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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

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EVALUATION OF THE TOXICOLOGICAL AND ANTIOXIDANT EFFICACY OF THE ETHANOLIC ROOTS EXTRACT OF *FUNTUMIA ELASTICA* ON LIVER AND KIDNEY OF WISTAR RATS.

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ABSTRACT

Background: Toxicological profiling of medicinal plants is becoming increasingly necessary because of the high dependence on these plants by low-income earners and the increased need for cheap and less toxic natural products.

Aim: This study evaluated the toxicological evaluation of the ethanolic extract of *Funtumia elastica* on the liver and kidney of Wistar rats.

Method: Twenty (20) adult Wistar rats randomly assigned into 4 groups; A to D (n = 5) and administered 200 mg/kg bw, 500 mg/kg bw and 1000 mg/kg bw of the ethanolic extracts of *F. elastica* orally and consecutively for 28 days. The wistar rats were sacrificed via cervical dislocation, organs of interest were then harvested and biochemical and histological analysis carried out.

Results: Our findings from this study in comparison with control, include a statistically significant increase ($p < 0.05$) in the catalase activity in the liver of Wistar rats administered 200 mg/kg bw of *F. elastic*, and decrease in malondialdehyde in the groups administered 500 mg/kg/bw and 1000 mg/kg bw. Gluthatione was reduced significantly in the liver across all the groups administered with the extract. The kidney didn't show any form of changes in the antioxidant status on administration of the extracts. We observed the presence of active interstitial infiltrates of lymphocytes and active interstitial congestion alongside normal glomeruli and tubules in the kidney of Wistar rats administered 1000 mg/kg bw of *F. elastica*.

Conclusion: *F. elastica* showed no obvious signs of toxicity on the liver and kidney morphology and could be said to be safe for therapeutic purposes.

Keywords: Antioxidant, *Funtumia elastica,* Histology, Kidney, Liver, Oxidative stress, Toxicity.

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

INTRODUCTION

Funtumia elastica, commonly known as the Lagos rubber tree, silk rubber (local Asante-Twi name is "Frumtum/Ofruntum"), rubber vine or rubber tree is a plant species belonging to the Apocynaceae family[1]. It is a large tree native to West and Central Africa found primarily in the tropical regions of West Africa, particularly in countries like Nigeria, Côte d'Ivoire, and Ghana[2]. *F. elastica* has been traditionally used for various medicinal purposes. *F. elastica* is traditionally used to treat whooping cough[1], inflammatory diseases such as asthma, blennorhea, and painful menstruation[3], cutaneous fungal infections, hemorrhoids, syphilis, gonorrhea[1,4] and wounds[5].

Preliminary studies have suggested that its extracts possess antioxidant properties owing to the presence of phenolic compounds, flavonoids, and other phytochemicals[6,7]. Some steroidal alkaloids (holarrhetine, conessine, holarrhesine and isoconessimine) have been isolated from the stem bark and conanine group, namely, irehdiamine A and D, irehamine, conkuchine and irehine from leaves of *F. elastica*[8].

Antioxidants (AOX) play a vital role in maintaining overall health, mitigating oxidative stress and preventing various diseases by neutralizing free radicals, which are highly reactive molecules, produced during normal metabolic processes or as a result of exposure to environmental factors such as pollution, radiation, and tobacco smoke; thus protecting body cells from oxidative stress[9,10]. The human body has in place an intricate antioxidant defense system, to maintain a healthy life; the task of the human antioxidant defense system is to eliminate excessive amounts of reactive species without hindering them from maintaining their beneficial role[11]. The cellular AOX system tightly controls the amount of reactive species, to maintain the natural balance that exists in the cells, known as 'redox homeostasis'[11]. The cellular antioxidant system consists of a series of components including enzymatic and non-enzymatic species. Enzymatic species are mainly superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) while glutathione, vitamins C and E, carotenoids and flavonoids are non-enzymatic antioxidants[12,13] that serve as natural antioxidant defense mechanisms that mitigate against oxidative damage. The function of SOD is catalyzing the dismutation reaction of $O_2^{\bullet-}$ having end-products of oxygen and hydrogen peroxide[14]. CAT and GPx decompose hydrogen peroxide into water and oxygen[11]. On the other hand, reduced glutathione (GSH) is an

Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

essential non-enzymatic antioxidant in mammalian cells[15]. GSH can act directly as an antioxidant to protect cells against free radicals and pro-oxidants, and as a cofactor for antioxidant and detoxification enzymes such as glutathione peroxidases, glutathione S-transferases, and glyoxalases[15].

Unfortunately, the body's natural antioxidant defense mechanisms can be overwhelmed particularly in pathological conditions by excessive free radical production leading to an imbalance and increased oxidative stress[16]. Oxidative stress is characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms [17,18,19] and is caused by free radicals, which can cause oxidative stress by damaging cellular components like proteins, lipids, and DNA, leading to cell dysfunction and damage as well as tissue damage[9,20]. Vital organs such as the liver and kidneys are particularly vulnerable and susceptible to oxidative damage due to their high metabolic activity and exposure to environmental toxins[18,19.21]. The liver is the primary organ responsible for detoxification and metabolic processes, making it susceptible to oxidative stress-induced damage[22]. Similarly, the kidneys are essential for filtering waste products and maintaining fluid balance[23], and oxidative stress can contribute to the progression of chronic kidney disease (CKD) and renal dysfunction[24,25]. Prolonged oxidative stress in these organs can lead to severe complications, such as non-alcoholic fatty liver disease (NAFLD), hepatotoxicity, chronic kidney disease (CKD), renal dysfunction, impaired fertility, and hormonal imbalances[19,22,24,26]. Products generated from oxidative damage of proteins, lipids and DNA are often used to quantify the extent of oxidative damage rather than direct measurement of reactive species. These oxidative damage products are usually known as biomarkers[11]. There are several biomarkers of oxidative stress that have been used as a biomarker to measure oxidative stress in various biological samples, these biomarkers of oxidative stress are terminal products of oxidation reaction and are relevant in the evaluation of the disease status and of the health-enhancing effects of antioxidants[11,27]. One of such biomarkers is malondialdehyde[11].

Oxidative stress is a significant contributing factor to various pathological conditions, playing a crucial role in the pathogenesis of various diseases and complications including liver diseases and kidney disorders[17-21]. Oxidative stress has been implicated in the pathogenesis of various diseases, including cardiovascular disorders, neurodegenerative diseases, cancer, and aging[12,28,29] and can have

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

detrimental effects on vital organs like the liver, kidneys, and testis[28,30]. This makes it essential to explore external sources of antioxidants to consolidate the natural endogenous antioxidants since maintaining organ health is crucial for overall well-being. While synthetic antioxidants are available, there is a growing interest in exploring exogenous natural sources of antioxidants, such as those derived from medicinal plants like *F. elastica*, due to their perceived safety and biocompatibility[31] thus necessitating the study of natural products such as plant extracts and discovering their potential antioxidant properties as a beam of light to pharmacology especially in light of the significant burden of oxidative stress-related diseases and the need for safe and effective antioxidant interventions.

