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Changes associated with administration of *Garcinia kola* seed hydroethanol extract on DMBA-Induced Mammary Gland Toxicity in Female Wistar Rats

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Abstract

Oxidative stress plays a critical role in the pathogenesis of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary gland toxicity and associated systemic complications. *Garcinia kola* seeds are rich in bioactive phytochemicals with established antioxidant and anti-inflammatory properties. However, there is paucity of information on its potential effect on cancer related diseases. This study evaluated the protective effects of hydroethanolic seed extract of *Garcinia kola* on haematological and renal changes associated with DMBA-induced mammary gland toxicity in female Wistar rats. Thirty-five female Wistar rats were randomly assigned to five groups: normal control, DMBA control, DMBA plus *Garcinia kola* extract, DMBA plus vitamin C, and *Garcinia kola* extract only. Mammary gland toxicity was induced by a single oral dose of DMBA (50 mg/kg body weight). Following a seven-day induction period, animals received daily oral treatments of *Garcinia kola* extract or vitamin C for four weeks. Haematological parameters and renal function biomarkers were subsequently evaluated using standard analytical procedures. DMBA administration revealed a statistically significant changes in red blood cell count (8.54±0.33 to 8.87±0.14), haemoglobin concentration (16.20±0.21 to 19.91±0.16), haematocrit level (52.20±6.7 to 58.90±1.8) and neutrophil count (19.12±0.12 to 13.11±0.02) but insignificant in the white blood cell count indicating systemic inflammation and oxidative stress. Electrolyte imbalance was evidenced with a significant decrease in potassium (6.14±0.06 to 5.62±0.23) and chloride concentration (103.2±1.32 to 100±2.7). Treatment with *Garcinia kola* extract significantly ameliorated these abnormalities, restoring haematological and renal parameters toward normal values. Hydroethanolic seed extract of *Garcinia kola* exhibits haematoprotective and nephroprotective activities against DMBA-induced toxicity, likely through antioxidant and anti-inflammatory properties. These findings support its potential as a natural therapeutic agent for mitigating carcinogen-induced systemic damage.

Keywords: *Breast cancer, Garcinia kola, DMBA, mammary toxicity, oxidative stress, renal toxicity*

INTRODUCTION

Breast cancer is one of the most prevalent malignancies affecting women worldwide and remains a major public health challenge, particularly in low- and middle-income countries (Alabi *et al.*, 2023). According to global cancer statistics, breast cancer accounts for a substantial proportion of cancer-related morbidity and mortality, with increasing incidence linked to environmental, genetic, and lifestyle factors (Sung *et al.*, 2021). In Nigeria

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and other sub-Saharan African countries, delayed diagnosis, inadequate healthcare facilities, and exposure to environmental carcinogens contribute significantly to poor disease outcomes (Adnyaswari, *et al.,* 2025, Jedy-Agba *et al.,* 2020). Consequently, there is a growing need to better understand the mechanisms underlying breast cancer development and to identify effective strategies for prevention and management.

To address this need, experimental induction of breast cancer using chemical carcinogens has become an important approach for elucidating disease mechanisms and evaluating potential therapeutic agents. Among these carcinogens, 7,12-dimethylbenz[a]anthracene (DMBA), a potent polycyclic aromatic hydrocarbon, is widely employed in mammary carcinogenesis studies because it closely mimics several pathological features of human breast cancer. DMBA undergoes metabolic activation in the liver through cytochrome P450 enzymes, producing reactive intermediates that bind to DNA and generate reactive oxygen species (ROS), resulting in oxidative stress, mutations, cellular transformation, and carcinogenesis (Khan *et al.,* 2020; Russo and Russo, 2018). The generation of ROS during DMBA metabolism highlights the critical role of oxidative stress in mediating its toxic and carcinogenic effects.

Oxidative stress is a major mechanism underlying DMBA-induced toxicity. Excessive ROS production causes lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction, ultimately leading to cellular injury and tissue degeneration (Reczek and Chandel, 2021). Although DMBA primarily targets mammary tissues, its metabolites may circulate systemically and exert toxic effects on vital organs such as the liver and kidneys (Maued, *et al.,* 2023, Okolie *et al.,* 2022). Furthermore, DMBA disrupts endogenous antioxidant defense systems by reducing the activities of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, thereby promoting inflammation, apoptosis, and tissue damage (Adedara *et al.,* 2021). Beyond organ damage, these oxidative and inflammatory processes can also adversely affect blood cell production and immune function.

