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Effects of Aqueous Rhizome Extract of *Zingiber officinale* on Arsenic Trioxide-Induced Kidney Damage in Adult Wistar Rats

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Abstract

The kidneys are crucial for eliminating toxins, but exposure to substances like arsenic can damage them. Arsenic trioxide, used in cancer treatment, is nephrotoxic. With few kidney-protective drugs available, interest has grown in plant-based alternatives. *Zingiber officinale* (Ginger), known for its antioxidants, is one such plant. The aim of this study was to assess the effect of ginger against arsenic trioxide-induced nephrotoxicity in Wistar rats. Thirty (30) adult Wistar rats (n=5) were randomly assigned into six groups (A-F). Group A served as control; Group B - 10 mg/kg As_2O_3 only; Group C - 190 mg/kg body weight of *Zingiber officinale* stem extract and 10 mg/kg As_2O_3; Group D - 380 mg/kg body weight of *Zingiber officinale* stem extract and 10 mg/kg As_2O_3; Group E - 50 mg/kg body weight of standard drug (silymarin) and 10 mg/kg As_2O_3. Group F - 380 mg/kg body weight of *Zingiber officinale* stem extract. The administration lasted 28 days, given orally via an orogastric tube. Afterward, the animals were anesthetized, sacrificed, and samples were taken for oxidative stress, kidney function assessments, and histological evaluation. Findings showed significant changes ($p<0.05$) in the arsenic trioxide-only group, including decreased SOD and GSH levels, increased MDA levels, and elevated levels of potassium, sodium, urea, and creatinine, indicating renal dysfunction. Histological analysis showed severe kidney damage evidenced by vascular stenosis, tubular necrosis, and inflammatory cell infiltrates. However, pre-treatment with *Zingiber officinale* protected against these effects, leading to increased ($p<0.05$) SOD and GSH levels, decreased ($p<0.05$) MDA levels, and improved histological findings with relatively normal kidney architecture. In conclusion, these findings suggest that *Zingiber officinale* possesses a protective effect against arsenic trioxide-induced nephrotoxicity, possibly through its antioxidant, anti-inflammatory, and reno-protective properties.

Keywords: *Kidney, Nephrotoxicity, Arsenic trioxide, Zingiber officinale, Wistar rat.*

Introduction

The Kidney plays a vital role in the excretion of toxic substances that enter the body (Lentini *et al*., 2017); consequently, there has been increasing evidence of kidney damage and reduced renal function caused by exposure to certain substances, including medications, chemicals, or environmental toxins (Lisowska-Myjak, 2015). One such toxin is arsenic, a naturally occurring element found in various forms in the environment (Sarkar and Paul, 2016). It has been used for various purposes throughout history, including in industry, in agriculture as a pesticide and wood preservative, and in traditional medicines for its perceived medicinal properties (Abdul *et al*., 2015). Arsenic trioxide, a common form of arsenic, has been used in medicine for its therapeutic properties (Wang *et al*., 2018), particularly in the treatment of certain types of cancer, such as acute promyelocytic leukaemia (APL) (Raza *et al*., 2017). However, arsenic is also highly toxic and exposure to high levels of arsenic can lead to a range of health concerns (Sarkar and Paul, 2016).

Arsenic trioxide has been associated with nephrotoxicity, primarily due to its ability to accumulate in the kidneys and disrupt normal renal function (Zheng *et al*., 2015; Orr and Bridges, 2017). Studies have shown that chronic exposure to arsenic can lead to kidney damage, including tubular necrosis, interstitial fibrosis, and impaired renal function (Lentini *et al*., 2017; Mishra *et al*., 2022; Ren *et al*., 2024).

