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Histological and Biochemical Effects of Lutein on Paraquat-induced Renal Toxicity in Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Paraquat (PQ) poisoning in humans predominantly results from the generation of reactive oxygen species (ROS). To date, no proven antidote exists for PQ poisoning, which is characterized by severe kidney injury and high mortality rates globally. However, free radical scavengers and antioxidant agents have shown potentials to mitigate PQ toxicity.
Aim: The study is aimed at investigating lutein, an antioxidant, for possible mitigation of paraquat-induced renal toxicity.
Study Design: Preclinical experimental study.
Place and Duration of Study: Department of Anatomy, Obafemi Awolowo University (OAU), Nigeria, between 2022 and 2023.

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Methods: Forty wistar rats weighing 150-180 grammes were randomly grouped (A to E) for this study. Paraquat (PQ) toxicity was induced in groups B to E. Lutein was administered at graded doses of 50 mg/kg, 100 mg/kg and 150 mg/kg to groups C to E for twenty-one days respectively. Group A (positive control) was given only normal saline, while group B had paraquat only. Twenty-four hours after the last administration, urine and blood samples were collected and the animals were sacrificed before the excision of the kidneys.

Results: A marked histological distortion, which was characterized by compromised Bowman's space and renal tubule dimensions, was observed in Group B. In contrast, the lutein-treated groups exhibited dose-dependent improvements, with outcomes comparable to the control group. Notably, Group B showed significant elevations in plasma creatinine (P = 0.003) and urine protein (P = 0.001), accompanied by reduced plasma protein (P = 0.004), relative to the treated groups. However, Group E, which received the highest lutein dose, demonstrated substantial improvement in histoarchitectural and biochemical findings similar to the control group."

Conclusion: This study demonstrated significant alterations in the histoarchitecture and biochemical profiles of renal tissue following paraquat exposure. Notably, the lutein-treated groups exhibited substantial improvement, with results comparable to the control group. These findings suggest that lutein may possess potential therapeutic properties to mitigate paraquat-induced renal toxicity.

Keywords: Paraquat; lutein; histological; biochemical; kidneys.

1. INTRODUCTION

Paraquat (1, 1′-dimethyl-4,4′-dipyridylium) is one of the most widely used herbicides worldwide [Gawarammana, I. B., & Buckley, N. A. 2011, Adejumo, O. A., et al. 2016]. The toxic phytochemical was first produced in 1882 as a redox indicator, but its herbicidal property was recognised in the 1950s [Shashibhushan, J., et al. 2015]. Paraquat poisoning in humans has been reported globally. The most common route of human exposure to paraquat poison is oral ingestion, which can occur after intake of contaminated foods or through deliberate self-harm [Gawarammana, I. B., & Buckley, N. A. 2011, Eizadi-Mood, N., et al. 2011]. The chemical poisoning is also possible after skin exposure, especially in the presence of preexisting skin lesions [Zhou, Q., et al. 2013].

Paraquat-induced toxicity results from its ability to generate reactive oxygen species (ROS) in many organs. The lethal dose (LD50) of the poisoning in humans is approximately 35 mg/kg (10-15 mL of a 20% v/v solution) [Shashibhushan, J., et al. 2015]. Ingestion of a little quantity usually leads to toxicity in few target organs, while fulminant multi-organ failure may result from ingestion of large volume [Ito, H. (2019)]. The lungs, kidneys and liver have been found to have the highest concentrations of paraquat following accidental ingestion in humans and animals [Ujowundu, C. O., et al. 2018]. The toxic features tend to develop over days to weeks [Gawarammana, I. B., & Buckley, N. A. 2011, Wunnapuk, K., et al. 2014].

Lutein is an active carotenoid and a natural source of antioxidants. It is widely distributed in carotenoids in fruits and vegetables. The carotenoid has been found to have protective effects against oxidative damage [Severins, N., et al. 2015]. Lutein has a free radical scavenging ability as a result of its polarity, conjugated double bond, and the two hydroxyl groups on both ends, making it stronger antioxidant as compared to other carotenoids. It promotes significantly the antioxidant enzyme system in blood and liver tissue [Hirdyani, H., & Sheth, M. 2017]. The carotenoid has numerous pharmacological and biological benefits, which are not limited to hepatoprotective [Li, S., et al. 2015], nephroprotective [Bilgiç, S., et al. 2022], cardioprotective [Liu, X. H., et al. 2014, Ouyang, B., et al. 2019] and anti-neoplastic effects [Zhang, W. L., et al. 2018].