In addition to organ toxicity, DMBA exposure significantly affects the haematopoietic system. Haematological indices such as packed cell volume (PCV), haemoglobin concentration (Hb), red blood cell count (RBC), white blood cell count (WBC), and platelet count serve as important indicators of physiological and pathological conditions. Studies have shown that DMBA-induced oxidative stress may suppress bone marrow activity, damage erythrocytes, and alter immune responses, resulting in anaemia, leukocytosis, thrombocytopenia, and other haematological abnormalities (Khan *et al.,* 2020, Adewale *et al.,* 2019). Such alterations reflect systemic toxicity and provide valuable information regarding the severity of carcinogen-induced damage. Given the multifaceted toxic effects of DMBA, there is increasing interest in identifying natural compounds capable of mitigating oxidative stress and its associated pathological consequences.

The growing burden of chemically induced diseases has stimulated interest in medicinal plants as alternative therapeutic agents. Natural products are generally considered affordable, accessible, and relatively safe, especially in developing countries. Among these medicinal plants, *Garcinia kola* Heckel, commonly known as bitter kola, is widely distributed throughout West and Central Africa and has long been utilized in traditional medicine for the management of cough, liver disorders, infections, inflammation, poisoning, and gastrointestinal diseases (Farombi *et al.,* 2019). Its extensive ethnomedicinal use has prompted scientific investigations into its phytochemical composition and biological activities.

RELATED WORKS

Phytochemical investigations have revealed that *Garcinia kola* seeds contain numerous bioactive compounds, including flavonoids, tannins, saponins, alkaloids, phenolics, and biflavonoids such as kolaviron, which possess potent antioxidant and anti-inflammatory activities (Akinmoladun *et al.,* 2021). Several experimental studies have demonstrated the hepatoprotective, nephroprotective, cardioprotective, antimicrobial, anti-inflammatory, and anticancer properties of *Garcinia kola*. Farombi *et al.,* 2019 reported that kolaviron inhibited CCl_4 -induced decrease in liver microsomal enzymes. These pharmacological effects have been largely attributed to its ability to scavenge

free radicals, reduce lipid peroxidation, and enhance endogenous antioxidant defenses (Emmanuel *et al.*, 2022; Tauchen *et al.*, 2023). Such findings suggest that *Garcinia kola* may be particularly useful in conditions where oxidative stress plays a central pathogenic role. Recent studies have further shown that *Garcinia kola* extract stabilizes antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase, thereby protecting tissues against oxidative damage induced by toxic agents (Tauchen *et al.*, 2023). Given that oxidative stress is a major mechanism involved in DMBA-induced mammary gland and renal toxicity, *Garcinia kola* may offer significant protection against the deleterious effects of DMBA exposure. However, despite its demonstrated antioxidant and organ-protective properties, its role in ameliorating DMBA-induced haematological and renal dysfunction remains inadequately explored.

Despite increasing scientific evidence supporting the medicinal benefits of *Garcinia kola*, limited information is available regarding its protective effects on haematological and renal alterations associated with DMBA-induced mammary gland toxicity. Therefore, this study was designed to evaluate the protective effects of *Garcinia kola* seed hydroethanolic extract against DMBA-induced mammary gland toxicity in female Wistar rats by assessing haematological indices and renal function biomarkers. The study seeks to provide further evidence on the potential chemoprotective and organ-protective properties of *Garcinia kola* against carcinogen-induced oxidative damage.

METHODOLOGY

Experimental Animals

Thirty-five (35) healthy nulliparous female Wistar rats weighing between 80 and 120 g were used for this study. The animals were obtained from the Animal House Facility of Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria. Upon arrival, the rats were acclimatized for one week under standard laboratory conditions, including a temperature of 25 ± 2 °C, relative humidity of 50–60%, and a 12 h light/12 h dark photoperiod. Animals were housed in clean polypropylene cages and provided with standard commercial pellet diet and clean drinking water ad libitum throughout the experimental period.

All experimental procedures involving animals were conducted in accordance with internationally accepted guidelines for the care and use of laboratory animals and were approved by Gateway ICT Polytechnic Research Ethics committee with reference number GPS/25/REC/021.

