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Luteolin Mitigates Oxidative and Inflammatory Processes in Hepato-Renal Tissues of Rats Treated with Diethylnitrosamine and Carbon Tetrachloride

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Abstract

Luteolin (LT), a flavonoid known for its health benefits was investigated for possible ameliorative effects against hepato-renal toxicity induced by diethylnitrosamine and carbon tetrachloride in rats. Thirty-six male Wistar rats were assigned into six groups; One and two served as control and intoxicated groups, groups three-five were intoxicated and treated with LT at 10, 20 and 40mg/kg, respectively and group six received LT only (20mg/kg). The LT was given orally three times a week while Diethylnitrosamine (DEN) (50mg/kg) and CCl_4 (0.5mL/kg) were administered intraperitoneally once a week for four consecutive weeks. Toxicants exposure significantly increased the activities of serum aminotransferases (ALT and AST) by 28% and 30%, and levels of serum urea and creatinine by 15% and 28%, respectively. The intoxication increased lipid peroxidation by 81% and 25%, and also decreased superoxide dismutase by 16% and 17%, and reduced glutathione by 31% and 25% in the liver and kidney of rats, respectively. In addition, inflammatory markers, myeloperoxidase and nitric oxide increased in the liver by 650% and 49%, and in the kidney by 367% and 11%, respectively in the intoxicated rats. Histology of liver revealed necrosis and multifocal hepatocellular coagulation while glomerular atrophy and tubular epithelial necrosis were seen in kidneys of intoxicated rats. Interestingly, LT pretreatment significantly attenuated markers of oxidative stress and inflammation in the liver and kidney of intoxicated rats. In conclusion, luteolin may serve as chemotherapeutic agent to mitigate the adverse effects of chemicals on the hepato-renal tissues of animals.

Keywords: Hepato-renal, Oxidative stress, Inflammation, Luteolin, Toxicants.

INTRODUCTION

Luteolin (3',4',5,7-tetrahydroxyflavone), LT is a naturally occurring flavonoid widely found in various fruits, vegetables, and medicinal herbs. It is recognized for its potent antioxidant, anti-inflammatory, and anti-carcinogenic properties, making it a subject of significant interest in the field of biomedical research. The therapeutic potential of luteolin is largely attributed to its ability to modulate key signaling pathways and molecular mechanisms involved in oxidative stress and inflammation (Zhang *et al.,* 2021). Recent studies have highlighted the efficacy of luteolin in mitigating oxidative damage and inflammatory responses in various disease models. For instance, luteolin has been shown to protect against neurodegenerative diseases by inhibiting microglial activation and reducing the production of pro-inflammatory cytokines. (Xu *et al.,* 2022). Additionally, its hepatoprotective effects have been demonstrated in models of liver injury induced by toxins and high-fat diets, where luteolin alleviated liver damage by modulating oxidative stress markers and inflammatory mediators (Zhang *et al.,* 2021). Diethylnitrosamine (DEN) and carbon tetrachloride (CCl_4) are well-established chemical agents used to induce hepatic and renal toxicity in experimental models. DEN is a potent hepatocarcinogen, while CCl_4 is commonly used to induce acute and chronic liver injury due to its ability to generate reactive oxygen species (ROS) and subsequent lipid peroxidation. Combined exposure to DEN and CCl_4

results in severe oxidative stress, inflammation, and tissue damage, mimicking the pathological conditions observed in various human liver and kidney diseases (Wang *et al.,* 2022). In the context of hepato-renal toxicity, the role of luteolin as a protective agent is particularly relevant. Studies have suggested that luteolin can counteract the harmful effects of DEN and CCl_4 by enhancing the antioxidant defense system and inhibiting inflammatory pathways. For example, luteolin has been reported to reduce lipid peroxidation, increase the activity of antioxidant enzymes, and suppress the expression of pro-inflammatory cytokines in liver tissues exposed to these toxicants (Zhao *et al.,* 2021). The current study aims to further elucidate the protective mechanisms of luteolin against DEN and CCl_4 induced oxidative and inflammatory damage in hepato-renal tissues. By investigating the biochemical and histopathological changes in rats treated with different dosages of Luteolin, DEN, and CCl_4, this study was designed to provide a comprehensive understanding of luteolin's therapeutic potential in mitigating hepato-renal toxicity.

MATERIALS AND METHODS

Chemicals

Luteolin, DEN, CCL_4, Thiobarbituric acid, ethylenediaminetetraacetic acid, trichloroacetic acid, 50, 50-dithiobis-2-nitrobenzoicacid, sodium azide, phosphoric acid, sodium hydroxide, copper sulfate, sodium chloride, reduced glutathione and epinephrine (adrenaline) were bought from Sigma Aldrich Chemical, USA. Kits for Urea, Creatinine, Alanine and Aspartate aminotransferases were purchased from Randox TM Laboratories Limited, United Kingdom. Other chemicals used were of diagnostic grade.

Animals

Thirty-six (36) male *Wistar* rats, weighing between 150g-200g were procured from the Central Animal House, College of Medicine, University of Ibadan, Nigeria. They were kept in well-aired cages at 25ºC and maintained on standard rodent feed and water. The study was permitted by the Faculty of Basic Medical Sciences, University of Ibadan Animal Ethics Committee.

Study Design

Based on their weight distribution, 36 male rats were sorted into six groups of six each. Group 1 which is the control received corn oil while group 2 received DEN (50mg/kg) + CCl_4 (0.5ml/kg). Group 3 received DEN + CCl_4 +LT1 (10mg/kg). Group 4 received DEN + CCl_4 + LT2 (20mg/kg). Group 5 received DEN + CCl_4 + LT3 (40mg/kg). Group 6 received LT2 (20mg/kg) LT was given via oral gavage three times per week and DEN+CCl_4 was given once a week via the intraperitoneal route for a consecutive period of four weeks.