Even in the best of intensive care units, the probability of death from PQ poisoning exceeds 50% [Goudarzi, F., et al. 2014]. Till date, there is no proven antidote nor widely accepted guidelines for treatment of affected patients [Gawarammana, I. B., & Buckley, N. A. 2011, Adejumo, O. A., et al. 2016]; hence, there is a need to investigate a probable treatment using an antioxidant agent, lutein, for possible mitigation of paraquat-induced renal toxicity. This is aimed at providing an effective interventional strategy towards reducing the burden of the

poisoning in terms of morbidity and mortality in humans.

2. MATERIALS AND METHODS

Forty male Wistar rats weighing between 150-180 grams were used for this study after obtaining an ethical approval. They were acclimatized for two weeks and fed with standard laboratory rat pellets with access to clean water ad libitum. The rats were randomly assigned into five groups of eight rats per group (Groups A, B, C, D, and E). Group A served as the positive control (which was given normal saline), group B was the negative control (had only paraquat), and groups C, D and E were the treated groups. Administrations of all drugs and other substances were given through the mouth by oral cannula.

Paraquat toxicity was induced in groups B, C, D, and E by administration of 5 mg/kg of paraquat for three days. At the same time, group A was given an equivalent volume of normal saline. Twenty-four hours after the last dose, groups C, D, and E were given lutein at graded dosages of 50, 100, and 150 mg/kg once daily, respectively, for twenty-one days, after the dissolution of the compound in normal saline.

2.1 Animal Sacrifice, Histological Preparation

Twenty-four hour after the last administration, the animals were euthanized. A mid-line incision was made along the anterior abdominal wall and the kidneys were exercised. The excised organ was fixed in 10% formol saline and processed using paraffin wax embedding method. The sectioning was done at 5µm thickness using a rotary microtome and stained with haematoxylin and eosin for general histoarchitecture. The tissue was processed using the recommended procedure by Bancroft and Gamble (2002).

2.2 Photomicrography, Processing and Biochemical Assay

The stained section was examined under 'Motic Scanner' and photomicrograph was taken at various magnifications. Image analysis and processing for Java (image J) and public domain software were used for the measurement of the kidney tubules and bowman space.

Blood samples were collected via ocular puncture in heparinized tubes and centrifuged at 2500 revolution per minutes (rpm) for 15 minutes after which the plasma was separated and stored at – 20^0C for analysis. Blood protein was assayed as described by Holme and poeck, (1998). Electrolytes were also measured by Henry 1974 method.

3. RESULTS

3.1 Heamatoxylin and Eosin Staining with Renal Dimensional Evaluation

Plates 1 and 2 show normal histoarchitecture of the kidney tissue in the control group A, characterised by the uniform tubules with viable epithelial cells. However, group B showed increased cytoplasmic eosinophilia, with some non-nucleated epithelial cells, giving a ghost town appearance, which is a characteristic of acute tubular necrosis. There was also evidence of glomerular sclerosis; its glassy nature is a sign of kidney disease. In the groups with high dosages of lutein (D and E), there were well-arranged tubular epithelial cells with near-normal glomeruli. There was also a significant reduction in the Bowman space of the glomeruli (P = 0.000, F = 2.30) and a significant increase in the tubules (P = 0.000, F = 12.05) of the animals in the PQ only (group B) when compared to the control group (Figs. 1 and 2). In the treated groups C, D, and E, there was no significant tubular difference when compared to the control.

3.2 Biochemical Parameters of the Kidneys

The concentration of urine protein in group B was significantly higher (P = 0.001, F = 8.23) when compared to the treated groups (C, D, and E) and the control group A. Meanwhile, there was no significant difference between the treated groups and the positive control. Regarding plasma concentration of protein, there was a significant decrease (P = 0.004, F = 1.04) in group B when compared to groups C, D, E, and group A. However, there was no significant difference in control group A when compared with the treated groups C, D, and E (Fig. 3).