Experimental Design

Following acclimatization, the animals were randomly allocated into five experimental groups (n = 7 per group):

Group I (Normal Control): Received distilled water and standard feed throughout the experimental period.

Group II (DMBA Control): Received a single oral dose of 7,12-dimethylbenz[a]anthracene (DMBA; 50 mg/kg body weight).

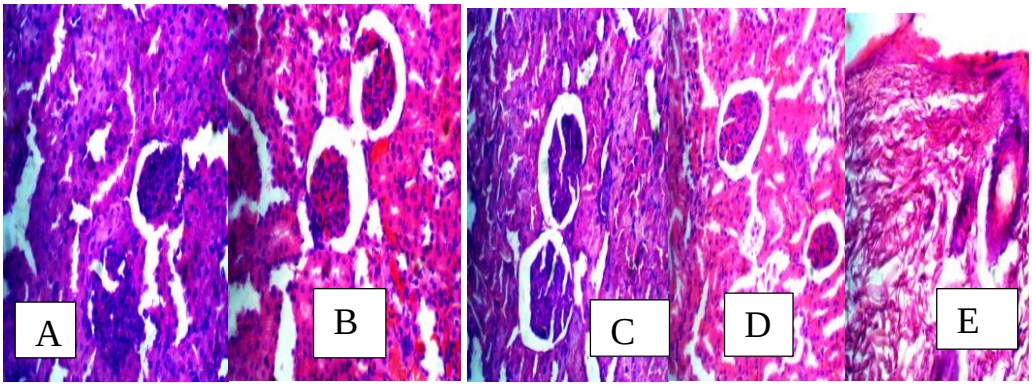


Figure 1. Plate 1-The photomicrograph of the kidney in administration with (A) distilled water. (B) DMBA only (C) DMBA + Garcinia kola (D) DMBA + Vitamin C (E) Garcinia kola only.

Group III (DMBA + *Garcinia kola*): Received DMBA (50 mg/kg body weight) followed by treatment with 500 mg/kg *Garcinia kola* seed hydroethanolic extract.

Group IV (DMBA + Vitamin C): Received DMBA (50 mg/kg body weight) followed by treatment with 500 mg/kg Vitamin C. **Group V (*Garcinia kola* Only):** Received 500 mg/kg *Garcinia kola* seed hydroethanolic extract only.

Collection and Authentication of Plant Material

Fresh seeds of *Garcinia kola* Heckel were purchased from a local market in Sagamu, Ogun State, Nigeria. The seeds were thoroughly washed with distilled water to remove adhering contaminants and subsequently air-dried under shade at room temperature in the Biochemistry Laboratory, Gateway ICT Polytechnic, Saapade, Ogun State, Nigeria.

Botanical identification and authentication of the plant material were carried out at the Department of Botany, University of Lagos, Akoka, Lagos State, Nigeria. A voucher specimen (LUH 100772) was deposited in the departmental herbarium for future reference.

Preparation of Hydroethanolic Extract of Garcinia kola Seeds

The dried seeds were pulverized into a fine powder using a laboratory grinder. A total of 110 g of the powdered sample was macerated in 1 L of hydroethanolic solvent consisting of distilled water and ethanol in a 1:1 ratio (500 mL each). The mixture was allowed to stand for 72 h with intermittent agitation to facilitate extraction of bioactive constituents.

Subsequently, the extract was refrigerated for five days with continuous stirring for approximately 2 h daily. The resulting mixture was filtered through sterile muslin cloth, and the filtrate was lyophilized to remove the solvent. The concentrated extract was further dried in a hot-air oven at 40 °C to obtain a stable residue. The dried extract was stored in airtight containers at −4 °C until required for experimental use.

Induction of Mammary Gland Toxicity

Mammary gland toxicity was induced using 7,12-dimethylbenz[a]anthracene (DMBA), a well-established chemical carcinogen widely employed in experimental mammary carcinogenesis studies. Animals in Groups II, III, and IV received a single oral dose of DMBA at 50 mg/kg body weight. Following administration, the animals were monitored daily for seven days to allow for the development of mammary gland toxicity before commencement of treatment interventions.