However, medicinal plants may contain toxic constituents alongside their pharmacologically active constituents making them intrinsically toxic with the possibility of causing adverse effects if used inadequately and improperly[32]. Therefore, toxicological profiling of plant extracts is of utmost importance during the discovery of pharmacological properties and perspectives of any plant and the determination of their efficacy in order to safeguard the exposed population from the possible harms of the test compounds and determine appropriate dose for extract administration[33]. Animal models are recommended for executing toxicological evaluations. The use of animal models for such toxicological evaluation of plant extracts aid controlled exposure time, examination of different tissues for possible harms, and determining the effect on different biomarkers [32,34]. Histopathology is the microscopic examination of tissue in order to study the manifestations of disease. Histopathological evaluation, which basically compares experimentally altered tissues from sacrificed animals who were administered plant extracts with matching sample from healthy or control counterparts[35] is one of the many methods of toxicological profiling of plant extracts[36]. It has been observed from literature that the potential antioxidant capacity of *F. elastica* root extract on vital organs, such as the liver and kidneys, as well as its toxicological profile has not been extensively investigated. Therefore, this study aimed at evaluating the *in-vivo* antioxidant effects and toxicological profile of the ethanol extract of *F. elastica* using the liver and kidney of Wistar rats in view of providing insights into the antioxidant activity and toxicological profile of *F. elastica* thereby guiding its potential applications in promoting overall health and well-being. Investigating the antioxidant capacity of plant extracts like those derived from *F. elastica*, by researchers can

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

contribute to the development of novel and effective antioxidant therapies, ultimately promoting better organ health and overall well-being[37,38] while findings of its toxicological profile will help identify expected hazards resulting from usage and dosing to ensure the safety and suitability of the extract for human use[39].

This study assessed various parameters including, AOX enzyme activities such as Catalase, Superoxide dismutase and Glutathione peroxidase; oxidative stress markers such as Reduced glutathione and malondialdehyde; as well as histological changes associated with agent administration to determine the potential protective effects of the extract against oxidative damage and safety of its use, thus contributing to the development of preventive measures for oxidative stress-related diseases and complications as well as novel therapeutic approaches or nutraceutical products for promoting overall health and well-being.

MATERIALS AND METHOD

Research Design: This study adopted an experimental research design using Wistar rats. 20 adult Wistar rats of average weight of 150g upon purchase from Animal Holdings of the Department of Biochemistry, University of Benin, Benin City, Nigeria were randomly assigned into 4 groups; groups A to D making a total of five rats per group (n = 5). Group A served as control while groups B to D served as treatment groups. Animal acclimatization lasted a period of 2 weeks (14 days). Materials used in this study include Standard Animal feed, Plastic rat cages, Feed trays, Hand gloves, Gavage, Syringe and Needle, Mortar and Pestle and Sample collection tubes.

Plant material and chemicals: Roots of *F. elastica* were collected in April, 2024 from Ebhoran in Etsako west local government (LGA), Edo State, Nigeria. Unless stated otherwise, all the chemicals were purchased from Pyrex Lg Scientific Supply Company, Benin City, Edo State, Nigeria.

Plant root preparation and extraction: The plant materials were cleaned and air-dried at room temperature and then pulverized. 20 kg of the roots was dissolved in 40% ethanol in a 1:5 w/v. The mixture was kept in a shaker at room temperature for 72 hrs[41], this was followed by filtration. The filtrate was then kept in a rotary evaporator to allow for evaporation of the solvents in order to concentrate the extract followed by lyophilization using a freeze drier. The ethanol extracts then obtained was kept in a desiccator.[40]

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

Percentage yield was calculated as;

$$\frac{\text{Weight of dried extract obtained x 100}}{\text{Weight of plant root used}}$$

Agent Administration: The yielded root extracts were dissolved in distilled water before administration. Agent administration was done by direct feeding using a gavage for a period of 28 days as specified in Table 1.

Table 1: Dosage of Agent Administration

Groups	Dosage of *F. elastic*
A (Control)	Distilled water
B	200 mg/kg bw
C	500 mg/kg bw
D	1000 mg/kg bw

Animal Sacrifice: The Wistar rats were sacrificed via cervical dislocation. Organs of interest i.e. the liver and kidney were then harvested. A portion of these organs was cut and fixed in 10% formalin for further histological analysis.