The concentration of creatinine in plasma in group B was significantly elevated (P = 0.003, F = 2.52) when compared to the treated groups C, D, E, and the control. However, there was no significant difference noticed between the control groups A and the treated groups, as shown in Fig. 4a. There was a decrease in the concentration of urine creatinine in group B but no significant difference when compared to the

treated groups C, D, and E. Meanwhile, group A showed a significant increase in creatinine concentration when compared to group B (*P* = 0.03). Comparing the treated groups with the control, there was no significant difference (Fig. 4b).

The plasma concentrations of potassium in both groups B (paraquat only) and C (which had the lowest dose of lutein) were significantly lower (*P* = 0.003, F = 6.01) when compared to the other treated groups (D, E) and the control (Fig. 5). Similarly, the concentration of plasma sodium in group B was significantly lower (*P* = 0.001, F = 7.49) when compared to all the treated groups C, D, E, and the control. However, there was no significant difference between the control (group A) and the treated groups, as shown in Fig. 6.

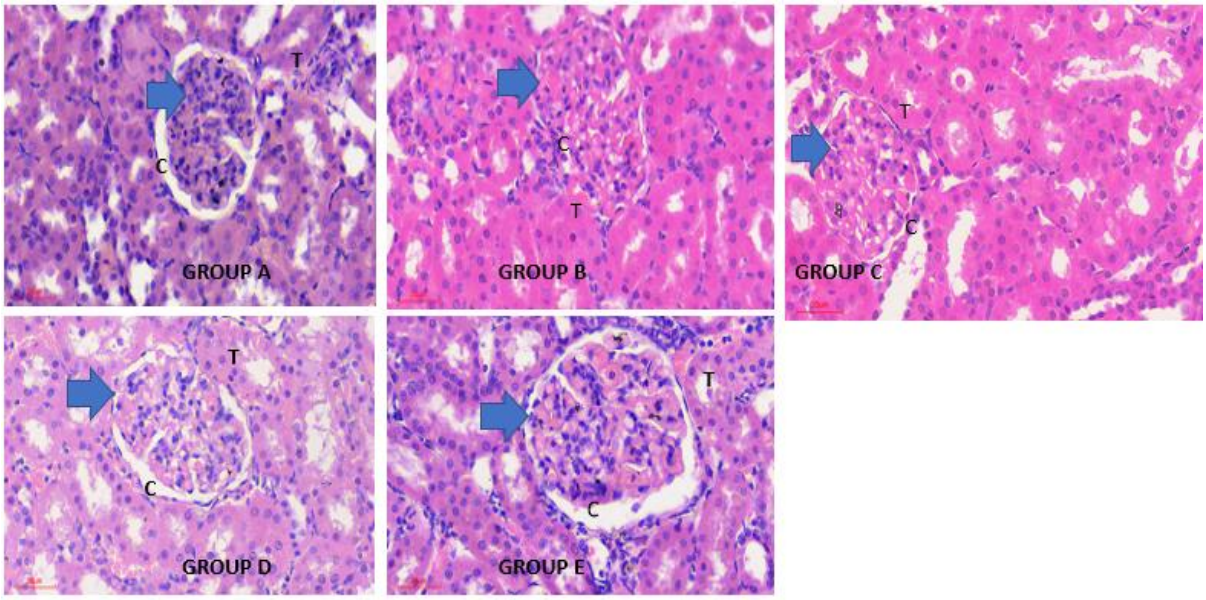


Plate 1. Photomicrographs of kidney section (glomeruli with few tubules) using Motic scanner
*Group A (Control), B (Paraquat +Normal Saline), C (Paraquat+50 mg/kg of Lutein), D (Paraquat+100 mg/kg of Lutein) and E (Paraquat +150 mg/kg of Lutein). Blue arrow shows the glomerulus, **T** shows tubules and **C** is bowman space H & E× 400*