Administration of Treatments

After the induction period, animals in Group III received 500 mg/kg *Garcinia kola* seed hydroethanolic extract orally once daily for four weeks, while animals in Group IV received 500 mg/kg Vitamin C orally for the same duration. Group V received 500 mg/kg *Garcinia kola* extract only throughout the treatment period. The treatment regimen was designed to evaluate the potential protective

Following DMBA administration, animals were left untreated for seven days to permit the establishment of mammary gland toxicity. Thereafter, treatment with *Garcinia kola* extract and Vitamin C was administered orally once daily for four consecutive week

effects of the extract against DMBA-induced systemic toxicity.

Sample Collection

Twenty-four hours after the final treatment, the animals were fasted overnight and euthanized under appropriate experimental conditions. Blood samples were collected via cardiac puncture into EDTA-containing and plain sample bottles for haematological and biochemical analyses, respectively.

The mammary glands and kidneys were carefully excised, rinsed in ice-cold physiological saline to remove blood contaminants, blotted dry, and processed for histopathological examination.

Haematological Analysis

Haematological parameters were determined using an automated haematology analyzer according to the manufacturer's instructions.

Assessment of Renal Function Biomarkers

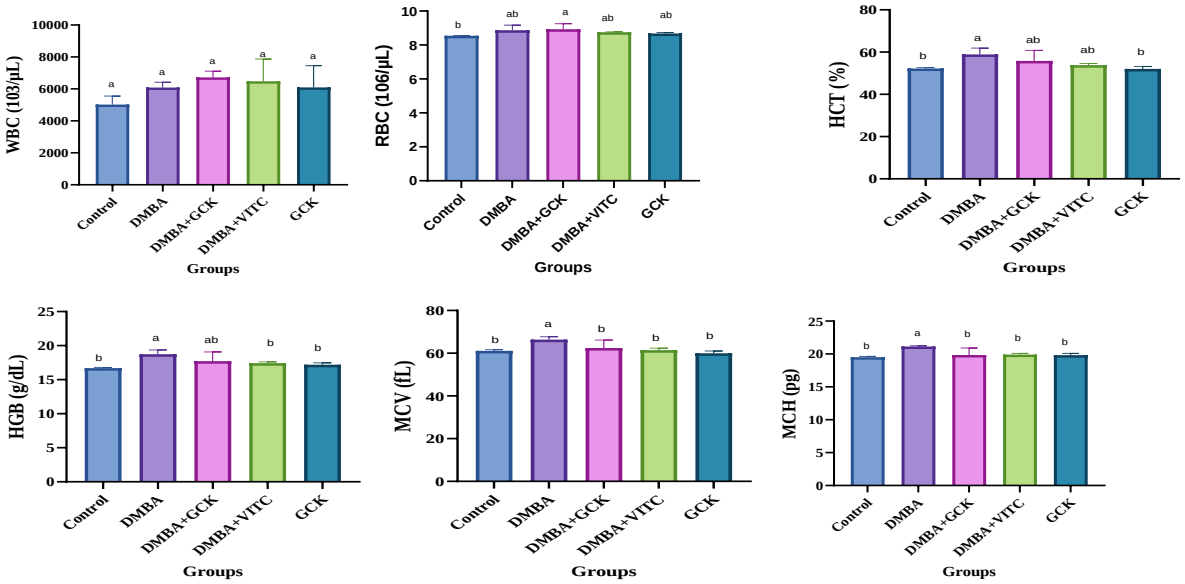
Serum obtained from centrifuged blood samples was used for the determination of renal function biomarkers. Parameters evaluated included serum urea, creatinine, sodium (Na^+), potassium (K^+), chloride (Cl^-), and bicarbonate (HCO_3^-) concentrations using standard diagnostic procedures and commercially available assay kits according to the manufacturers' protocols. These biomarkers were assessed to determine the extent of renal impairment and the renoprotective effects of *Garcinia kola* extract.

Histopathological Examination

Kidney and mammary gland tissues were fixed in 10% neutral-buffered formalin for 24–48 h, dehydrated through graded ethanol concentrations, cleared in xylene, and embedded in paraffin wax. Tissue sections of approximately 5 µm thickness were prepared using a rotary microtome and stained with haematoxylin and eosin (H&E). Histological changes were examined under a light microscope and photomicrographs were obtained where necessary.

