kigelia africana*

Root samples of *Acacia nilotica* and dried fruits of *Kigelia africana* were prepared at the Sheda Science and Technology Complex (SHESTCO), Abuja. The plant materials were air-dried to constant weight and pulverised using a grinding machine. The powders were stored in airtight containers at room temperature. Aqueous extracts were prepared using the cold maceration method described by Adzu and colleagues. Five hundred grams (500 g) each of the powdered roots of *Acacia nilotica* and dried fruits of *Kigelia africana* were soaked in 2 L of distilled, deionised water and left to stand for forty-eight (48) hours. Each suspension was filtered first with muslin cloth and subsequently with Whatman No. 1 filter paper. The filtrates were freeze-

dried using an AMSCO/FINN-AQUA GT2 freeze-dryer (Germany).

Animals and Treatment

Forty (40) male Wistar rats, aged 6–8 weeks and weighing 50–60 g, were used for the study. They were housed in a well-ventilated animal house at room temperature, fed standard chow (Livestock Feeds, Jos), and given water ad libitum. Animals were randomly divided into eight (8) groups of five (5) animals each. During the study, one animal each in groups 2, 7, and 8 died before the day of sample collection; statistical analyses were therefore based on the surviving animals (n = 4 in groups 2, 7, and 8; n = 5 in all other groups). The eight treatment groups were as follows:

Group 1 (negative control): received 2 mL of distilled water daily.

Group 2 (positive control): received a single intraperitoneal dose of DEN (100 mg/kg body weight).

Group 3: received a single intraperitoneal dose of DEN (100 mg/kg) and oral phenobarbitone (0.25 mg/kg) twice weekly, beginning one week after DEN administration and continued until the day of sacrifice.

Group 4: received 250 mg/kg of *Acacia nilotica* root extract orally for one week before a single intraperitoneal dose of DEN (100 mg/kg), then oral phenobarbitone (0.25 mg/kg) twice weekly from one week after DEN until sacrifice.

Group 5: received 500 mg/kg of *Acacia nilotica* root extract orally for one week before a single intraperitoneal dose of DEN (100 mg/kg), then oral phenobarbitone (0.25 mg/kg) twice weekly from one week after DEN until sacrifice.

Group 6: received 250 mg/kg of *Kigelia africana* fruit extract orally for one week before a single intraperitoneal dose of DEN (100 mg/kg), then oral phenobarbitone (0.25 mg/kg) twice weekly from one week after DEN until sacrifice.

Group 7: received 500 mg/kg of *Kigelia africana* fruit extract orally for one week before a single intraperitoneal dose of DEN (100 mg/kg), then oral phenobarbitone (0.25 mg/kg) twice weekly from one week after DEN until sacrifice.

Group 8: received 10 mg/kg of sorafenib orally for one week before a single intraperitoneal dose of DEN (100 mg/kg), then oral phenobarbitone (0.25 mg/kg) twice weekly from one week after DEN until sacrifice.

The treatment period lasted 16 weeks (120 days). All animals were sacrificed by cervical dislocation, and blood samples were collected through the orbital sinus for evaluation of tumour markers. Liver tissue was harvested, fixed in neutral buffered formalin, and processed for histopathological evaluation following the method described by Krause.

Induction of Liver Cell Dysplasia

Liver cell dysplasia was induced by a single intraperitoneal dose of DEN (analytical grade; Sigma-Aldrich, Germany) at 100 mg/kg body weight. Promotion was achieved by oral administration of phenobarbitone (0.25 mg/kg), beginning one week after DEN administration and given twice weekly until the day of sacrifice.

Evaluation of Tumour Markers

AFP and CEA were estimated using the AFP ELISA test kit and the CEA enzyme immunoassay kit (Cat. No. 10106), respectively. CA-125 was determined using a CA-125 enzyme immunoassay kit. All assays were performed according to the respective manufacturers' instructions, and absorbance was read on a calibrated microplate reader. Because validated rat-specific reference intervals are not established for these markers, group means were interpreted relative to the negative control and to commonly cited human reference ranges, which should be regarded as indicative rather than definitive.