Animal Sacrifice and Sample Collection

After the completion of the treatment, foods were withdrawn from the rats overnight and they were sacrificed humanely the following day. Before the animals were sacrificed, blood samples were obtained from each rat's ocular vein via ocular puncture and placed into plain bottles for serum collection and to check for hepatorenal biomarkers. The livers and kidneys was carefully excised, rinsed in ice cold 1.15% KCl and blotted on a filter paper. The tissues were homogenized in 6 volumes of phosphate buffer (0.1 mM, pH 7.4) using a Teflon homogenizer. The resulting homogenates were centrifuged at 10,000g for 15 minutes at figure 4ºC to obtain the post mitochondrial fraction.

Biochemical Assays

The concentration of protein in the sample was assessed by the technique of Gornal and David (1949) using Biuret reagent. Creatinine levels were evaluated by the methods of Doumas and Biggs (1971) and Bartels *et al.* (1972), respectively. Serum urea and bilirubin levels were assessed by the process of Fawcett and Scott (1960) and Jendrassik (1938), respectively. The activities of alanine and aspartate aminotransferases were assessed by the methods of Mohun and Cook (1957) and Reitman and Frankel (1957). The activities of superoxide dismutase were evaluated by the techniques of Misra and Fridovich (1972). The level of reduced glutathione was assessed as described by Beutler *et al.,* (1963). In contrast, the level of lipid peroxidation in the tissues was assessed by the method of Buege and Aust (1978).

Histopathology of Tissues

The tissues were fixed in ethanol (95% v/v) to dehydrate the sample. Dehydrated samples were then cleared in xylene before paraffin treatment. Nearly 4 mm sections were made from the tissues, stained with hematoxylin and eosin (H&E) dye, and assessed using a microscope by histopathologist without prior knowledge of the treatment groups.

Statistical Analysis

The results were presented as mean ± S.D. of 6 animals in a group. Data were analyzed using one-way analysis of variance and, $p<0.05$ taken as the level of significance.

RESULTS

Dose-dependent effects of Luteolin on the body weights, organo-somatic weight and biochemical indices of hepatic and renal toxicities in DEN+CCL_4 treated rats.

The results revealed a decrease ($p<0.05$) in the body weight of DEN+CCl_4 intoxicated rats and others during this study (Table 1). However, there were no differences ($p<0.05$) in the organo-somatic weight of the liver and kidney of intoxicated rats relative to others. Administration of DEN+CCl_4 significantly increased ($p>0.05$) levels of cholesterol by 79.2% while also slightly increasing the levels of total and direct bilirubin

by 4.29% and 8.11% respectively (Table 2). Importantly, pretreatment with LT at varying doses (10mg/kg, 20mg/kg, 40mg/kg) brought about significant reductions (p>0.05) in the levels of cholesterol, total and direct bilirubin respectively. Furthermore, DEN+CCl_4 administration increased the activities of serum AST and ALT levels by 42% and 34% (figure 1) respectively when compared to the control (p>0.05) which similarly occurred in the levels of serum urea and creatinine levels that were by increased 33% and 28% respectively. (figure 2).

Table 1: Dose-dependent effects of Luteolin on the body weights and organo-somatic weights in rats treated with Diethylnitrosamine and carbon tetrachloride

	Body Weight		Weight Diff.(g)	Weight of Liver(g)	Weight of Kidney(g)	Organo-somatic Weight (% B.W wt.) Liver	Kidney
	Initial	Final					
CONTROL	(g) 159.2±2.95	(g) 191.4±18.86	(g) 32.2±19.29	(g) 4.68±0.65	(g) 1.01±0.16	(g) 2.45±0.28	(g) 0.53±0.06
DEN+CCl_4	156.57±7.48	176.28±11.84	19.71±14.63*	4.17±0.89	0.97±0.12	2.36±0.64	0.55±0.64
DEN+CCl_4+L1(10mg/kg)	169.14±6.47	181.5±9.75	12.17±7.93**	4.64±0.69	4.64±0.69	2.56±0.43	0.56±0.09
DEN+CCl_4+L2(20mg/kg)	142.14±7.56	150±19.58	8.33±12.42**	4.72±0.49	0.84±0.14	3.15±0.39	0.56±0.09
DEN+CCl_4+L3(40mg/kg)	185.86±5.15	190.00±18.03	4.14±15.49**	4.77±0.72	1.00±0.10	2.52±0.81	0.53±0.03
LT2(20mg/kg)	158.8±9.52	191.6±17.85	32.8±12.56	5.21±0.63	1.00±0.03	2.72±0.18	0.50±0.01

Values are represented as Mean ± SD; n= 6. * = P <0.05 statistically significant when compared to control. ** = P <0.05 statistically significant when compared to DEN+CCl_4. DEN = Diethylnitrosamine; CCl_4 = Carbon tetrachloride; LT = Luteolin

Table 2: Dose-dependent effects of Luteolin on the levels of serum cholesterol and bilirubin in rats treated with Diethylnitrosamine and carbon tetrachloride

Treatment	Total Bilirubin	Direct Bilirubin
CONTROL	3.50±0.43	0.19±0.05
DEN+CCL_4	3.65±0.57	0.20±0.12
DEN+CCl_4+L1(10mg/kg)	3.04±1.06	0.33±0.02**
DEN+CCl_4+L2(20mg/kg)	3.38±0.68	0.27±0.05
DEN+CCl_4+L3(40mg/kg)	4.73±0.10**	0.30±0.06
LT2(20mg/kg)	2.83±0.68**	0.39±0.04**

Values are represented as Mean ± SD; n= 6. * = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCl_4. DEN = Diethylnitrosamine; CCl_4 = Carbon tetrachloride; LT = Luteolin