Harvesting of Enzymes: Five gram (5g) of the liver and kidney each was homogenized in 10 volumes of 100mM Phosphate buffer containing 1mM EDTA (pH 7.4). The homogenate was centrifuged for 30minutes at 12000g at 4ºC. The supernatant was used for antioxidant assays[42].

Antioxidant Assays: The catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase and malondialdehyde were determined in the supernatant kidney and liver tissue samples. Catalase (CAT) activity was estimated by the method described by Cohen *et al.*[43], and the enzyme activity was expressed as µmoles of H_2O_2 decomposed/min/mg/protein. Superoxide Dismutase activity (SOD) was determined according to the methods of Misra and Fridorich[44]. Estimation of Gluthathione Peroxidase (GPx) and reduced Glutathione was determined using the method described by Ellman[45]. Malondialdehyde was determined using the thiobarbituric acid assay[46].

Histology: Hematoxylin and Eosin (H&E) staining technique[47] was used to examine histological alterations in liver and kidney tissues in this study.

Statistical Analysis: All measurements were done in pentaplicate (n = 5). The data obtained during laboratory analysis were analyzed using Statistical Product and Service Solutions (SPSS) version 21 one-way analysis of variance (ANOVA) to determine the difference between mean values between groups. Least Significant Difference (LSD) test was used to determine the statistical significance of observed differences at 0.05 level of significance. P

Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

values less than 0.05 (P<0.05) are regarded as statistically significant. The results are expressed as mean ± SEM,

Ethical Approval: Ethical approval for this study was obtained from Faculty of Life Sciences, University of Benin, Benin City, Research Ethics Committee (FLSREC).

RESULTS

Findings from this study on the antioxidant status of the liver and kidney of Wistar rats administered ethanol extract of *F. elastic* are presented below in Tables 2 and 3 respectively. Pictographs of the plates used for histological studies of the liver and the kidney of Wistar rats administered ethanol extract of *F. elastic* are presented in Figures 2 and 3 respectively.

In the liver, it was observed that there is a statistically significant increase ($p < 0.05$) in the catalase activity in the liver of Wistar rats administered 200mg of *F. elastic* ethanol extract daily (Group B) when compared with the control group while that of groups C and D remained unchanged. On the other hand, there is no statistically significant difference ($p > 0.05$) in the SOD activities in the liver of Wistar rats across all groups upon administration of all doses of *F. elastica*. For GPx activity, a decline was observed in all groups and this decline was highest in group D administered 1000mg of *F. elastic* ethanol extract daily. Notably, this decline was not statistically significant at $p > 0.05$. When compared to the control group, there is a statistically significant decrease ($p < 0.05$) in the levels of GSH across all experimental groups. In like vein, the MDA status of groups C and D also showed a statistically significant decrease ($p < 0.05$) when compared to that of the control group, the decrease in group D was highest. However, an increase in MDA concentration was observed in group B, although this increase was not statistically significant. These findings are presented in Table 2.

Table 2: Effect of ethanol extract of *F. elastica* on the antioxidant capacity levels of the liver of wistar rats

GROUPS	CAT(unit/g tissue)	SOD(unit/g tissue)	GPx(mg/g tissue)	GSH(mg/g tissue)	MDA(mg/g tissue)
A	0.27±0.02	0.27±0.04	1.64±0.08	0.57±0.15	0.27±0.12
B	0.47±0.02[a]	0.27±0.03	1.65±0.13	0.22±0.16[a]	0.37±0.15
C	0.25±0.01	0.20±0.03	1.58±0.21	0.21±0.09[a]	0.11±0.08[a]

Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

D	0.27±0.04	0.23±0.02	1.24±0.16	0.24±0.10[a]	0.05±0.00[a]

Data reported as mean ± standard error of mean (SEM), n=3. Values with superscript [a] are significantly different from the control group at $p \leq 0.05$.