Phytochemical Screening

Qualitative phytochemical screening of the extracts was performed using methods described by Ayeni and Yahaya, Maldini and colleagues, and Rayan and Elfadil. Constituents detected included tannins, flavonoids, phenols, alkaloids, anthraquinones, glycosides, and saponins. Bioactive compounds previously reported for *Acacia nilotica* include quercetin, 3,4-dihydroxybenzoic acid, and resveratrol, which are associated with anti-inflammatory, antioxidant, antineoplastic, and anticancer activities. Compounds reported for *Kigelia africana* include catechin and related cyclopropane fatty-acid esters, which have been associated with antiviral, anti-inflammatory, antimicrobial, and anticancer activities. These compounds are cited from the literature for the respective species; they were not independently quantified in the present study.

Ethical Approval

All experimental procedures involving animals were conducted in accordance with institutional guidelines for the care and use of laboratory animals and were approved by the University of Abuja Ethics Committee on Animal Use (UAECAU), Nigeria (Approval Number: UAECAU/2020/0003; Approval Date: 13 November 2020).

Statistical Analysis

Data are expressed as mean ± standard error of the mean (SEM). Differences among the eight groups were analysed by one-way analysis of variance (ANOVA), followed by Duncan's multiple range test for post-hoc comparisons. The assumptions of normality and homogeneity of variance were assessed

using the Shapiro–Wilk and Levene's tests, respectively. A probability value of $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Table 1. One-way ANOVA of serum tumour-marker concentrations across the eight animal groups.

Marker	Source	Sum of Squares	df	Mean Square	F	Sig.
CEA	Between groups	94.228	7	13.461	14.293	<0.001
	Within groups	27.313	29	0.942		
	Total	121.541	36			
AFP	Between groups	9.667	7	1.381	0.818	0.580
	Within groups	48.991	29	1.689		
	Total	58.658	36			
CA-125	Between groups	1263.320	7	180.474	23.865	<0.001
	Within groups	219.311	29	7.562		
	Total	1482.631	36			

Serum Carcinoembryonic Antigen (CEA)

Serum CEA levels differed significantly among the groups ($p < 0.001$; Table 1, Figure 1). Levels were markedly elevated in the induction groups, group 2 (DEN only) and group 3 (DEN + phenobarbitone), relative to the negative control, with overlapping error bars between these two groups. In the negative control (group 1) and treatment groups 4, 5, 6, 7, and 8, mean CEA values remained within the normal reference range, and error bars overlapped between the control group and groups 4, 5, and 7. Duncan's post-hoc test placed groups 1, 4, 5, 6, 7, and 8 in one homogeneous subset and the two induction groups (2 and 3) in a separate, higher subset (Table 2).

Table 2. Duncan's post-hoc homogeneous subsets for serum CEA (ng/mL).

Group	N	Subset 1	Subset 2
Group 4	5	1.83	
Group 7	4	1.96	
Group 1	5	2.08	
Group 5	5	2.48	
Group 8	4	2.85	
Group 6	5	3.27	
Group 3	5		5.70
Group 2	4		6.30
Sig.		0.056	0.359