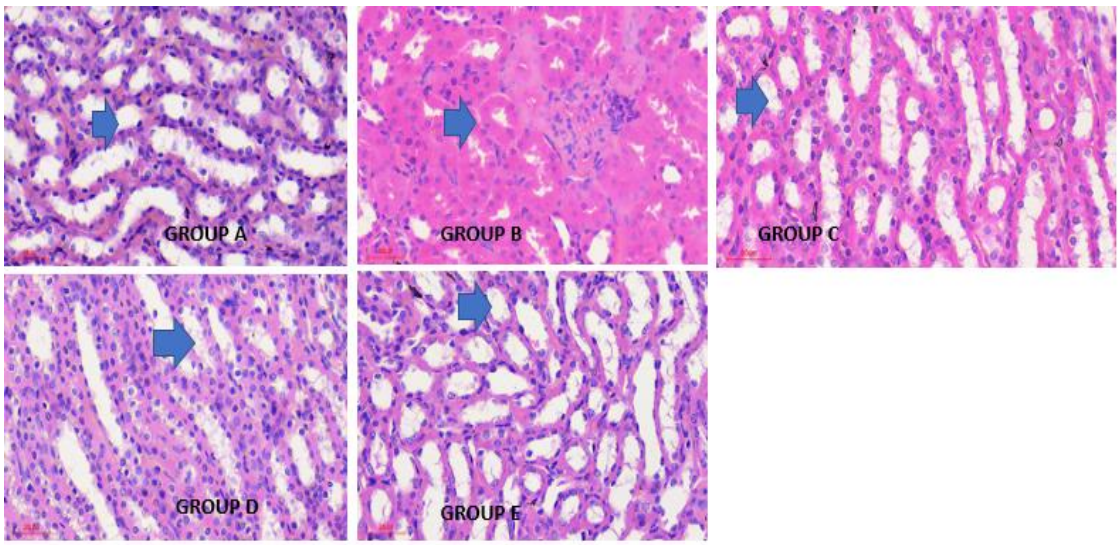


Plate 2. Photomicrographs of kidney tubules using Motic scanner
A Control, B (Paraquat+ normal saline), C (Paraquat+ 50mg/kg of Lutein), D (Paraquat+ 100 mg/kg), E (Paraquat+ 150 mg/kg), Blue arrow shows kidney tubules. H&E (X400)

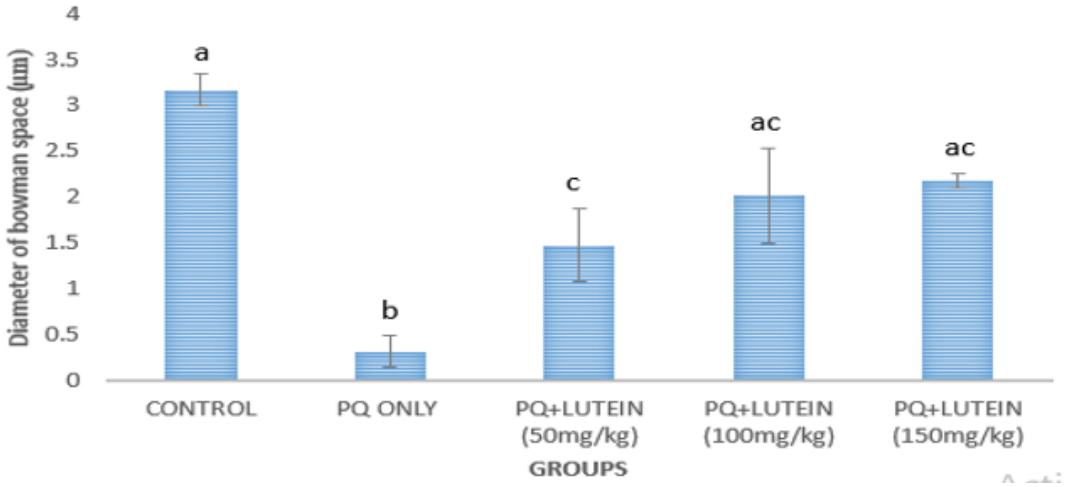


Fig. 1. Shows diameter of the bowman space in the kidney using image J: values are expressed as mean ± SEM in each group. a, b, c within column signifies that mean with different letters differs significantly at P= 0.05 while mean with the same letter does not differ significantly at P= 0.05. PQ=Paraquat