Statistical Analysis

Data were expressed as mean ± standard error



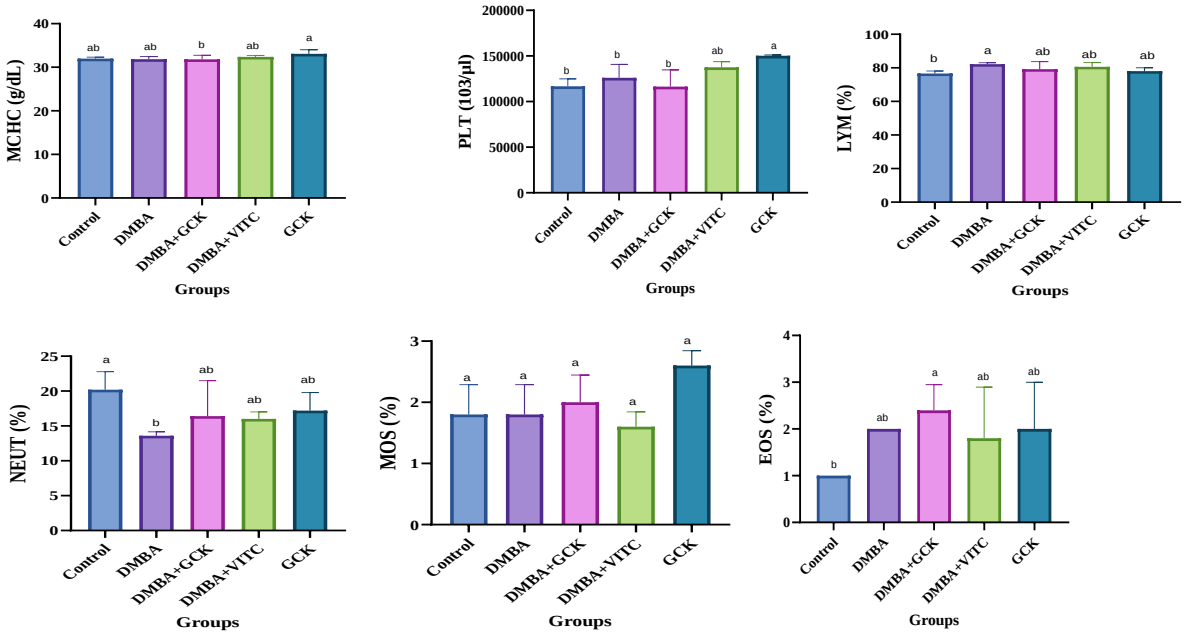


Figure 2. Effect of 10 ml/Kg distilled Water (Group I), 50 mg/kg DMBA only (Group II), 50 mg/kg DMBA + Garcinia kola (group III), 50 mg/kg DMBA + Vitamin C (Group IV) and *Garcinia kola* extract only (group V) on haematological parameters. Bars with the same superscript are not statistically significant at p<0.05. Key: WBC- White blood cell , RBC- Red blood cell count, HCT- Haematocrit value (Packed cell volume, HGB- Haemoglobin concentration, MCV- Mean corpuscular volume, MCH, Mean corpuscular haemoglobin, MCHC- Mean corpuscular haemoglobin concentration, PLT- platelets count, NEUT- Neutrophils count, MOS-Monocyte and EOS- Eosinophyll.