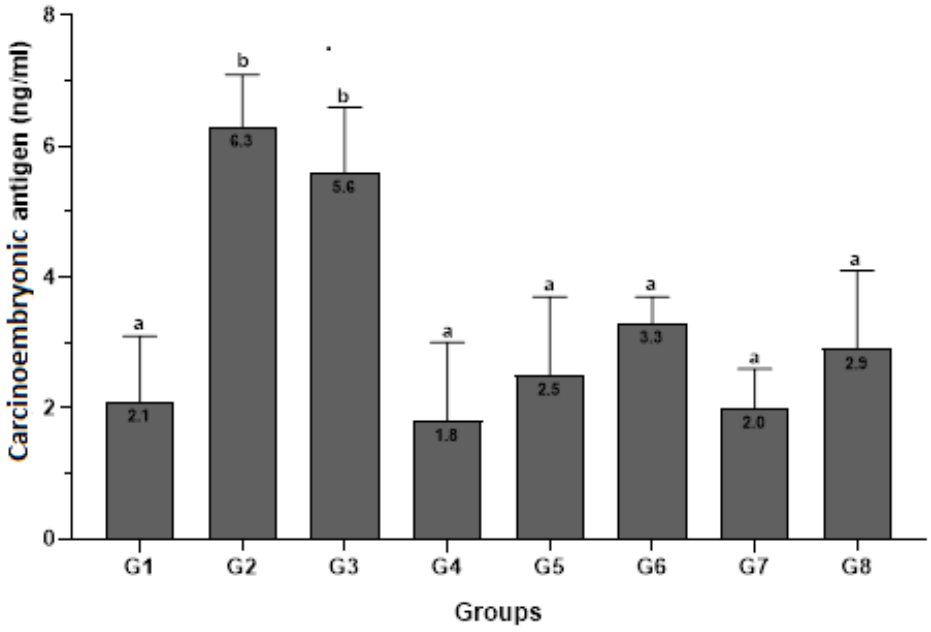

Figure 1: Serum levels of carcinoembryonic antigen (CEA) among the animal groups.
Bars represent mean ± SEM. Means sharing the same letter above the error bars are not significantly different (p > 0.05).

Serum Alpha-fetoprotein (AFP)

Serum AFP levels did not differ significantly among the groups (p = 0.580; Table 1, Figure 2), and all group means remained within the physiological range. The highest mean value was recorded in group 8 (DEN + sorafenib) and the lowest in group 2 (DEN only), but no significant differences were detected between the treatment groups and the control.

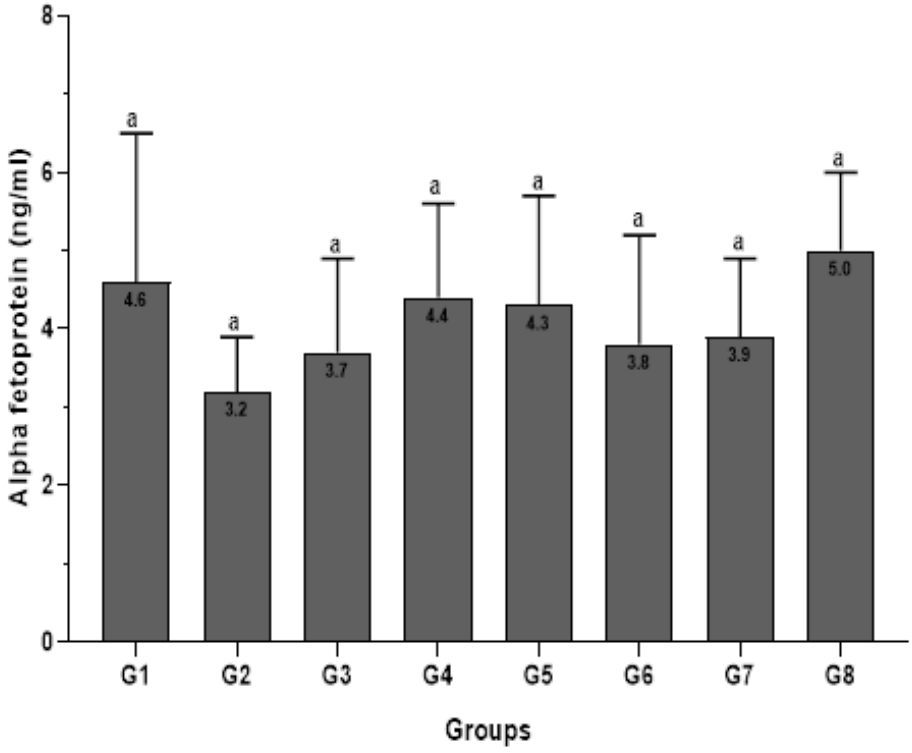

Figure 2: Serum levels of alpha-fetoprotein (AFP) among the animal groups.
Bars represent mean ± SEM. Means sharing the same letter above the error bars are not significantly different (p > 0.05).