The lack of satisfactory Kidney protective drugs in allopathic medical practices; necessitates the growing interest in exploring alternative treatment options, including the use of plant materials with potential nephroprotective properties. Several studies have investigated the potential nephroprotective effects of various plant materials. These studies have focused on the ability of plant compounds to mitigate the harmful effects of nephrotoxic agents and protect against kidney damage. *Zingiber officinale*, commonly known as ginger, is one plant that has garnered attention for its potential therapeutic properties. Ginger stands as one of the most frequently incorporated dietary seasonings worldwide (Ogori *et al*., 2021). Ginger is a flowering plant recognized for its rhizome, commonly referred to as ginger root. This rhizome holds widespread utility as both a spice and a traditional remedy (Azeez and Lunghar, 2021). Ginger is characterized by its herbaceous perennial nature, featuring annual pseudostems, which are essentially false stems formed from the rolled bases of leaves (Unuofin *et al*., 2021). Ginger contains bioactive compounds, such as gingerols and shogaols, which have antioxidant and anti-inflammatory properties (Azeez and Lunghar, 2021; Unuofin *et al*., 2021). Despite the well-established antioxidant properties of Ginger and its potential nephroprotective effects, there is limited research on its effectiveness in reducing the nephrotoxic effects of Arsenic trioxide exposure. Hence, this study aimed to investigate the potential nephroprotective activities of *Zingiber officinale* against Arsenic trioxide-induced nephrotoxicity in Wistar rats.

Materials and Methods

Plant Extract: *Ginger stems* were obtained from a nearby farm. It was identified and authenticated at the herbarium (*UBH-Z384*) of the Department of Plant Biology and Biotechnology, University of Benin, Nigeria. The stems were carefully sorted to remove damaged ones, they were washed, cleaned, and air-dried. Thereafter, it was put into a one litre beaker after being pulverized into a fine powder (500g) with a mechanical grinder and weighed with an electrical weighing balance. The ground plant materials were prepared for aqueous extraction according to the standard procedure described by Joseph *et al.* (2010).

Experimental Animals: Wistar rats were procured and bred in the Animal House, Department of Anatomy, University of Benin, Benin City, Edo State, Nigeria. The rats were acclimatized for 2 weeks before the commencement of the experiment and the animals were fed Top feeds grower mash and clean water. The study was approved by the Research Ethical Committee of the College of Medical Sciences, University of Benin with the approval number CMS/REC/2023/339.

Experimental Design: Thirty (30) adult Wistar rats weighing between 110 g and 200 g were randomly assigned into six (6) groups of five (5) rats each. Group A – Control; Group B - 10 mg/kg As_2O_3 only; Group C - 190 mg/kg body weight of *Zingiber officinale* stem extract and 10 mg/kg As_2O_3; Group D - 380 mg/kg body weight of *Zingiber officinale* stem extract and 10 mg/kg As_2O_3; Group E - 50 mg/kg body weight of standard drug (silymarin) and 10 mg/kg As_2O_3. Group F - 380 mg/kg body weight of *Zingiber officinale* stem extract. The administration lasted for 28 days and was done orally using an orogastric tube.

Sample collection: At the end of the treatment period (28 days), the rats were weighed and then sacrificed under chloroform anaethesia. Blood samples were collected into EDTA anticoagulant sample bottles for biochemical analysis and the kidney was harvested and immediately fixed on 10% formalin to avoid autolysis and used for histopathological evaluation.

Biochemical analysis: Creatinine and urea concentration assessment was carried out as

previously described by Higgins (2016); Calcium and Potassium electrolytes were assayed as previously described by Gounden (2018). Evaluation of antioxidant activity was carried out as previously described; Malondialdehyde (MDA) [Buege and Aust, 1978]; glutathione (GSH) [Nyman 1959]; Superoxide dismutase (SOD) [Misra and Fridovich 1972].

Histological Assessments: The harvested kidney tissues were processed and routinely stained using hematoxylin and eosin, according to the method previously reported by Drury and Wallington (1980).

RESULTS

Effect of Treatment on Oxidative Stress: There was a significant decrease (p<0.05) in superoxide and glutathione levels and a corresponding significant increase (p<0.05) in malondialdehyde concentration in Arsenic trioxide-only treated rats when compared to control. However, there was a significant increase (p<0.05) in superoxide and glutathione levels and a corresponding significant decrease (p<0.05) in malondialdehyde concentration in Arsenic trioxide rats pretreated with *Zingiber officinale,* and Silymarin.