From the results shown in table 3, it is evident that upon administration of *F. elastica* extracts at different doses stated earlier, there was an increase in the activity of CAT in group administered 200 mg/kg bw and decrease in MDA in the groups administered 500 mg/kg bw and 1000 mg/kg bw. Gluthatione was reduced significantly in all the groups to which the extract was administered when compared with control.

Table 3: Effect of ethanol extract of *F. elastica* on the antioxidant capacity levels of kidney of Wistar rats

GROUPS	CAT(unit/g tissue)	SOD(unit/g tissue)	GPx(mg/g tissue)	GSH(mg/g tissue)	MDA(mg/g tissue)
A	0.35±0.13	0.15±0.02	1.68±0.01	0.04±0.00	0.12±0.03
B	0.13±0.05	0.14±0.01	1.62±0.00	0.05±0.01	0.08±0.00
C	0.14±0.03	0.14±0.02	1.62±0.02	0.05±0.01	0.14±0.02
D	0.18±0.02	0.13±0.01	1.21±0.02	0.04±0.01	0.10±0.03

Data reported as mean ± standard error of mean (SEM), n=3. Values with superscript [a] are significantly different from the control group at $p \leq 0.05$.

Across all levels of concentration of the extracts administered, there was no statistical difference in all the parameters assayed for in the kidney.

Archives of Pharmaceutical Sciences and Biotechnology Journal

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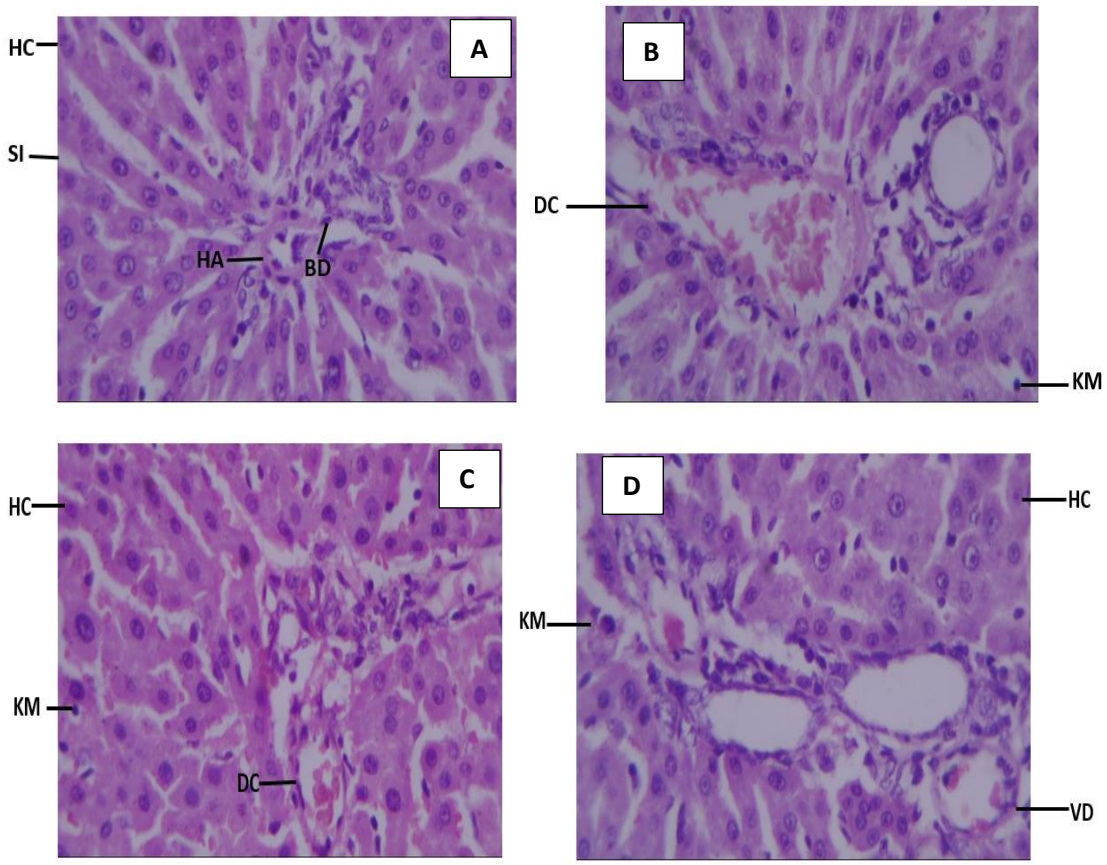
APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025