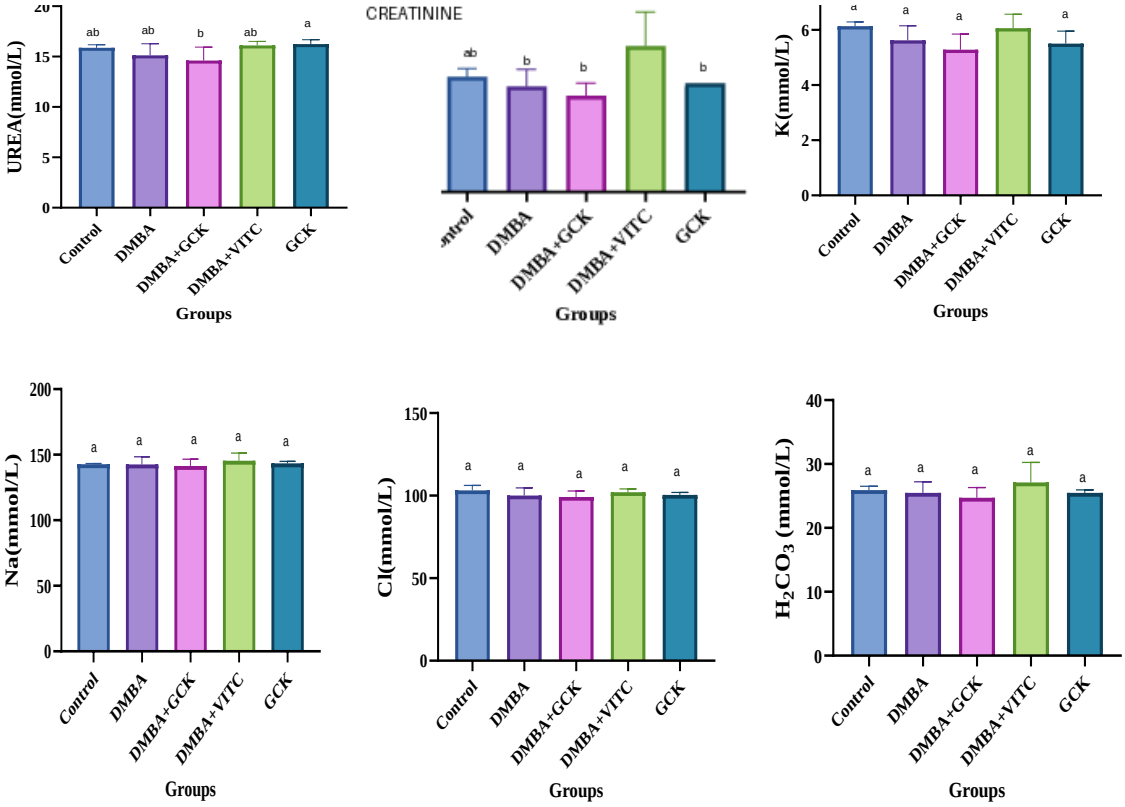


Figure 3. Effect of 10 ml/Kg distilled Water (Group I), 50 mg/kg DMBA only (Group 2), and 50 mg/kg DMBA + *Garcinia kola* (group III), and 50 mg/kg DMBA + Vitamin C (Group IV) and *Garcinia kola* extract only (group V) on kidney function parameters. Bars with the same superscript are not statistically significant at p<0.05

of the mean (SEM). Statistical analyses were performed using SPSS version 25.0 (IBM among groups were conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Effects of Garcinia kola Seed Hydroethanolic Extract on Haematological Indices in DMBA-Induced Mammary Gland Toxicity

DMBA administration induced marked alterations in haematological parameters, indicating systemic toxicity, oxidative stress, and inflammatory responses (Figure 1). The result showed an insignificant in the white blood count of the control ($P<0.05$) when compared with the DMBA induced group while a significant was noticed in the red blood count (8.54±0.33 to 8.87±0.14), haemoglobin concentration (16.20±0.21 to 19.91±0.16, haematocrit level (52.20±6.7 to 58.90±1.8 and neutrophil count (19.12±0.12 to 13.11±0.02. The insignificant elevated white blood cell (WBC) count, observed in the DMBA-treated group is consistent with inflammatory and immune activation commonly associated with toxicant-induced tissue injury (Al-Asady *et al.,* 2021). Treatment with *Garcinia kola* further improved WBC levels, suggesting enhanced immune responsiveness and immunomodulatory activity, in agreement with previous reports (Akinmoladun *et al.*, 2020).

The significant difference observed in red blood cell (RBC) count, haematocrit (HCT), and haemoglobin (Hb) concentration following DMBA exposure may be attributed to oxidative damage to erythrocytes and impaired erythropoiesis. Administration of *Garcinia kola* restored these parameters towards normal values, indicating preservation of erythrocyte integrity and haematopoietic function. These effects are likely mediated by the antioxidant activities of its flavonoids and biflavonoids, which protect erythrocyte membranes against oxidative haemolysis (Farombi *et al.*, 2019).

Similarly, the significant elevated mean corpuscular volume (MCV) (60.1±0.25 to66.11±1.22) and mean corpuscular haemoglobin (MCH) (18.11±0.11 to 23.15±0.01) observed in the DMBA group suggest disrupted erythrocyte maturation. Treatment with *Garcinia kola* normalized these indices, indicating improved red blood cell development and haemoglobin synthesis, consistent with the beneficial effects of plant-derived antioxidants on haematological function (Emmanuel *et al.,* 2022).