Serum Cancer Antigen 125 (CA-125)

Serum CA-125 levels differed significantly among the groups (p < 0.001; Table 1, Figure 3), with the highest values recorded in group 2 (DEN only) and group 8 (DEN + sorafenib); however, group means remained within the normal reference range. Error bars

overlapped between the negative control (group 1) and treatment groups 5, 6, and 7, indicating similar CA-125 levels among these groups. Duncan's post-hoc test separated the groups into three homogeneous subsets, with the control and higher-dose extract groups in the lowest subset and the DEN-only and sorafenib groups in the highest (Table 3).

Table 3. Duncan's post-hoc homogeneous subsets for serum CA-125 (U/mL).

Group	N	Subset 1	Subset 2	Subset 3
Group 7	4	13.18		
Group 5	5	13.88		
Group 1	5	14.00		
Group 6	5	14.50		
Group 4	5		19.12	
Group 3	5		20.14	
Group 8	4			27.13
Group 2	4			30.23
Sig.		0.514	0.579	0.099

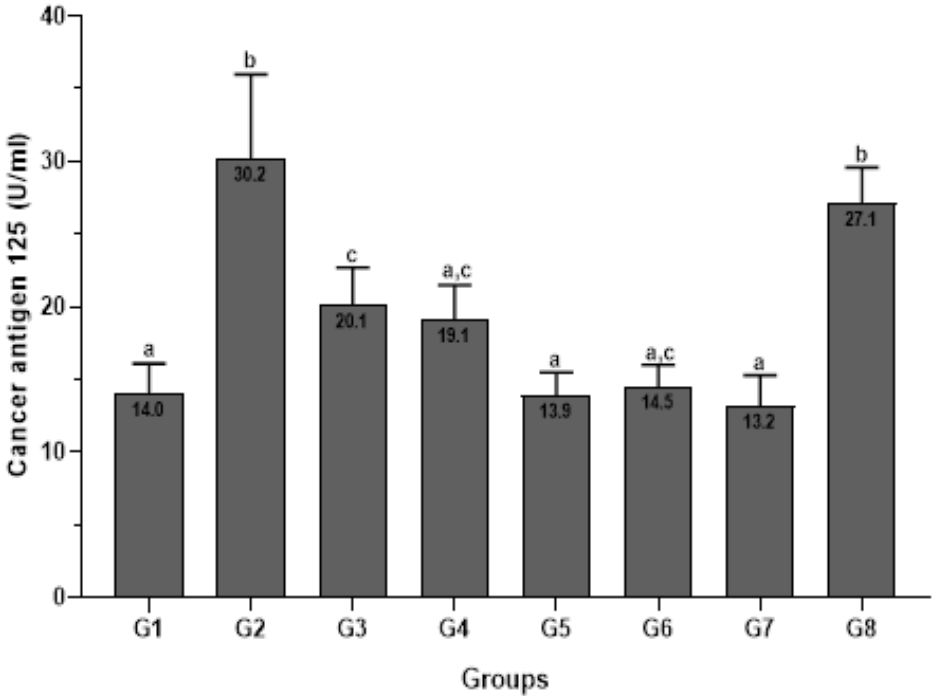

Figure 3: Serum levels of cancer antigen 125 (CA-125) among the animal groups.
Bars represent mean ± SEM. Means sharing the same letter above the error bars are not significantly different ($p > 0.05$).