KEY: HC = Hepatocyte, SI = Sinusoids, HA = Hepatic artery, BD = Bile ducts, KM = Sinusoids kupffer cell mobilization, DC = Vasodilatation and active congestion, VD = Vasodilatation

Plate 1: Pictographs showing liver of Wistar rats in Group A (Control) showing normal architecture with hepatocyte, sinusoids, hepatic artery and bile ducts; liver of Wistar rats in group B showing sinusoidal Kupffer cell mobilization, vasodilatation and active congestion as well as normal hepatocytes; liver of Wistar rats in group C showing normal hepatocytes, sinusoidal Kupffer cell mobilization, active vascular congestion and dilatation and liver of Wistar rats in group D showing normal hepatocytes, vasodilatation and sinusoidal Kupffer cell activation **(H&E x 400)**.

Archives of Pharmaceutical Sciences and Biotechnology Journal

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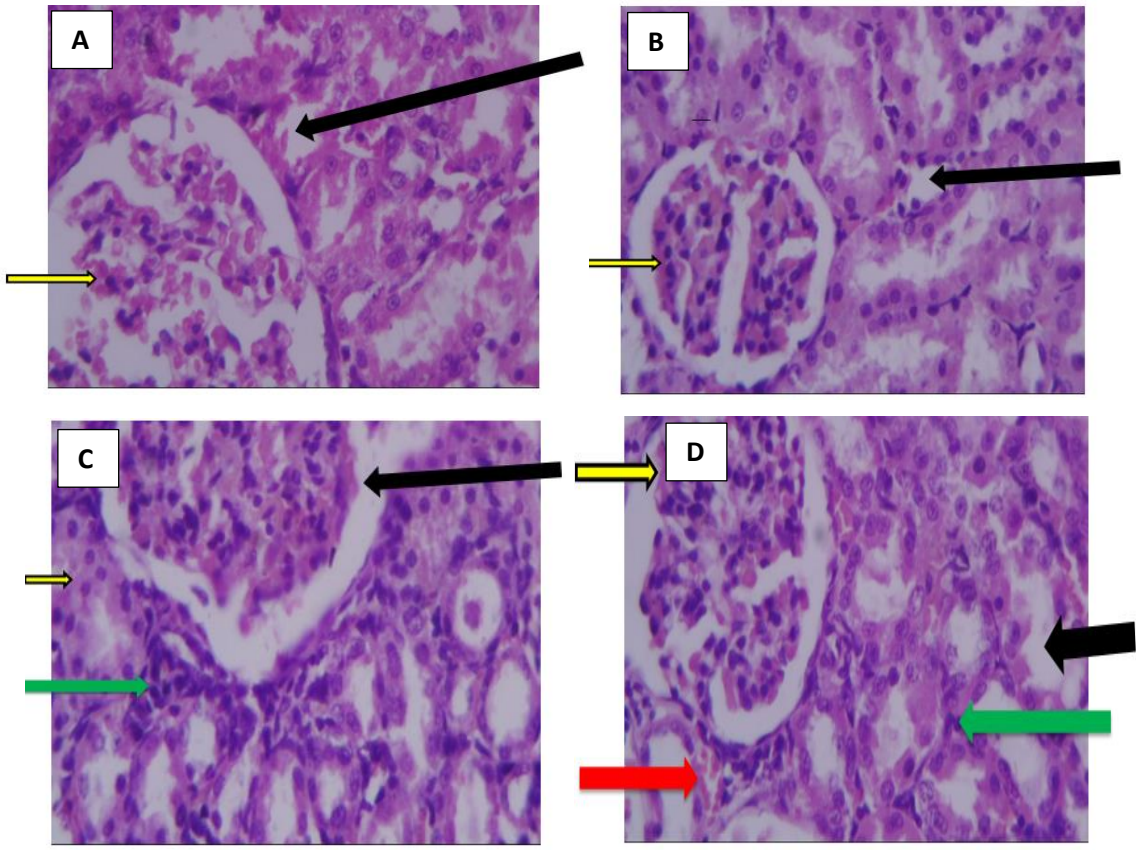
APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025