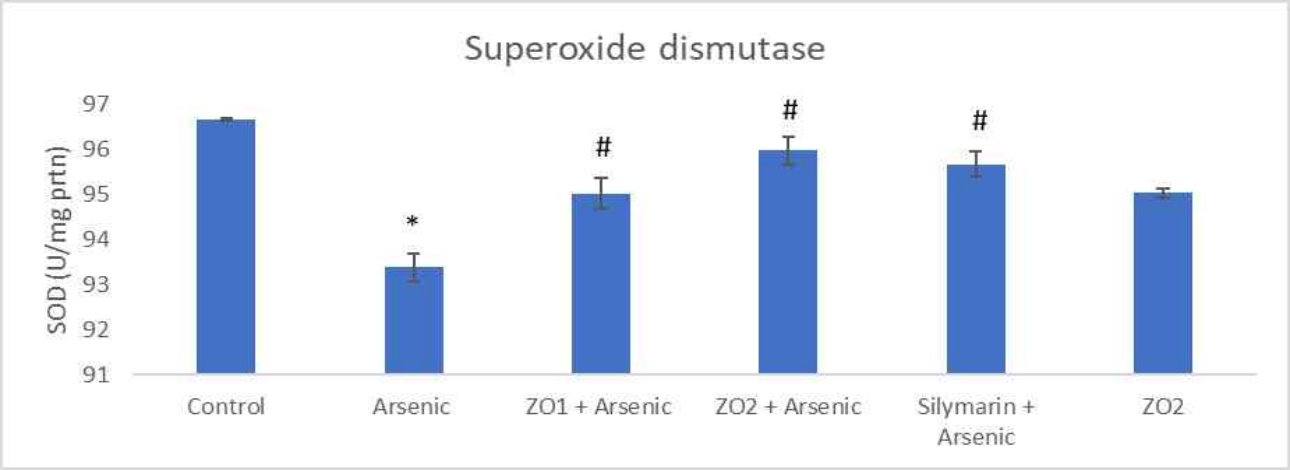

Figure 1: Chart showing Superoxide dismutase (SOD) activity across the experimental groups. Values are given as mean ± SEM. * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

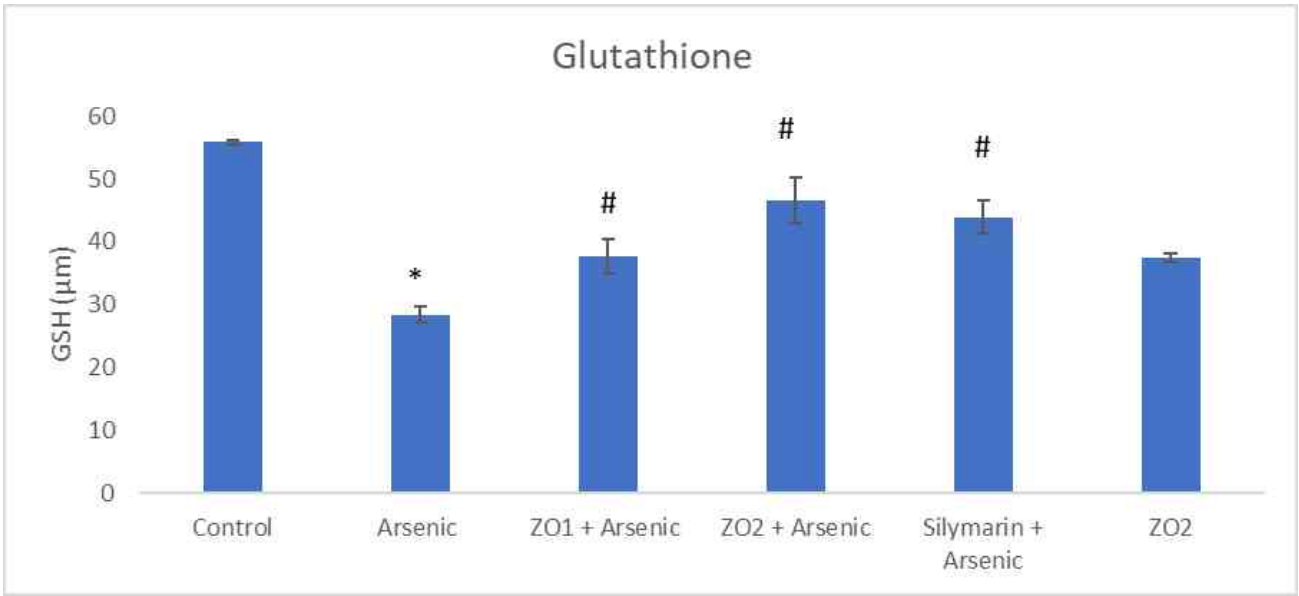

Figure 2: Chart showing Glutathione levels across the experimental groups. Values are given as mean ± SEM. * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