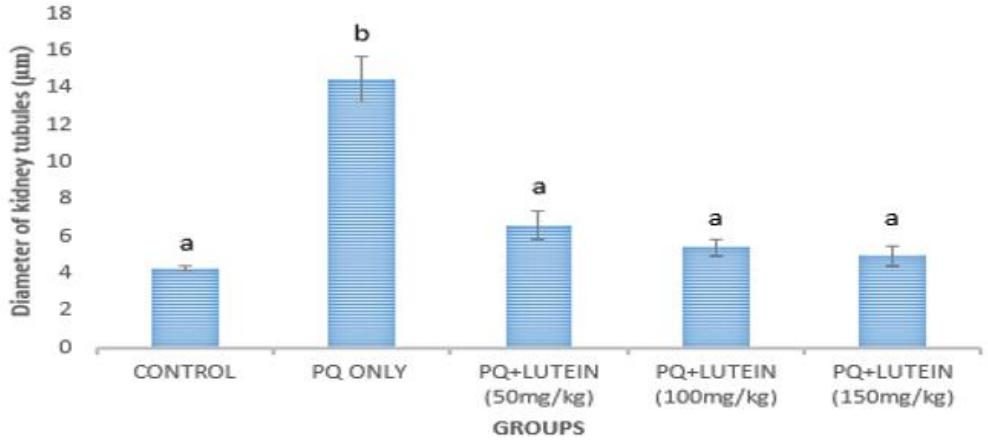


Fig. 2. Shows transverse diameter of the kidney tubules using image J: values are expressed as mean ± SEM in each group. a, b, within column signifies that mean with different letters differs significantly at P= 0.05 while mean with the same letter does not differ significantly at P= 0.05. PQ=Paraquat

4. DISCUSSION

The study showed that paraquat exposure caused severe histopathological changes in the kidneys, especially in the paraquat-only group (Group B). The finding was similar to the report by Jia et al., (2022) who observed degeneration in the glomeruli and tubules of the kidneys with evidence of necrosis. In the groups treated with lutein, the histomorphology of the glomeruli and tubules showed near-normal histoarchitecture in a dose-dependent manner. This finding may be associated with the antioxidant, anti-inflammatory, and anti-apoptotic properties of lutein, in line with Gundogdu et al. (2022) and Gad El-Karim et al., (2023) who reported that lutein successfully mitigated renal toxicity.

Singh et al. (2006) explain that the structural base of the antioxidative effect of lutein is believed to contribute to the delocalization of unpaired electrons by its conjugated double-bonded structure. This allows lutein to effectively scavenge free radicals. There was also a reduction in the Bowman space of Group-B relative to the control and lutein-treated groups, which may be linked to severe fibrosis associated with paraquat toxicity. Bowman capsules are lined by podocytes, which play a role in the restriction of plasma protein in the urine (2023).