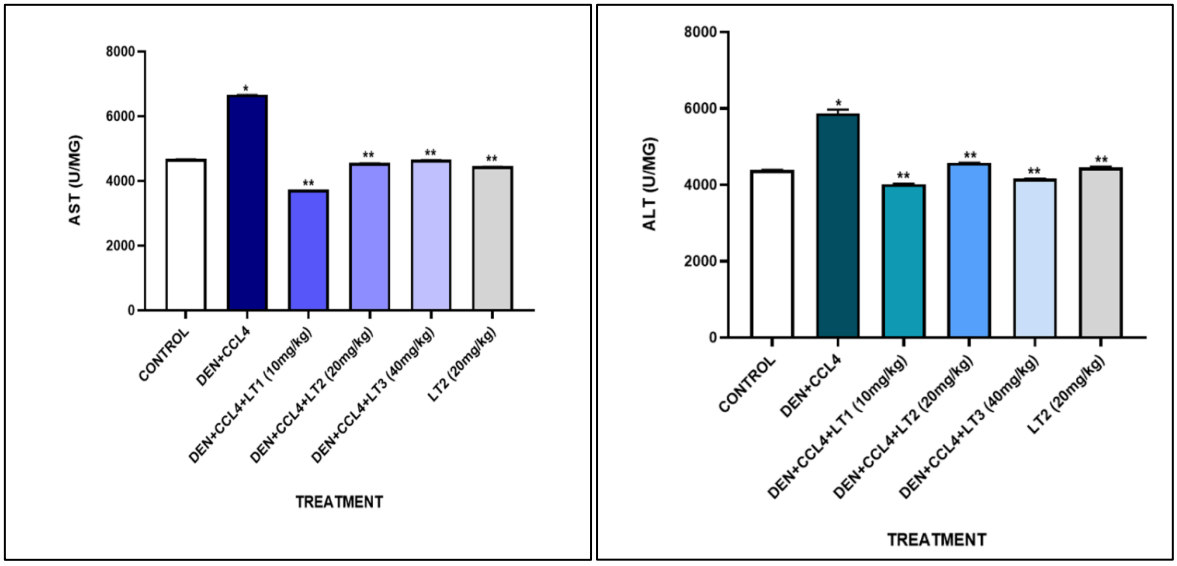


Figure 1: Dose-Dependent effects of Luteolin on the activities of serum aspartate and alanine aminotransferase (AST&ALT) in rats treated with Diethylnitrosamine and carbon tetrachloride

* = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCl_4. DEN = Diethylnitrosamine; CCl_4 = Carbon tetrachloride; LT = Luteolin

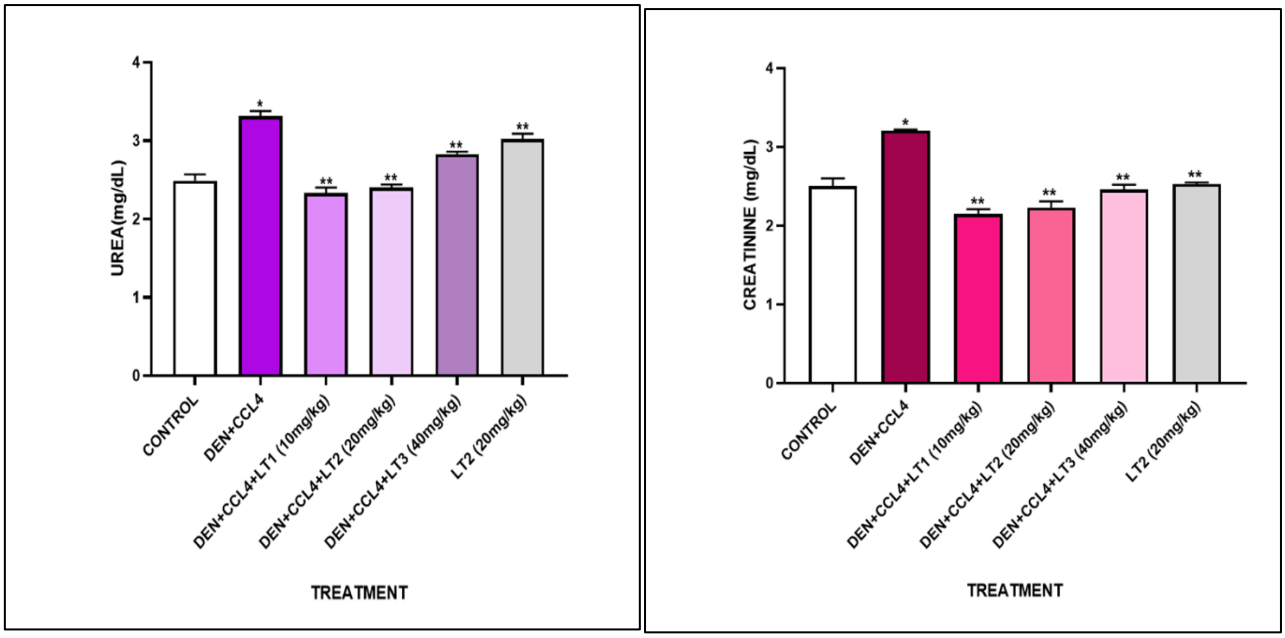
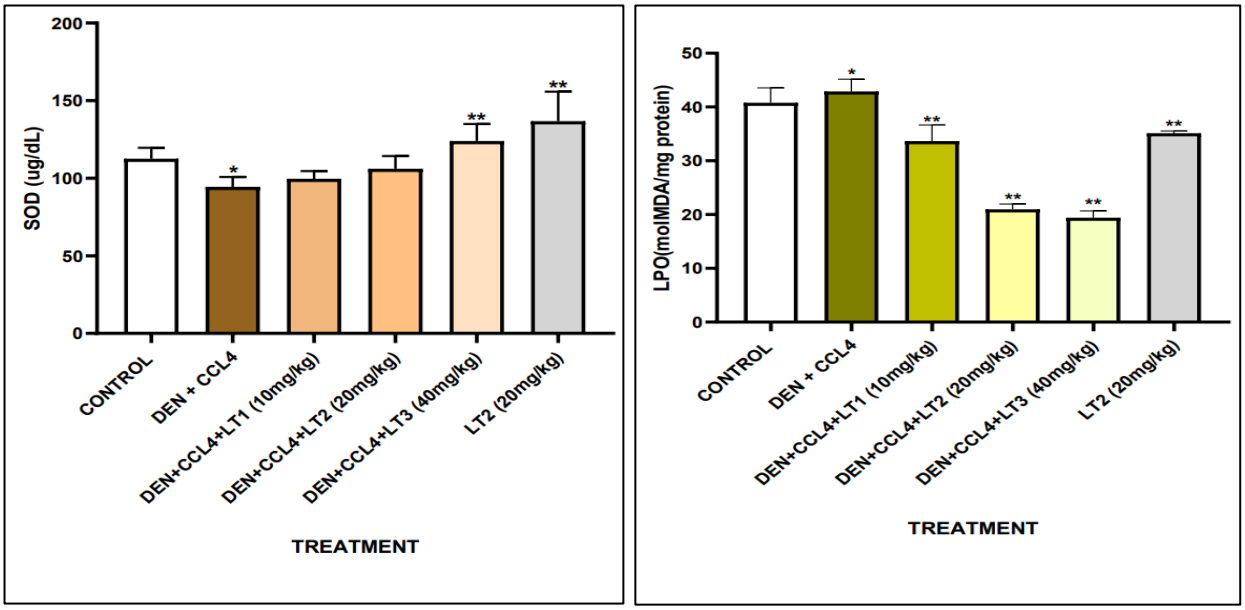