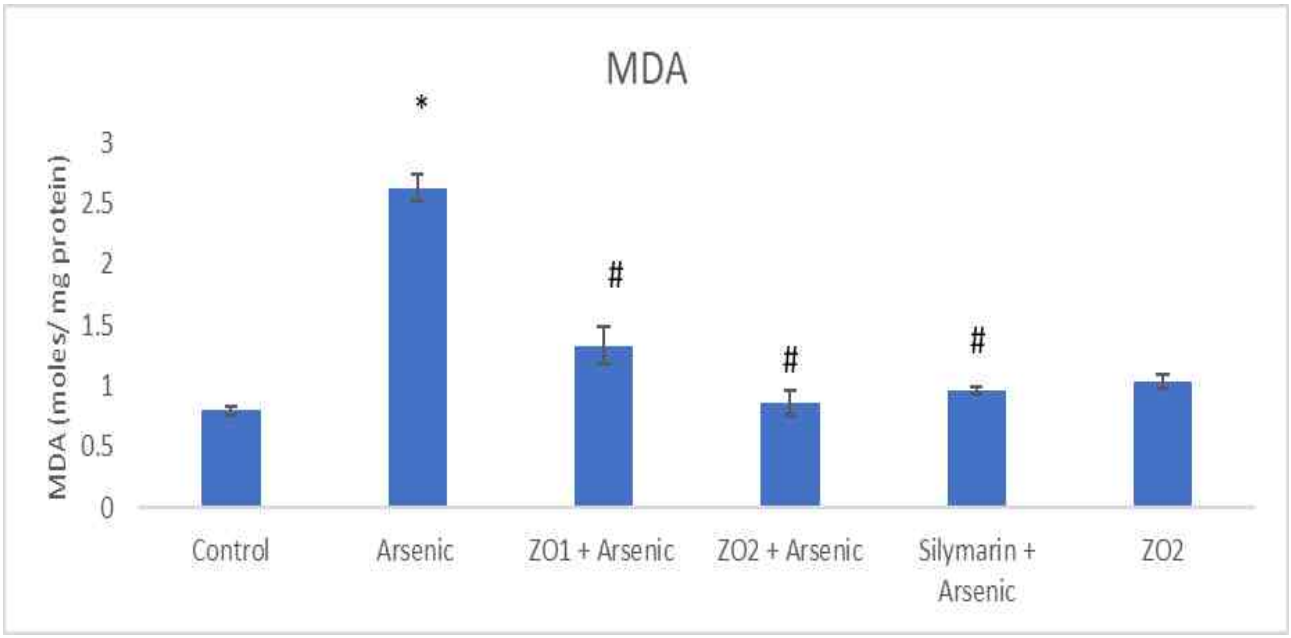

Figure 3: Chart showing Malondialdehyde concentration across the experimental groups. Values are given as mean ± SEM. * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

Effect of Treatment on Renal Function: There was a significant increase (p<0.05) in potassium, sodium, urea, and creatinine levels in Arsenic trioxide-only treated rats when compared to control. However, there was a significant decrease (p<0.05) in potassium, sodium, urea, and creatinine levels in Arsenic trioxide rats pretreated with *Zingiber officinale* and Silymarin.