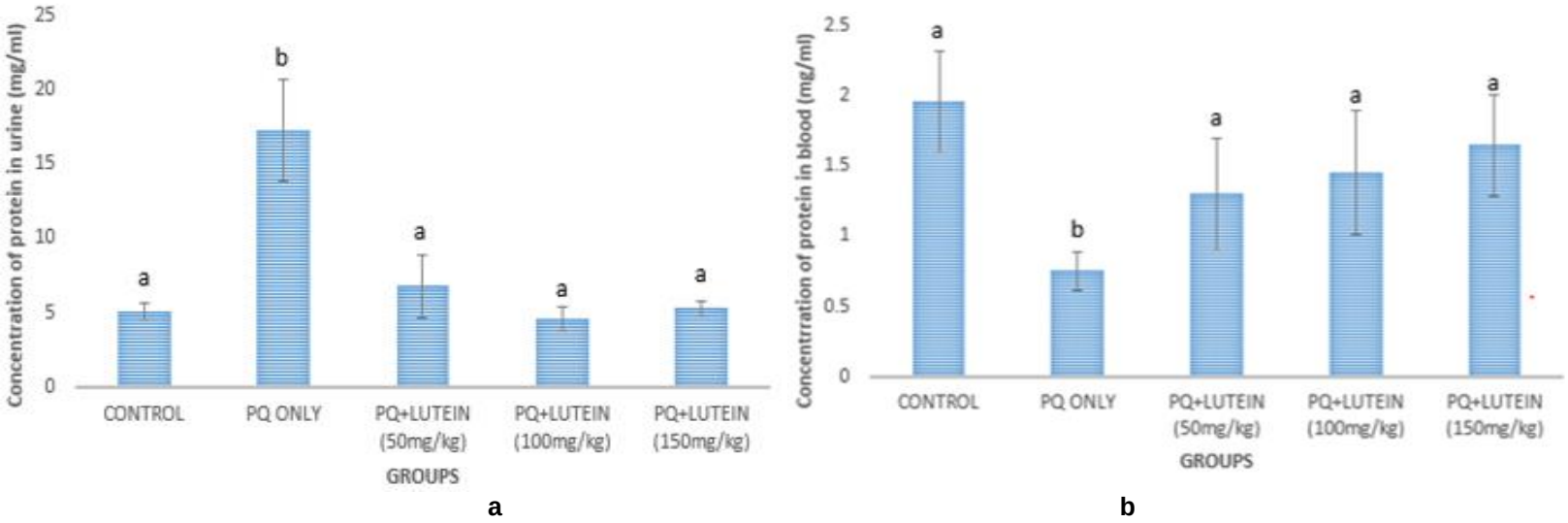
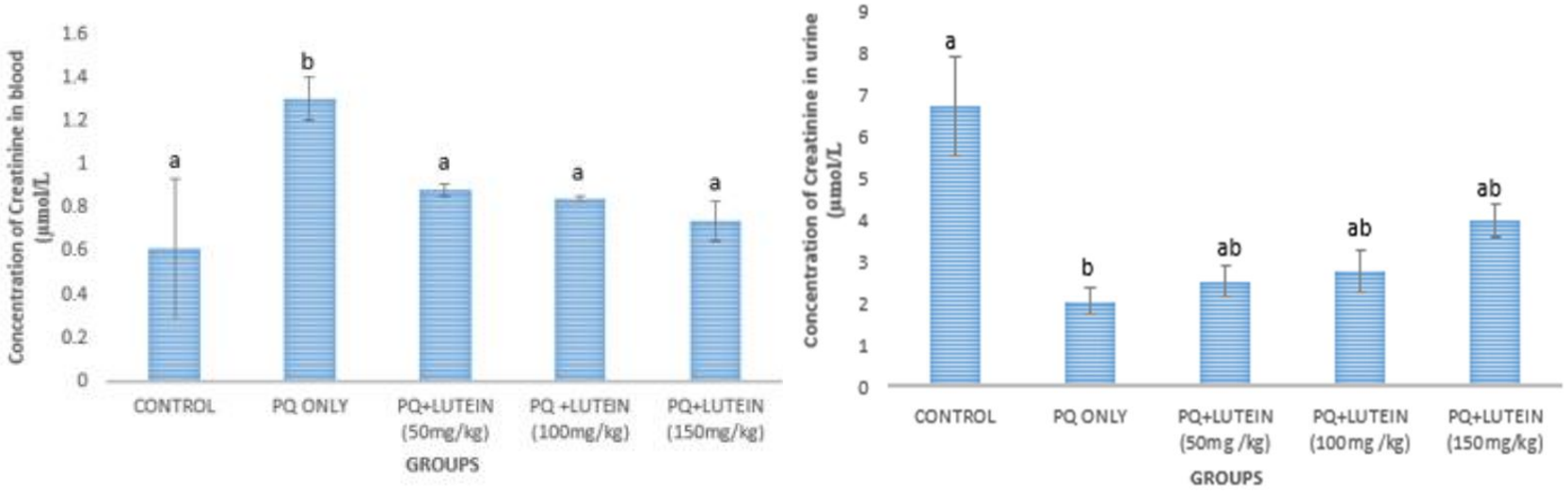