Figure 2: Dose-Dependent effects of Luteolin on the levels of serum urea and serum creatinine in rats treated with Diethylnitrosamine and carbon tetrachloride

* = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCl_4. DEN = Diethylnitrosamine; CCl_4 = Carbon tetrachloride; LT = Luteolin

Dose-dependent effects of Luteolin on enzymic and non-enzymic antioxidant markers in the livers and kidneys of rats treated with Diethylnitrosamine and carbon tetrachloride.

Administration of DEN+CCL_4 increased the levels of lipid peroxidation (LPO) in the liver and kidney by 79% and 30%, respectively (Figure 3&4). Pretreatment with LT (10mg/kg, 20 mg/kg and 40 mg/kg) reduced the level of hepatic LPO by 25%, 33%and 40%, and renal LPO by 36%, 60%, and 63% respectively. DEN+CCl_4 administration decreased the liver and kidney GSH levels by 31% and 25%, respectively. In comparison, pretreatment with LT (100 mg/kg and 200 mg/kg) increased the hepatic GSH by 34%, 13%, 144% and renal GSH by 4%, 9%, 152% respectively (Figure 3&4). In the same figures, there was a significant reduction ($p<0.05$) in the activities of liver and kidney SOD in all the DEN+CCl_4 treated groups by 16% and 17% relative to control. However, pretreatment with LT (10mg/kg, 20mg/kg and 40mg/kg) significantly increased the hepatic and renal SOD activities by 25%, 46% and 113%, 23%, 37% and 51% respectively relative to the DEN+CCl_4 groups.



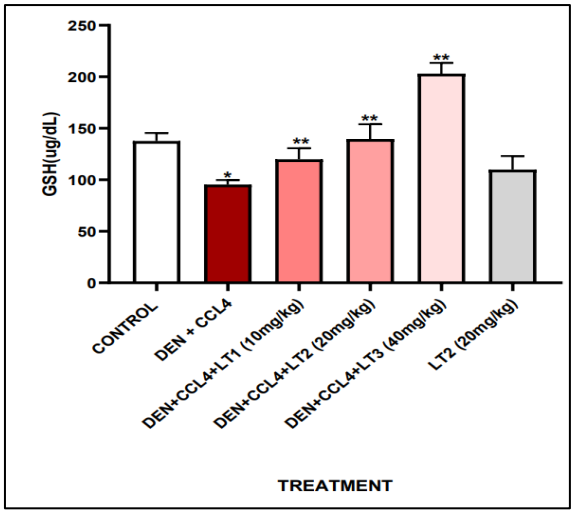


Figure 3: Dose-dependent effects of Luteolin on enzymic and non-enzymic antioxidant markers in the livers of rats treated with Diethylnitrosamine and carbon tetrachloride

* = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCl_4. DEN = Diethylnitrosamine; CCl_4 = Carbon tetrachloride; LT = Luteolin