KEY: =Normal architecture of the glomeruli (GL)

= Normal architecture tubules (TU)

= Active interstitial infiltrates of lymphocytes (LY)

= Active interstitial congestion (AC)

Plate 2: Pictographs showing kidney of Wistar rats in Group A (Control) showing normal architecture of the glomeruli and normal architecture tubules with overall normal kidney features; kidney of Wistar rats in group B showing normal architecture of the glomeruli, and normal architecture tubules both showing normal kidney features; kidney of Wistar rats in group C showing normal feature of glomeruli, normal feature of tubules and active interstitial infiltrates of lymphocytes and kidney of Wistar rats in group D showing normal glomeruli, normal tubules, active interstitial infiltrates of lymphocytes and active interstitial congestion. (H&E x 400).

DISCUSSION

Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

From the results of the antioxidant status of the liver and kidney of Wistar rats administered with ethanol extracts of *F. elastica* roots, it was evident that administration of the extracts significantly increased CAT activity in the liver of the Wistar rat only at a dose of 200mg/kg body weight possibly due to its antioxidant properties as the plant has been reported to contain compounds such as flavonoids and tannins, which are known to enhance the body's antioxidant defense mechanisms thereby stimulating the biosynthesis of catalase and increasing cells protection from oxidative damage[48,49].

Catalase deficiency or malfunctioning is associated with many diseases such as diabetes mellitus, vitiligo, cardiovascular diseases, Wilson disease, hypertension, anemia, some dermatological disorders, Alzheimer's disease, bipolar disorder, schizophrenia[50-52], Takahara disease[53], schizophrenia and atherosclerosis[54]. In mammals, catalase is found predominantly in the liver. Studies have shown that catalase deficiency or dysfunction in the liver can lead to metabolic dysregulation, including impaired glucose metabolism and lipid accumulation, highlighting its broader involvement in cellular homeostasis[55-57]. Thus, the increase of catalase holds promise as a therapeutic avenue and preservation of overall metabolic health as CAT mitigates ROS-mediated tissue damage and inflammation as well as diabetic complications[58,59]. Importantly, catalase, has also been implicated in both tumor suppressions where it exerts context-dependent effects on cancer initiation and progression. Similarly, in the early stages of carcinogenesis, catalase's antioxidant properties thwart ROS-induced DNA damage and mutagenesis, thereby suppressing tumor initiation[57,60,61]. Although not statistically significant, a slight decline was observed in the activity of GPx in the liver and kidney. Simiarly, a decline in the concentration of reduced glutathione in the liver of Wistar rats was observed in this study. The decline in glutathione (GSH) levels in Wistar rats upon administration of *F. elastica* could be as a result of metabolic changes caused by alteration of metabolic pathways induced by the administration of *F. elastica* thus affecting the synthesis and recycling of GSH[62] or as a result of the influence of the plant on the activity of enzymes involved in GSH metabolism, such as glutathione peroxidase (GPx) and glutathione reductase (GR), leading to reduced GSH levels[63], such alteration in GPx enzyme activity was observed in this study. Glutathione, an essential antioxidant, plays a vital role in the liver by neutralizing free radicals and reactive oxygen species (ROS). When the levels of GSH are low, oxidative stress increases as there is not

Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

enough antioxidant capacity to counteract the accumulation of ROS[15]. Additionally, GSH is crucial in the liver's detoxification process as it combines with toxins and aids in their neutralization and elimination from the body, which is crucial for maintaining liver health[64]. If GSH levels are reduced, this detoxification capacity of the liver is impaired, resulting in the buildup of harmful substances in the liver[65]. Consequently, a decrease in GSH levels can make liver cells more vulnerable to damage caused by oxidative stress, environmental toxins, and medications. This heightened susceptibility may elevate the risk of liver diseases such as hepatitis, fatty liver disease, and liver fibrosis.

The low levels of MDA in this study are indicative of decreased oxidative stress within the body, resulting in less harm to lipids and cellular structures caused by free radicals and reactive oxygen species. This implies a lower degree of damage occurring to cell membranes due to lipid peroxidation, ultimately preserving their integrity and functionality[66]. Additionally, reduced MDA levels may help in minimizing inflammation by preventing damage to cells and tissues that could trigger immune responses. Conversely, elevated MDA levels have been linked to various chronic illnesses such as cardiovascular diseases, neurodegenerative disorders, and certain cancers. Therefore, lower MDA levels may suggest a lower risk or severity of these[67].

Furthermore, histopathological examination of liver and kidney tissues which provided valuable insights into the structural changes induced by the extract at both low and high concentration revealed slight differences in the microscopic view of the liver from different groups, but none indicated a dysfunction in the liver. Vasodilatation observed indicates that lower dosage of the extract helps in increasing blood flow as blood vessels expand optimally to ensure maximum blood flow. Mild activation of Sinusoidal Kupffer cells is indicative of a mild activated immune system while the hepatocytes remained normal. The findings showed that at higher doses there is incidence of vasoconstriction in the liver. High doses of certain drugs can indeed cause vasoconstriction, but this effect is more commonly associated with blood vessels in general rather than specifically in the liver[68,69]. Some drugs, particularly those that stimulate alpha-adrenergic receptors, can cause vasoconstriction at high doses[69]. However, the liver is more commonly affected by drug-induced liver injury (DILI) due to the liver's role in metabolizing drugs.

From the histopathological analysis of the kidney shown in plates A to D in Figure 2 with Plate A as the control, slight differences were

Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

noticed from the microscopic view of the kidney from different groups. Active interstitial infiltrates of lymphocytes, which refers to the presence of lymphocytes within the interstitial spaces of tissues often associated with inflammatory or immune responses[70] while active renal interstitial congestion refers to the accumulation of fluid in the interstitial spaces of the kidneys[71] were observed in this study. These conditions as observed in this study can be caused by various factors but high administration of the extract doses seems to be the major cause. Studies have shown that high doses of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), certain antibiotics, and proton pump inhibitors are frequently implicated as a cause of renal interstitial congestion and active interstitial infiltrates[72]. From the above findings, it is safe to say that toxicological profiling of the plant extract via histopathology has shown that the plant extract is safe and has great antioxidant capacity especially at lower doses.

CONCLUSION

In conclusion, the ethanol extract of *F. elastica* appears to modulate antioxidant parameters in the liver and kidney of Wistar rats, with varying degrees of impact on different parameters. The observed effects could have implications for the potential use of this extract as an antioxidant intervention or in the management of oxidative stress-related conditions. In addition, it did not compromise liver or kidney integrity or inflict damage on the organs. However, further research is required to fully understand the mechanisms of action and to evaluate the safety and efficacy of this extract in clinical settings.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Archives of Pharmaceutical Sciences and Biotechnology Journal

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

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Volume 5 Issue 1 June, 2025 ISSN: 2971_611X

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

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Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

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APSB Journal

Page 103 - 122 Submitted 11/11/2024 Accepted 13/1/2025

-manifestations-and-diagnosis-of-acute-interstitial-nephritis