Fig. 3. Shows Concentration of protein in urine (a) and blood (b): values are expressed as mean ±SEM in each group. a, b, within column signifies that mean with different letters differs significantly at P=0.05. PQ=paraquat



(a) **(b)**

(b)

Fig. 4. Shows Concentration of creatinine in (a) blood and (b) urine: values are expressed as mean ±SEM in each group. a, b, within column signifiesthat mean with different letters differs significantly at P=0.05. PQ=paraquat

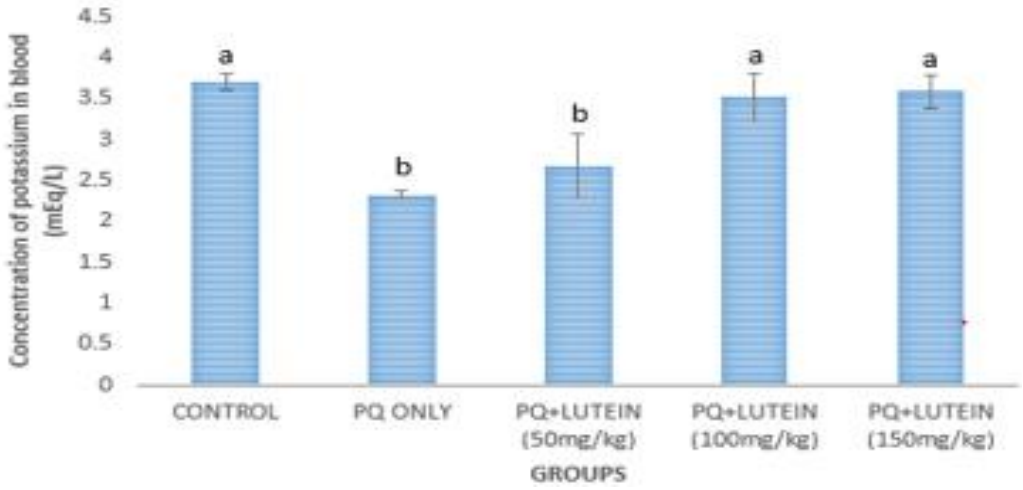


Fig. 5. Shows Concentration of Potassium in the blood: values are expressed as mean ± SEM in each group. a, b, within column signifies that mean with different letters differs significantly at P=0.05 while mean with the same letter does not differ significantly at P= 0.05. PQ=Paraquat

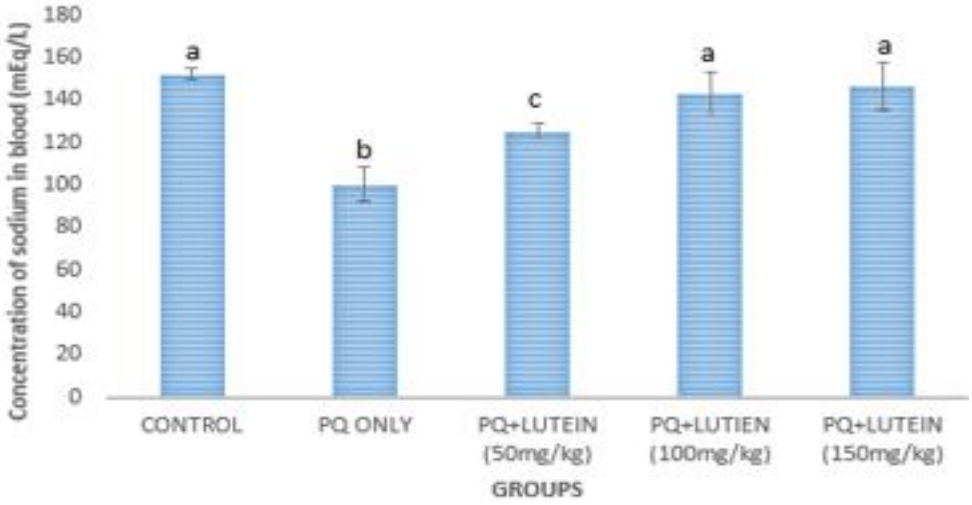


Fig. 6. Shows Concentration of Sodium in the blood: values are expressed as mean ± SEM in each group. a, b, within column signifies that mean with different letters differs significantly at P= 0.05 while mean with the same letter does not differ significantly at P= 0.05. PQ=Paraquat