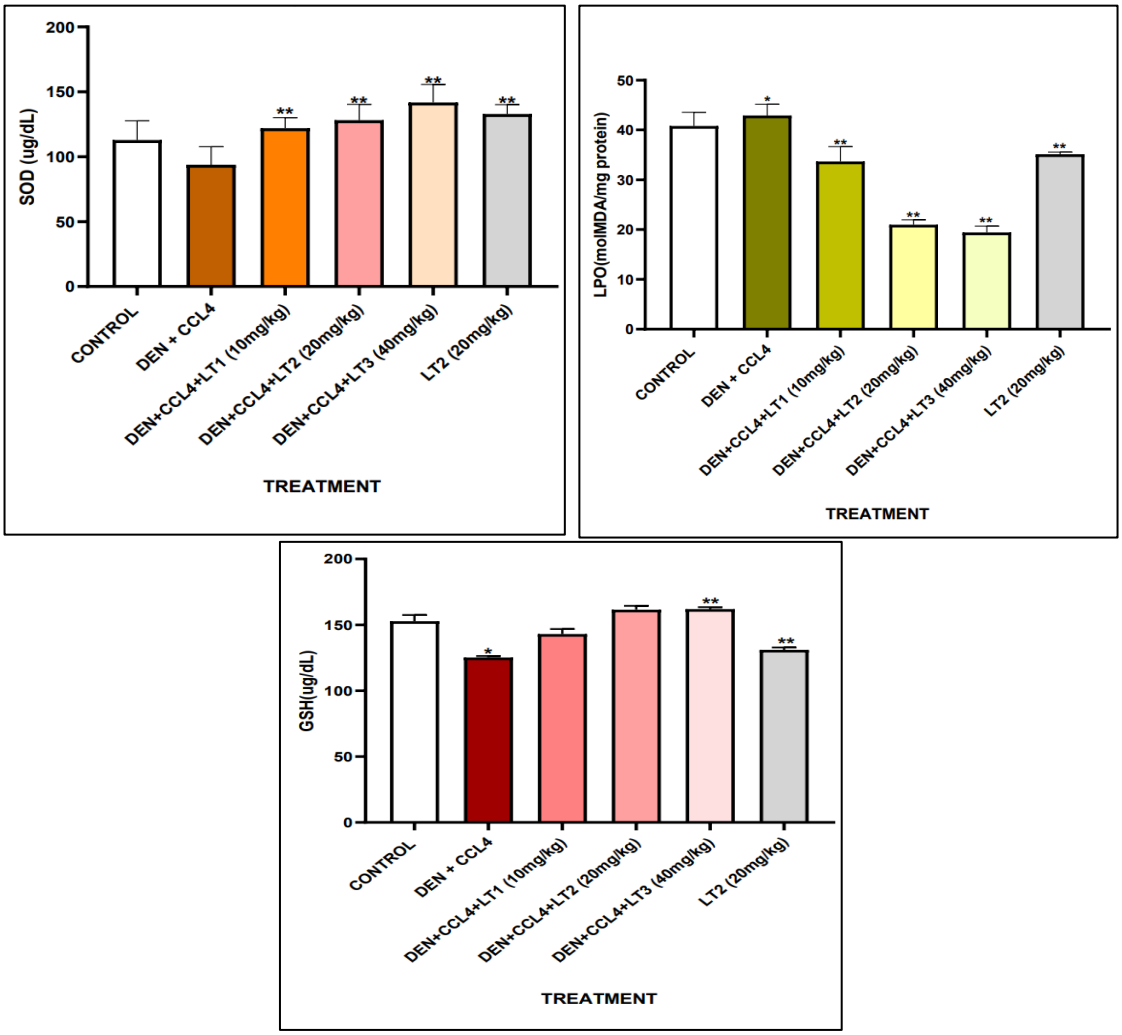


Figure 4: Dose-dependent effects of Luteolin on enzymic and non-enzymic antioxidant markers in the kidneys of rats treated with Diethylnitrosamine and carbon tetrachloride in the kidney

* = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCl_4. DEN = Diethylnitrosamine; CCl_4 = Carbon tetrachloride; LT = Luteolin

Dose-dependent effects of Luteolin on inflammatory markers in the livers and kidneys of rats treated with Diethylnitrosamine and carbon tetrachloride.

Figures 5 and 6 showed the dose-dependent effects of LT at 10mg/kg, 20mg/kg and 40mg/kg on the inflammatory markers (NO and MPO) in the livers and kidneys of rats treated with DEN+CCl_4. Administration of DEN+CCl_4 increased the levels of inflammation (NO and MPO in the liver and kidney by 49% and 11%, 479% and 376% respectively (Figure 5&6). Interestingly the pre-treatment with LT (10 mg/kg, 20 mg/kg and 40 mg/kg) significantly reduced ($p>0.05$) the level of hepatic inflammation (NO and MPO) by 14%, 29% and 42%, 66%, 62% and 44% and renal inflammation (NO and MPO) by 8%, 23%, and 25% and 64%, 106% and 84% respectively when compared relatively with the DEN+CCl_4 groups.

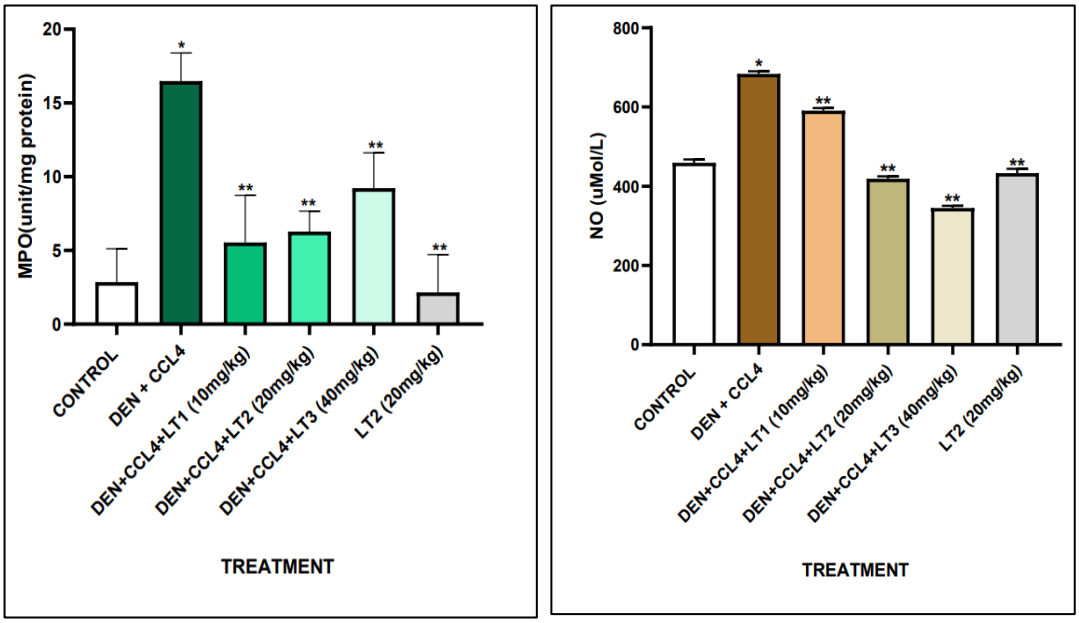


Figure 5: Dose-dependent effects of Luteolin on inflammatory markers in the livers of rats treated with Diethylnitrosamine and carbon tetrachloride

* = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCL_4. DEN = Diethylnitrosamine; CCL_4 = Carbon tetrachloride; LT = Luteolin

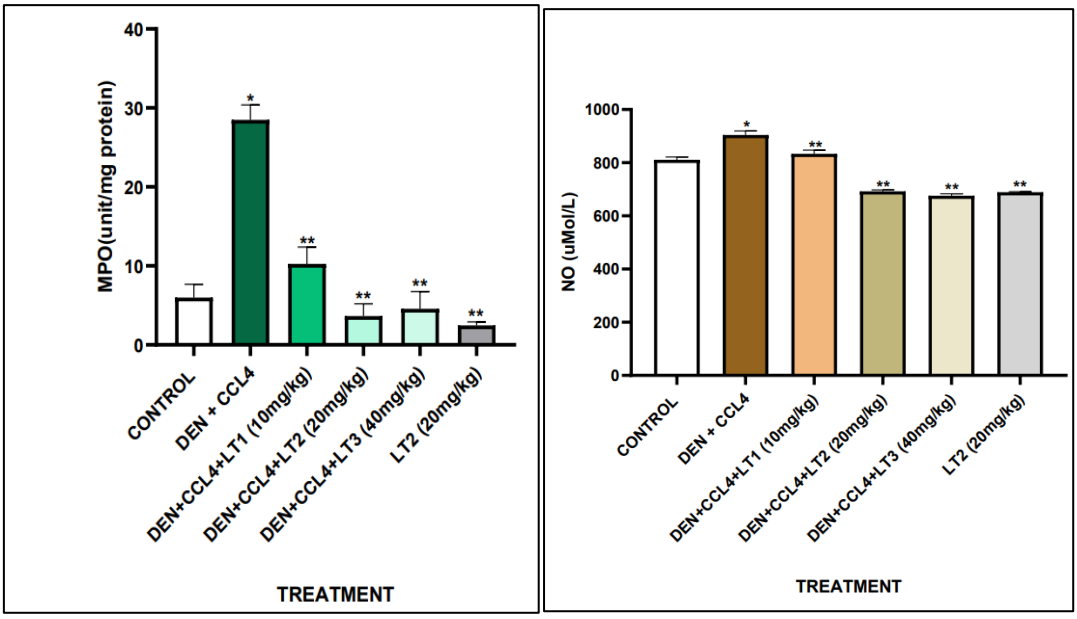


Figure 6: Dose-dependent effects of Luteolin on inflammatory markers in the kidney of rats treated with Diethylnitrosamine and carbon tetrachloride

* = P <0.05 Statistically significant when compared to control. ** = P <0.05 Statistically significant when compared to DEN+CCL_4. DEN = Diethylnitrosamine; CCL_4 = Carbon tetrachloride; LT = Luteolin

Dose-dependent effects of Luteolin on the cytostructure of liver and kidney in rats treated with DEN+CCL_4

Figures 7 and 8 are representative photomicrographs of the liver and kidney of rats treated with luteolin, Diethylnitrosamine and carbon tetrachloride. In control, the tissue displayed typical architectural arrangement with mild and no observable lesions (figures 7 and 8). Also, in the DEN+CCL_4 treated rats, there was multifocal hepatocellular coagulation necrosis and inflammation of hepatocytes (Figure 7). In contrast, random glomerular atrophy, tubular epithelial necrosis and inflammation can be observed in the renal tissues. (figure 8). Pretreatment with LT at varying doses restored the distorted structure close to normal in both tissues.