DMBA exposure also increased platelet count and altered differential leukocyte counts, characterized by lymphocytosis and reduced neutrophil levels, reflecting inflammatory stress and immune dysregulation. These abnormalities were attenuated by *Garcinia kola* treatment, suggesting restoration of haematopoietic balance and immune homeostasis. Such effects may be attributed to the antioxidant, anti-inflammatory, and immunoregulatory properties of its bioactive constituents (Assanti *et al.*, 2022; Adedara *et al.*, 2023).

Collectively, these findings demonstrate that *Garcinia kola* seed hydroethanolic extract effectively mitigates DMBA-induced haematological disturbances, supporting its potential as a chemoprotective agent against carcinogen-induced systemic toxicity.

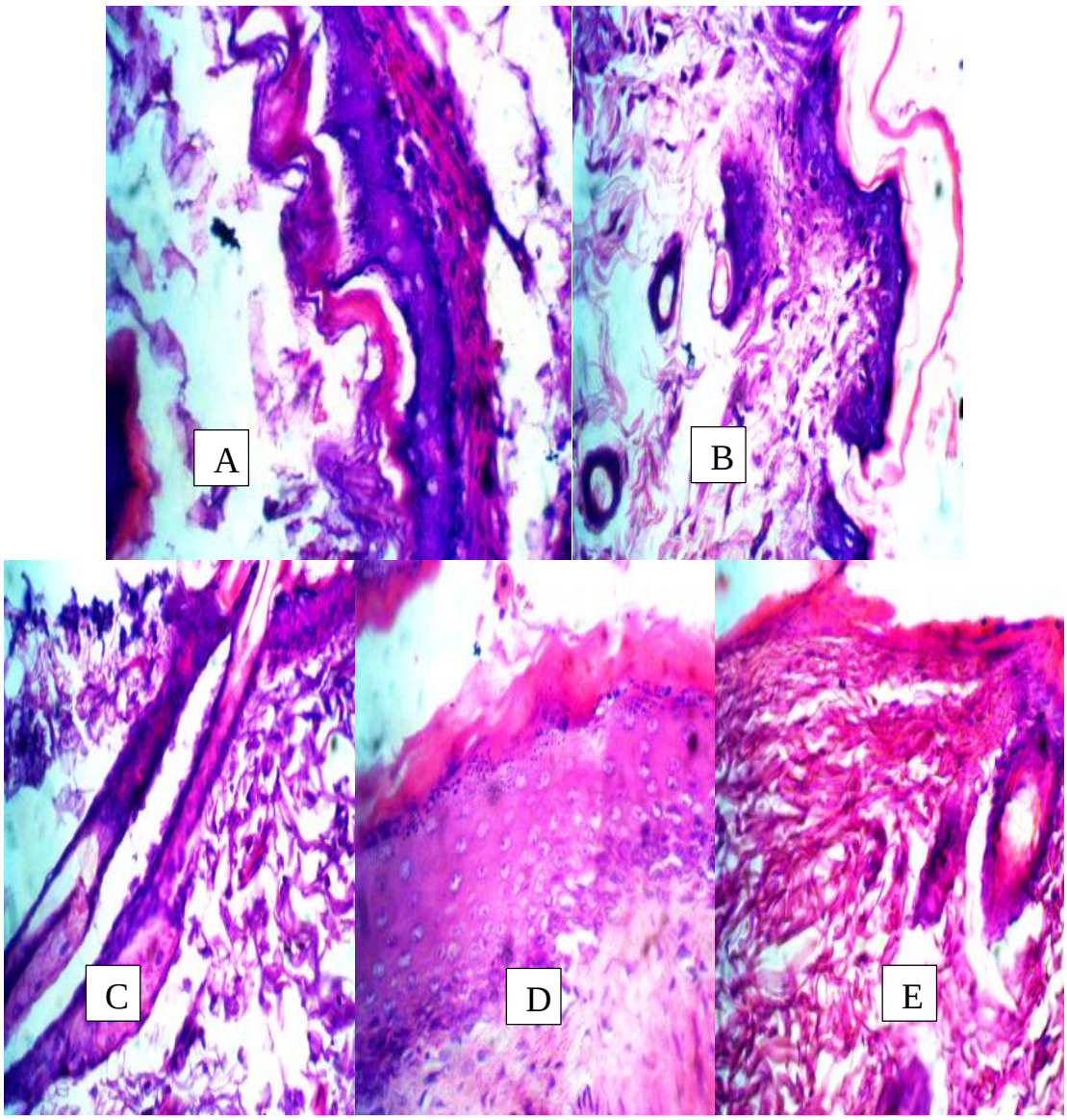


Figure 4. Plate 2: The photomicrograph of the mammary gland in administration with (A) distilled water. (B) DMBA only (C) DMBA + *Garcinia kola* (D) DMBA + Vitamin C (E) *Garcinia kola* only.