The study shows a significant increase in the serum creatinine level in PQ-only group in line with other findings [Ujowundu, C. O., et al. (2018), Jia et al., (2022), Huang, W., et al. (2023)]. This probably reflects increased generation of creatine and creatinine to meet energy demand following significant oxidative stress [Mohamed, F., et al. (2015)]. Direct oxidative damage to the renal tubules by PQ can induce elevated blood creatinine [Kim, S. J., et al. 2009, Roberts, D. M., et al. 2011]. Studies by Roberts et al. [2014] and Mohamed et al. [2015] also found decrease in glomerular filtration capacity with elevated blood creatinine concentration, which is closely related to acute kidney injury and direct reflection of progressive kidney damage. Significant decrease in the serum creatinine in the rats treated with lutein may be due to the reno-protective anti-inflammatory and anti-oxidant properties of the agent [VijayaPadma, V., et al. 2014, Mammadov, R., et al. 2019]. This is due to the free radical scavenging ability of its polarity, conjugated double bond, and the two hydroxyl groups [Hirdyani, H., & Sheth, M. 2017, Fuad, N. I., et al. 2020].

There was an increase in urine protein (proteinuria) in this study, which may be as a result of the glomerular and tubular injury; the

injury is evident from the histological findings and corroborated by other studies [Williams, J. H., et al. 2016, Asaduzzaman, M., et al. 2023]. It has been reported that albuminuria can result from paraquat-induced glomerular damage with an associated increase in filtration of albumin or from tubular injury that impairs reabsorption [Gawarammana, I. B., & Buckley, N. A. (2011)].

In this study, there was a significant decrease in the sodium and potassium levels of the rats treated with paraquat only. This finding is supported by other works [Cirilo, M. A., et al. 2024], which observed that increased production of reactive oxygen and lipid peroxidation in paraquat-poisoning tends to provoke inhibition of the medullary sodium-potassium ($Na,^{+}$ K^{+}) ATPase. Dedeke, G. A., et al. (2018) also explained that ROS-mediated alterations in the renal renin angiotensin-aldosterone system (RAAS) and active Na+ transport machinery could lead to fluid wasting and electrolyte depletion in herbicide-associated acute kidney injury.

Low serum potassium is common among subjects with paraquat poisoning, as reported by various authors [Wunnapuk, K., et al. 2013, Biswas, S., et al. 2021, Yu, J., et al. 2022]. The mechanism of PQ-induced hypokalaemia may also be multifactorial; this includes renal tubular necrosis leading to alteration in potassium re-absorption in the renal tubules [Wunnapuk, K., et al. 2013]. Polyuric renal injury may also cause wastage of sodium and potassium, leading to hyponatraemia and hypokalaemia. Gastrointestinal ulceration with mucosal excoriation tends to occur in PQ-poisoning, and this may cause hypokalaemia and loss of other electrolytes [Biswas, S., et al. 2021, Yu, J., et al. 2022].

Following PQ-induced oxidative stress, there may be an increase in the secretion of catecholamines and glucocorticoids with enhanced activity of sodium-potassium pump entry; this tends to promote the transfer and entry of potassium from the extracellular compartment into the cells, ultimately potentiating hypokalaemia. Significant loss of potassium with accompanying hypokalaemia may also result from the use of diuretic agents, which have the capacity to promote PQ excretion after poisoning [Yu, J., et al. 2022]. Hypokalaemia may be a poor prognostic marker and determinant of mortality following PQ poisoning [Yu, J., et al. 2022].

5. CONCLUSION

This study demonstrated significant alterations in the histoarchitecture and biochemical profiles of renal tissue following paraquat exposure. Notably, the lutein-treated groups exhibited substantial improvement, with results comparable to the control group. These findings suggest that lutein may possess potential therapeutic properties to mitigate paraquat-induced renal toxicity.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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