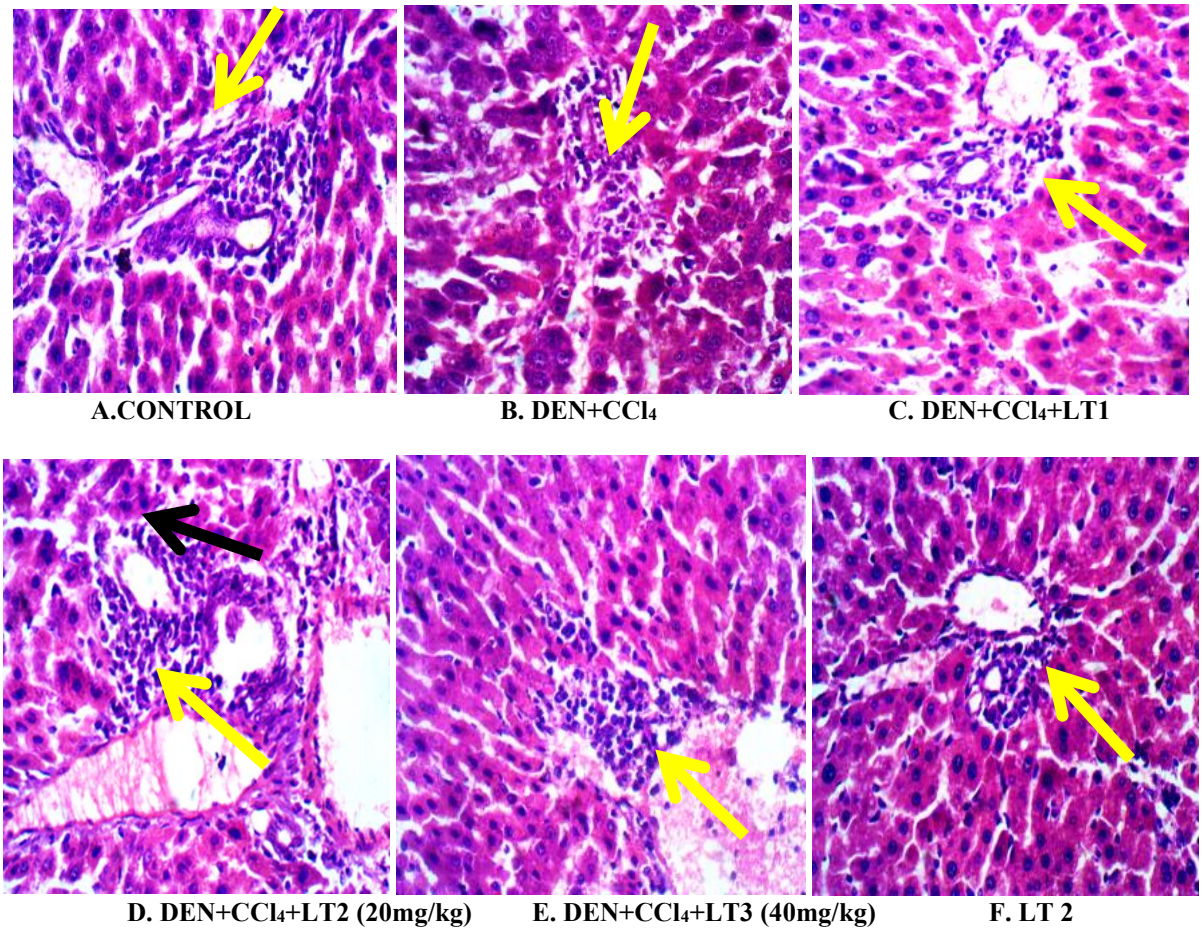


Figure 7: The photomicrographs of liver tissuesshowing effects of Luteolin in rats treated with Diethylnitrosamine and carbon tetrachloride. (HE x400)

A: There is portal inflammation (arrow). B. There is multifocal hepatocellular coagulation necrosis and inflammation (arrow). C. There is multifocal hepatocellular coagulation necrosis and inflammation (arrow). D. There is zone 1 hepatocellular coagulation necrosis (black arrow) and inflammation (yellow arrow). E. There is zone 1 hepatocellular coagulation necrosis and inflammation (arrow). F. There is zone 1 hepatocellular coagulation necrosis and inflammation (arrow)

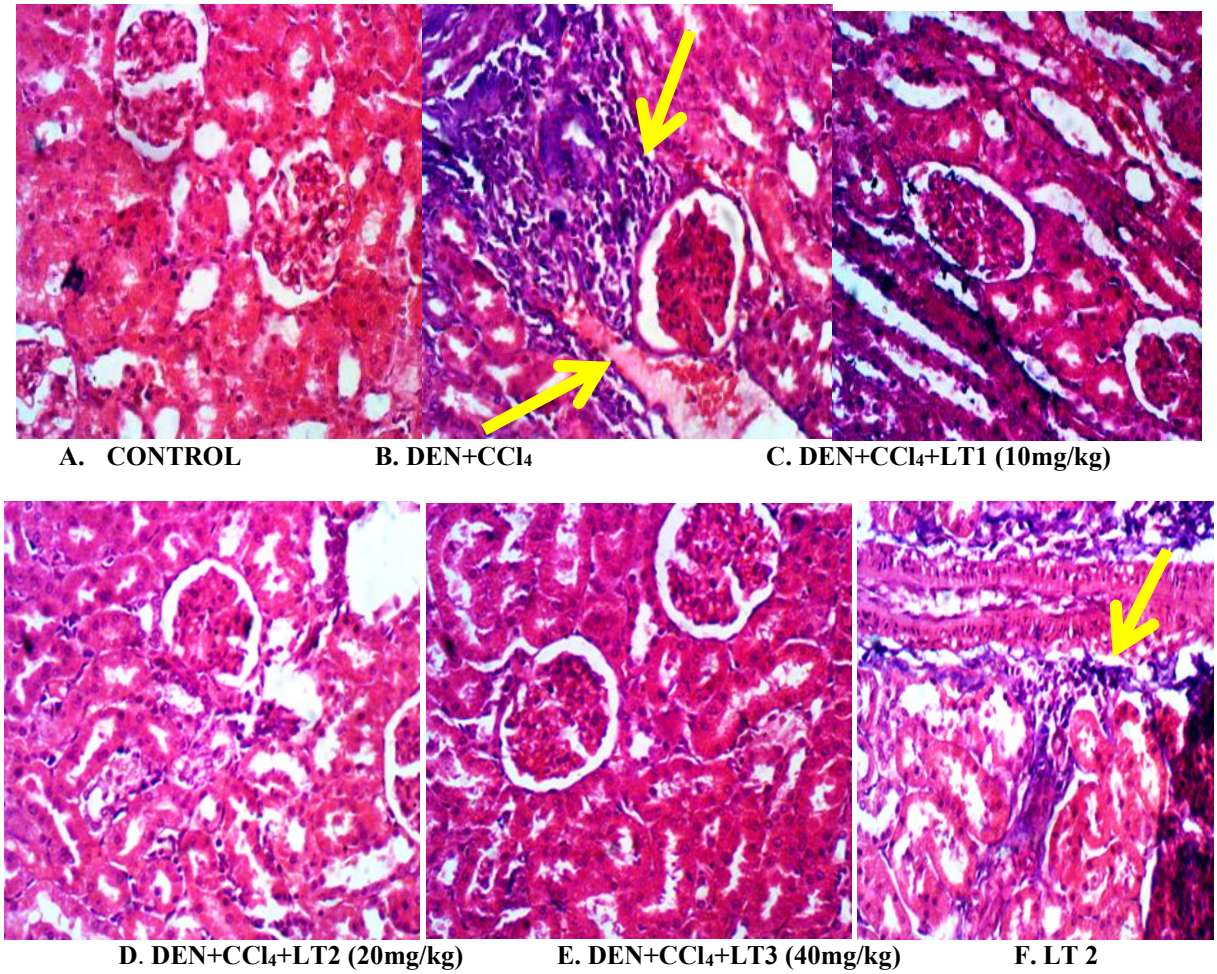


Figure 8: The photomicrographs of kidney tissues showing effects of Luteolin in rats treated with Diethylnitrosamine and carbon tetrachloride