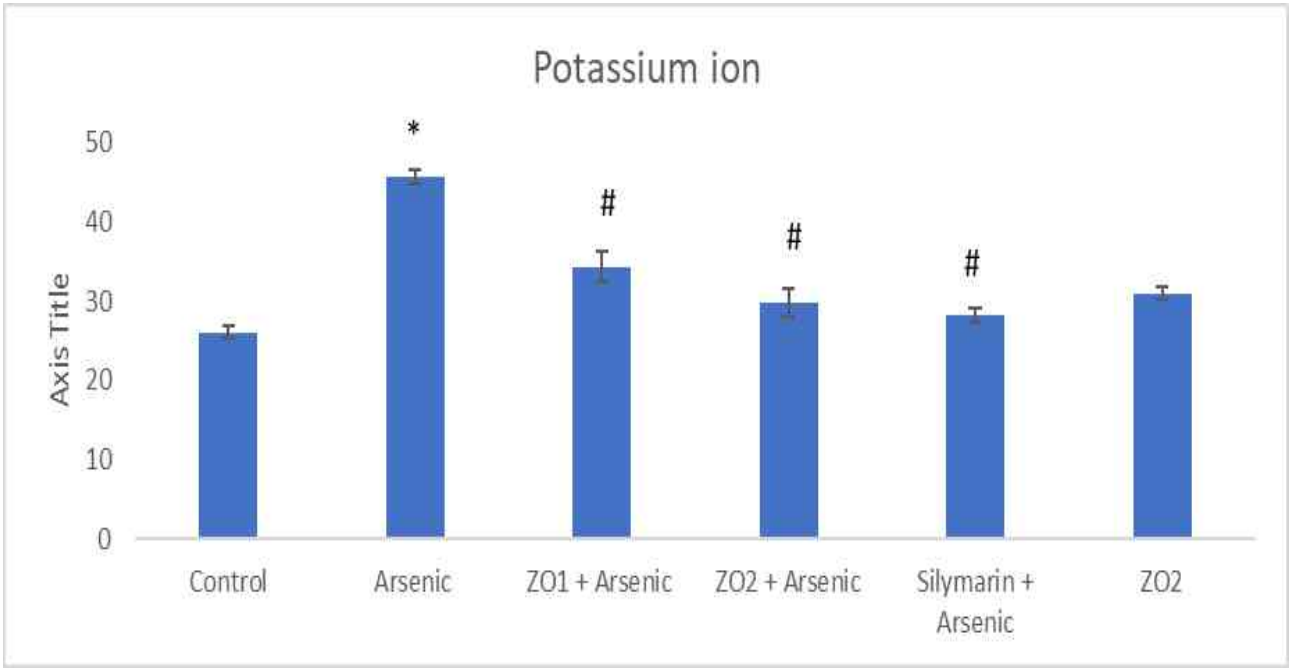

Figure 4: Chart showing Potassium ion levels across the experimental groups. Values are given as mean ± SEM. # p< 0.05 compared with the control group; * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

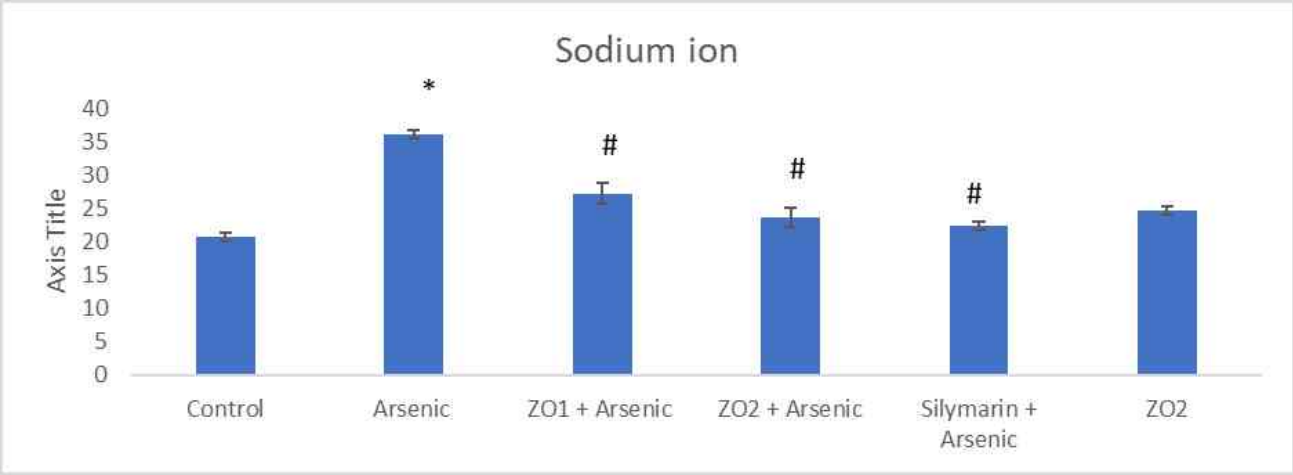

Figure 5: Chart showing Sodium ion levels across the experimental groups. Values are given as mean ± SEM. * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