Histopathological Findings

Histological examination of liver sections supported the biomarker findings and revealed a dose-dependent pattern of injury and protection across the groups. The negative control (group 1) showed normal hepatocytes, sinusoids, and hepatic cords throughout (Figures 4–7). The induction groups showed the most severe changes: group 2 (DEN only) exhibited hyperchromasia, karyomegaly, karyorrhexis, pyknosis, and dilated sinusoids, while group 3 (DEN + phenobarbitone) showed pyknosis, karyomegaly, hyperchromasia, karyorrhexis, and karyolysis (Figure 4).

Among the *Acacia nilotica*–treated groups, group 4 (250 mg/kg) showed necrosis, ghost cells, karyorrhexis, regenerating hepatocytes, and mildly dilated sinusoids, while group 5 (500 mg/kg) showed only mild karyorrhexis with mildly dilated sinusoids and scattered normal and regenerating hepatocytes (Figure 5). Among the Kigelia africana–treated groups,

group 6 (250 mg/kg) showed necrosis with ghost cells, karyolysis, binucleation, and dilated sinusoids, whereas group 7 (500 mg/kg) showed normal hepatocytes with mildly dilated sinusoids, approaching normal liver architecture (Figure 6). The sorafenib-treated group (group 8) showed proliferating hepatocytes with normal sinusoids and occasional pyknosis (Figure 7). Overall, both extracts attenuated DEN-induced histological injury in a dose-dependent manner, with the higher dose of *Kigelia africana* producing the most pronounced recovery toward normal architecture.

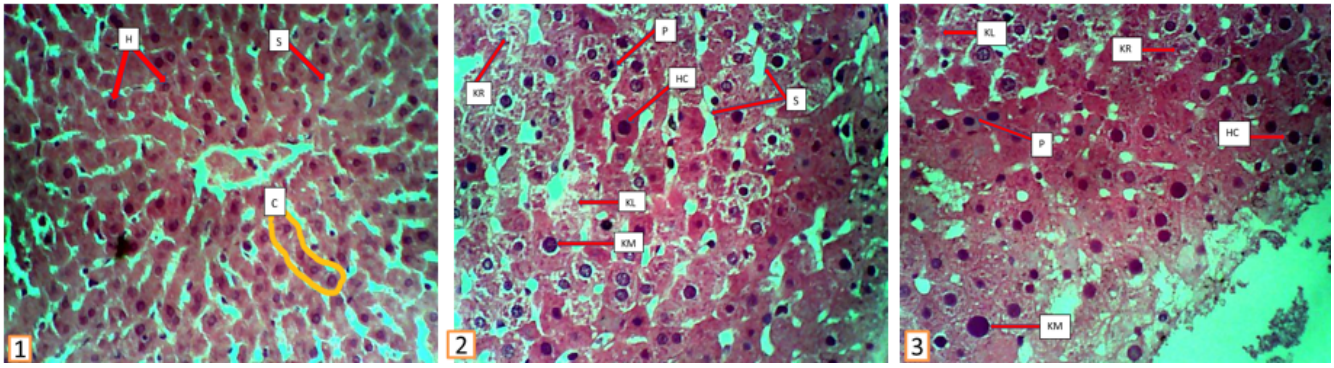

Figure 4: Photomicrographs of liver from the control and induction groups (H&E).
G1: normal hepatocytes (H), normal sinusoids (S), and normal hepatic cords (HC).
G2: hyperchromasia (HC), karyomegaly (KM), karyorrhexis (KR), pyknosis (P), and dilated sinusoids (S).
G3: pyknosis (P), karyomegaly (KM), hyperchromasia (HC), karyorrhexis (KR), and karyolysis (KL).