A: There is no observable lesion. B. There is random glomerular atrophy, tubular epithelial necrosis and inflammation (arrows). C. There is no observable lesion. D. There is no observable lesion. E. There is no observable lesion. F. There is moderate perivasculitis (arrow) in the interstitium. (HE x400)

DISCUSSIONS

The outcome of our study showed that pretreatment of rats with luteolin ameliorated DEN+CCl_4 induced hepatorenal toxicity in rats evidenced by the attenuation of biochemical indices, improved antioxidant status, and restoration of histological structure of the tissues. The findings indicate that luteolin significantly enhances the antioxidant defense mechanisms in the liver. This is evidenced by increased activities of superoxide dismutase (SOD) and levels of reduced glutathione (GSH). SOD is crucial in converting superoxide radicals into hydrogen peroxide, while GSH scavenges free radicals and detoxifies reactive oxygen species (ROS) (Akinmoladun *et al.,* 2014). Superoxide dismutase (SOD) plays a pivotal role in antioxidant defense by catalyzing the dismutation of superoxide radicals into hydrogen peroxide and oxygen, thus mitigating oxidative damage within cells. Meanwhile, glutathione (GSH) is a vital antioxidant that participates in the detoxification of reactive oxygen species (ROS) and the scavenging of free radicals, thereby protecting cells from oxidative stress and maintaining redox balance (Halliwell *et al.,* 2015). The upregulation of these enzymes suggests that luteolin bolsters the liver's antioxidant capacity, thereby protecting against oxidative stress-induced hepatotoxicity. Moreover, luteolin treatment significantly reduced lipid peroxidation in the liver, as indicated by lower levels of malondialdehyde (MDA). Lipid peroxidation leads to the formation of reactive aldehydes and oxidative damage to cell membranes (Sahu *et al.,* 2013). The inhibition of this process by luteolin suggests its ability to scavenge free radicals and prevent lipid peroxidation chain reactions, further supporting its hepatoprotective effects. Additionally, the study showed that luteolin reduced the activities of myeloperoxidase (MPO) and nitric oxide (NO) levels in the liver, markers of inflammation and oxidative stress. This reduction indicates that luteolin possesses anti-inflammatory properties and can mitigate the inflammatory response associated with hepatotoxicity. These results are consistent with previous studies demonstrating the antioxidant and anti-inflammatory

effects of luteolin in various disease models (Wu *et al.,* 2016)

Parallel to its hepatoprotective effects, luteolin also exhibited significant nephroprotective properties. DEN and CCl_4 exposure led to marked elevations in serum creatinine and blood urea nitrogen levels, indicative of impaired kidney function. Histopathological analysis revealed tubular necrosis and interstitial inflammation, confirming renal damage. Luteolin administration ameliorated these detrimental effects dose-dependently, with higher doses showing more pronounced improvements in kidney function parameters and histopathological changes. The nephroprotective effects of luteolin are attributed to its antioxidant and anti-inflammatory properties (Lin *et al.,* 2015). Luteolin attenuated oxidative stress by reducing MDA levels and enhancing SOD and GSH activities in the kidneys. The reduction in lipid peroxidation indicates a decrease in oxidative stress, leading to reduced kidney tissue injury and failure of the antioxidant defense mechanism to mop up excess free radicals (Altuner *et al.,* 2012). Furthermore, inflammatory markers such as MPO and NO were significantly elevated in DEN and CCl_4-treated rats. Luteolin treatment decreased these markers, indicating a reduction in inflammation and oxidative stress in the kidneys. This aligns with previous research highlighting the nephroprotective properties of luteolin, known for its antioxidant and anti-inflammatory actions in various disease models, including nephropathy and renal fibrosis (Lu *et al.,* 2019).

The combined hepatorenal protective effects of luteolin can be understood through its dual antioxidant and anti-inflammatory actions (Zhang *et al.,* 2019). By upregulating antioxidant enzymes like SOD and increasing GSH levels, luteolin bolsters the antioxidant defense mechanisms in both the liver and kidneys. This enhancement is crucial for neutralizing ROS and reducing oxidative damage, which is a common pathological mechanism in both hepatic and renal injuries induced by DEN and CCl_4. (Furthermore, luteolin's ability to reduce lipid peroxidation and its associated damage to cellular membranes is vital for maintaining the structural integrity of liver and kidney tissues. The significant decrease in MDA levels observed in this study underscores luteolin's effectiveness in preventing oxidative degradation of lipids, thereby protecting cellular components from oxidative stress. The anti-inflammatory effects of luteolin, evidenced by reduced MPO and NO levels, further contribute to its protective roles (Abdel-Moneim*et al.,* 2015). By mitigating inflammation, luteolin not only prevents further oxidative damage but also aids in the healing and restoration of normal tissue function in both the liver and kidneys (Gong *et al.,* 2020). This dual action of reducing oxidative stress and inflammation makes luteolin a potent protective agent against hepatorenal toxicity induced by chemical agents like DEN and CCl_4.

CONCLUSION

In conclusion, the study demonstrates that luteolin significantly enhances the antioxidant defense mechanisms and reduces inflammation in both the liver and kidneys in a dose dependent manner. These effects collectively contribute to its potent hepatorenal protective properties, making luteolin a promising therapeutic agent for mitigating oxidative and inflammatory damage in hepatorenal tissues. Further research could focus on the molecular pathways involved in luteolin's protective mechanisms, potentially paving the way for its application in clinical settings for the treatment of liver and kidney diseases.

Abbreviation

LT - Luteolin
DEN - Diethylnitrosamine
CCl_4 – Carbon tetrachloride
ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
LPO – Lipid peroxidation
GSH - Glutathione
SOD – Super oxide dismutase

Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable

Availability of Data and Materials: Not applicable

Competing Interest: The authors declare no competing interests.

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Authors' Contributions

M.A.A. and R.S.O carried out the research and wrote the manuscript; A.A.O. wrote and edit the manuscript; S.E.O and O.A.A supervise the research and edit the manuscript, carry out the research

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