Effects of Garcinia kola Seed Hydroethanolic Extract on Renal Function Indices in DMBA-Induced Mammary Gland Toxicity

DMBA administration resulted in mild but significant alterations in potassium and chloride ion (6.14±0.06 to 5.62±0.23) and (103.2±1.32 to 100±2.7 respectively) renal function biomarkers and electrolyte balance, indicating inbalancing An insignificant relationship was observed in the urea, creatinine, Sodium ion and bicarbonate (Figure 2). Treatment with *Garcinia kola* significantly reduced these parameters, indicating attenuation of DMBA-induced nephrotoxicity and preservation of renal integrity. This protective effect may be attributed to the antioxidant properties of *Garcinia kola*, particularly its flavonoids and kolaviron constituents, which possess potent free radical scavenging and organ-protective activities (Tauchen *et al.*, 2023).

The significant alterations in serum potassium and chloride levels further indicate disruption of renal tubular function following DMBA exposure. Restoration of these electrolytes toward normal values by *Garcinia kola* treatment suggests improved tubular function and maintenance of electrolyte homeostasis, consistent with previous reports of its nephroprotective effects in experimental models (Dogara *et al.*, 2022). The relatively stable sodium and bicarbonate concentrations across the groups indicate that renal compensatory mechanisms remained largely intact, while the near-normal values observed in

the Vitamin C-treated group further support the role of antioxidant therapy in mitigating oxidative tissue damage.

The renoprotective effects of *Garcinia kola* may be linked to its bioactive phytochemicals, including kolaviron, biflavonoids, and phenolic compounds, which reduce lipid peroxidation, enhance endogenous antioxidant defenses, and protect renal tissues against toxic injury (Ojatula *et al.,.,* 2023). Overall, these findings demonstrate that *Garcinia kola* confers significant protection against DMBA-induced renal dysfunction through antioxidant-mediated mechanisms that preserve renal function and electrolyte balance.

Histological Findings

1. Kidney

The photomicrograph showed no observable lesion in the control (A). (B) showed enlargement of the renal glomeruli while (C) and (D) showed moderate tubular epithilia coagulation and E showed normal renal glomeruli and tubules (X 400). Plate1

(A) distilled water only. (B) DMBA induced only (C) DMBA induced treated with *Garcinia kola* (D) DMBA induced treated with Vitamin C (E) *Garcinia kola* only.

2. Mammary Gland

The photomicrograph showed no observable lesion in the control (A). B showed enlargement of the mammary gland while C and D showed a moderate recovery and E showed normal (X400). (A) distilled water only. (B) DMBA induced only (C) DMBA induced treated with *Garcinia kola* (D) DMBA induced treated with Vitamin C (E) *Garcinia kola* only.

CONCLUSION

DMBA exposure induced significant haematological alterations and mild renal dysfunction in female Wistar rats, reflecting systemic toxicity associated with oxidative stress and inflammation. Treatment with *Garcinia kola* seed hydroethanolic extract markedly ameliorated some of these changes, as evidenced by the restoration of haematological indices and electrolyte balance toward normal levels. The observed protective effects are likely attributable to the antioxidant and anti-inflammatory activities of its bioactive constituents, particularly flavonoids and biflavonoids such as kolaviron. Overall, the findings demonstrate that *Garcinia kola* possesses significant haematoprotective and nephroprotective properties and may serve as a promising natural agent for mitigating carcinogen-induced oxidative damage and its associated systemic complications.

RECOMMENDATIONS

Based on the findings of this study, *Garcinia kola* seed hydroethanolic extract demonstrates considerable potential as a natural protective agent against DMBA-induced haematological and renal toxicity. Further studies are recommended to investigate the molecular mechanisms underlying the protective effects of *Garcinia kola*, particularly its influence on oxidative stress, inflammatory pathways, and antioxidant enzyme activities. Its long-term safety, efficacy, and dose-response relationship of *Garcinia kola* extract in experimental models should also be looked into

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