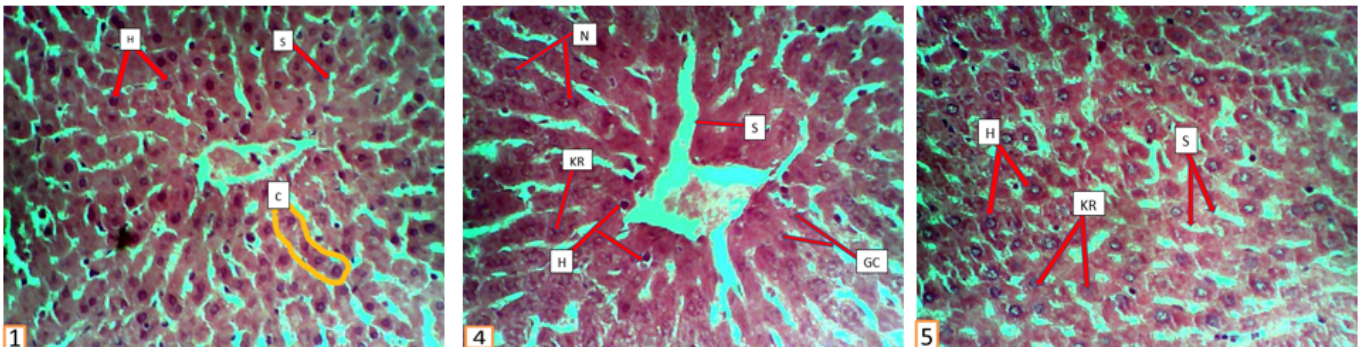

Figure 5: Photomicrographs of liver from the control and *Acacia nilotica*–treated groups (250 and 500 mg/kg; H&E).
G1: normal liver histology.
G4: necrosis (N), regenerating hepatocytes (H), karyorrhexis (KR), ghost cells (GC), and mildly dilated sinusoids (S).
G5: mild karyorrhexis (KR), mildly dilated sinusoids, and scattered normal and regenerating hepatocytes.

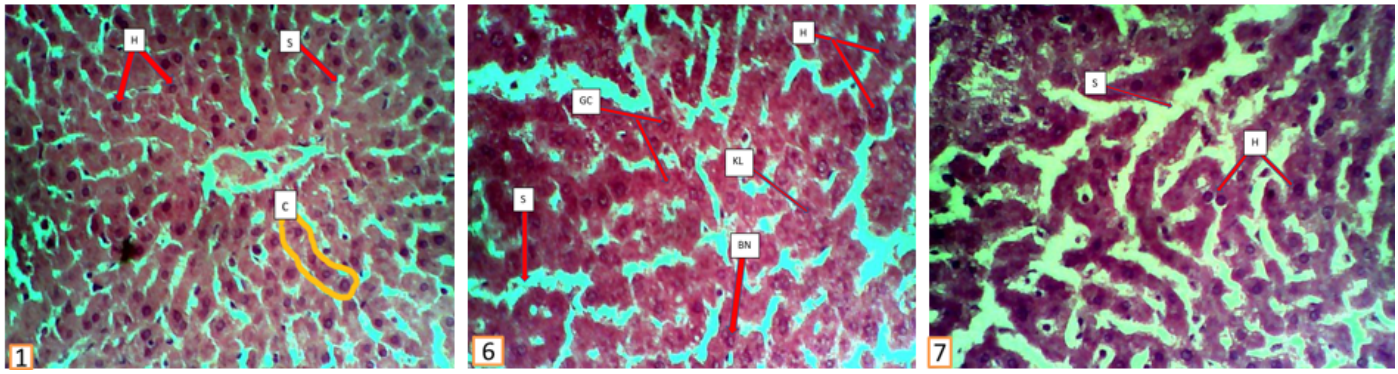

Figure 6: Photomicrographs of liver from the control and Kigelia africana–treated groups (250 and 500 mg/kg; H&E).
G1: normal liver histology.
G6: necrosis with ghost cells (GC), karyolysis (KL), binucleation (BN), and dilated sinusoids (S).
G7: normal hepatocytes (H) with mildly dilated sinusoids (S).

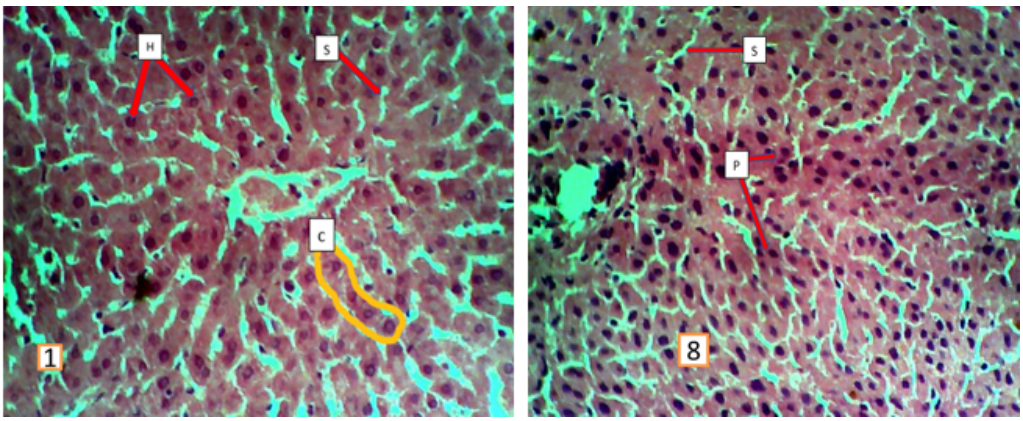

Figure 7: Photomicrographs of liver from the control and sorafenib-treated group (10 mg/kg; H&E).
G1: normal liver histology.
G8: proliferating hepatocytes with normal sinusoids (S) and occasional pyknosis (P).

Discussion

This study evaluated the effects of chemical induction, pharmacological promotion, plant-based intervention, and a standard anticancer drug (sorafenib) on the tumour-associated markers CEA, AFP, and CA-125 across eight experimental groups, complemented by histopathological assessment. The observed biomarker and tissue profiles reflect differential pathological and therapeutic responses to the various interventions.

CEA differed significantly among the groups, with the highest levels in groups 2 and 3, which received DEN alone and DEN combined with phenobarbitone, respectively. The elevated CEA in these groups is consistent with increased neoplastic activity and confirms successful induction and promotion. In contrast, CEA was lowest in the control group and in the extract-treated groups 4 and 7, suggesting that the extracts may exert protective and anti-proliferative effects against DEN-induced hepatic injury. These findings agree with reports that aqueous plant- and algae-derived extracts attenuate the rise in hepatic tumour markers in the DEN/phenobarbitone model of hepatocarcinogenesis [13,14].

Although mean CEA and CA-125 concentrations largely remained within commonly cited physiological reference ranges, the statistically significant differences observed between the DEN-induced groups and the extract-treated groups remain biologically meaningful. In experimental models of early hepatic dysplasia, subtle relative changes in circulating tumour markers may precede the marked elevations typically observed in advanced malignancy. Therefore, the observed reductions following treatment are more appropriately interpreted as evidence of attenuation of early pathological processes rather than complete prevention of tumour development.

AFP did not differ significantly among the groups, and all values remained within the physiological range. The relatively higher mean values in the control and sorafenib-treated groups may reflect baseline physiological expression or hepatic regeneration and drug-induced cellular stress rather than active tumour progression, while the intermediate values in the *Acacia nilotica*–treated groups may indicate a moderate regenerative or protective response. The absence of significant AFP changes suggests that the dysplastic changes induced over the study period were insufficient to produce marked alterations in circulating AFP, consistent with the known limitations of AFP as an early marker of hepatic dysplasia [15].

CA-125 differed significantly among the groups, although group means remained within the normal reference range. The highest values occurred in groups 2 and 8. The elevation in group 2 further supports the presence of significant pathological and inflammatory changes induced by DEN, while the increase in the sorafenib group may reflect epithelial irritation or treatment-related cellular turnover rather than disease progression, as sorafenib is known to induce stress responses despite its antitumour activity. The lower CA-125 values in the control group and in groups 5, 6, and 7 (higher-dose extracts) suggest reduced epithelial activation and inflammation, supporting a protective effect of the extracts and consistent with the recognised role of CA-125 as a marker of serosal and hepatic inflammation rather than a gynaecological-specific marker [12].

The absence of marked elevations beyond the physiological range is likely attributable to the relatively early dysplastic stage produced in this model, in which inflammatory and cellular alterations are present histologically but extensive tumour burden has not yet developed. Consequently, CA-125 appears to

reflect subtle biological responses associated with early hepatic injury rather than advanced malignancy.

The histopathological findings reinforced the biomarker results. Both extracts showed dose-dependent chemoprotective properties against DEN-induced dysplasia relative to the induction groups, with *Kigelia africana* showing greater efficacy than *Acacia nilotica*. This is evident on comparing the *Acacia nilotica*–treated groups (4 and 5) with the Kigelia africana–treated groups (6 and 7): groups 4 and 5 showed focal inflammatory changes and residual karyorrhexis, whereas group 6 showed regenerating, near-normal hepatocytes and group 7 showed essentially normal hepatocytes and cytoarchitecture. Sorafenib-treated animals (group 8) showed proliferating hepatocytes with occasional pyknosis. Together, these findings highlight the value of combining multiple tumour markers with histopathology to assess carcinogenic progression and therapeutic efficacy, and suggest that *Acacia nilotica* and *Kigelia africana* extracts offer promising protection against chemically induced hepatic carcinogenesis.

This study has several limitations. The sample size per group was relatively small, and three animals were lost before sample collection. Marker concentrations were interpreted against human-derived reference ranges, as validated rat-specific intervals are not established, and the investigation was limited to selected tumour markers and qualitative histopathology without molecular characterisation of carcinogenic pathways. Future studies incorporating larger sample sizes, semi-quantitative histological grading, gene-expression profiling, oxidative-stress markers, and longer follow-up are recommended to clarify the mechanisms underlying the observed chemoprotective effects.

Although the loss of three animals slightly reduced the sample size in three experimental groups, the remaining group sizes were sufficient to detect statistically significant differences for CEA and CA-125. Nevertheless, the reduced sample size may have modestly decreased statistical power, particularly for AFP, and this should be considered when interpreting non-significant findings.

Conclusion

DEN-induced hepatic dysplasia was associated with significant alterations in serum CEA and CA-125, whereas AFP remained within the physiological range and did not differ significantly among groups. Treatment with aqueous extracts of *Acacia nilotica* and *Kigelia africana* attenuated both biochemical and histopathological manifestations of hepatic injury in a dose-dependent manner, with the higher dose of *Kigelia africana* producing the greatest protective effect. These findings suggest that both plant extracts possess promising chemoprotective activity in this experimental animal model. However, further mechanistic investigations, long-term preclinical studies, and eventual clinical studies are required before any therapeutic application can be inferred.

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Ethical Approval: Approved by the University of Abuja Ethics Committee on Animal Use (UAECAU); Approval Number: UAECAU/2020/0003.

Consent for Publication: Not applicable.

Availability of Data and Materials: The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: JAA conceived and designed the study, conducted the experiments, analysed the data, and drafted the manuscript. BAI supervised the study, contributed to data interpretation, critically revised the manuscript, and approved the final version. Both authors read and approved the final manuscript.

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Disclosure of AI Use: No generative artificial intelligence tools were used in the collection, analysis, or interpretation of data, or in the preparation of the final scientific content of this manuscript. Language-editing assistance, where applicable, did not influence the scientific conclusions of the study.

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