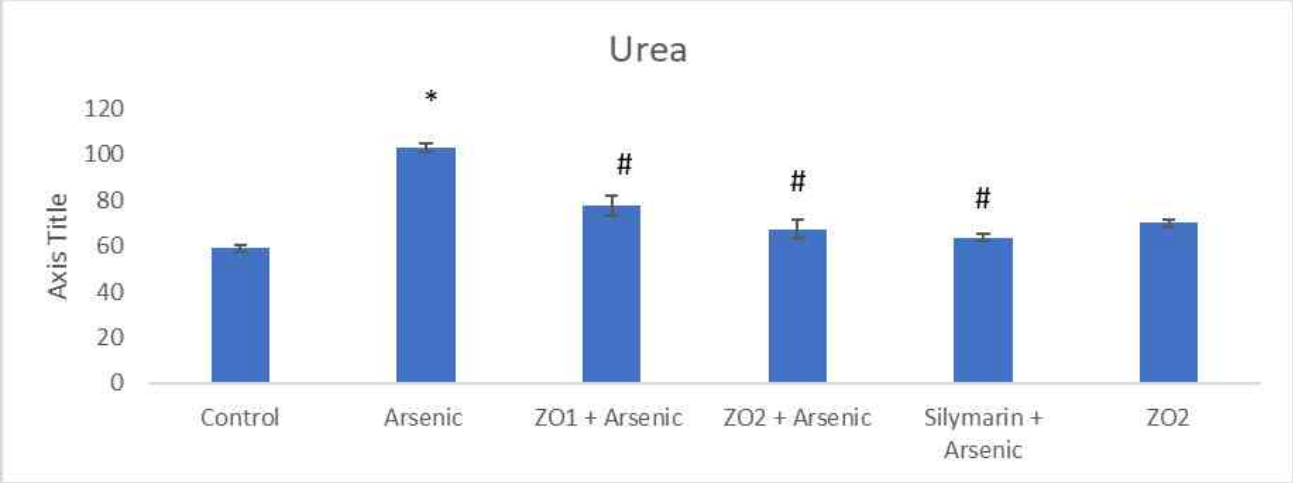

Figure 6: Chart showing Urea levels across the experimental groups. Values are given as mean ± SEM. * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

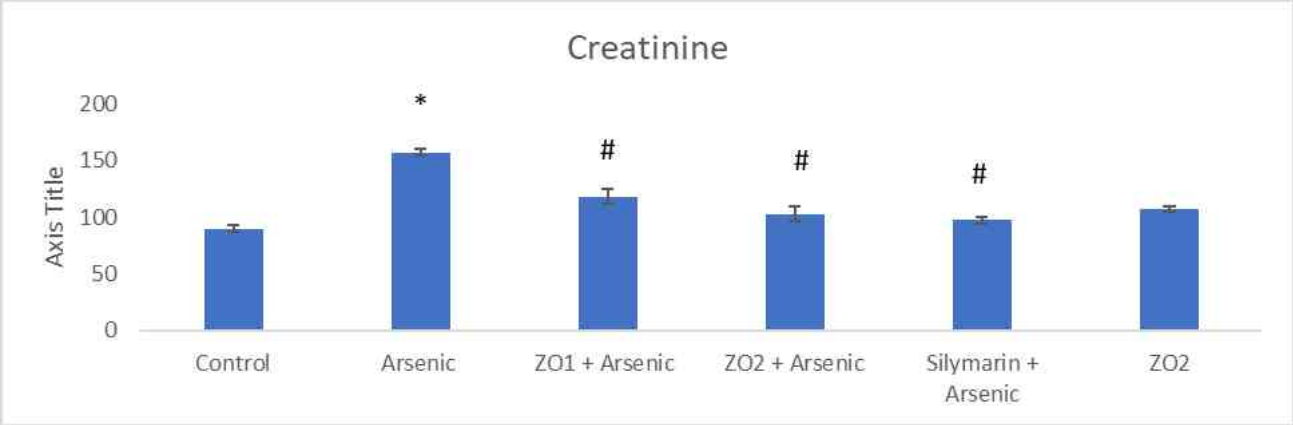

Figure 7: Chart showing Creatinine levels across the experimental groups. Values are given as mean ± SEM. * p< 0.05 compared with the control group; # p< 0.05 compared with the Arsenic only group.

Effect of Treatment on Histology:

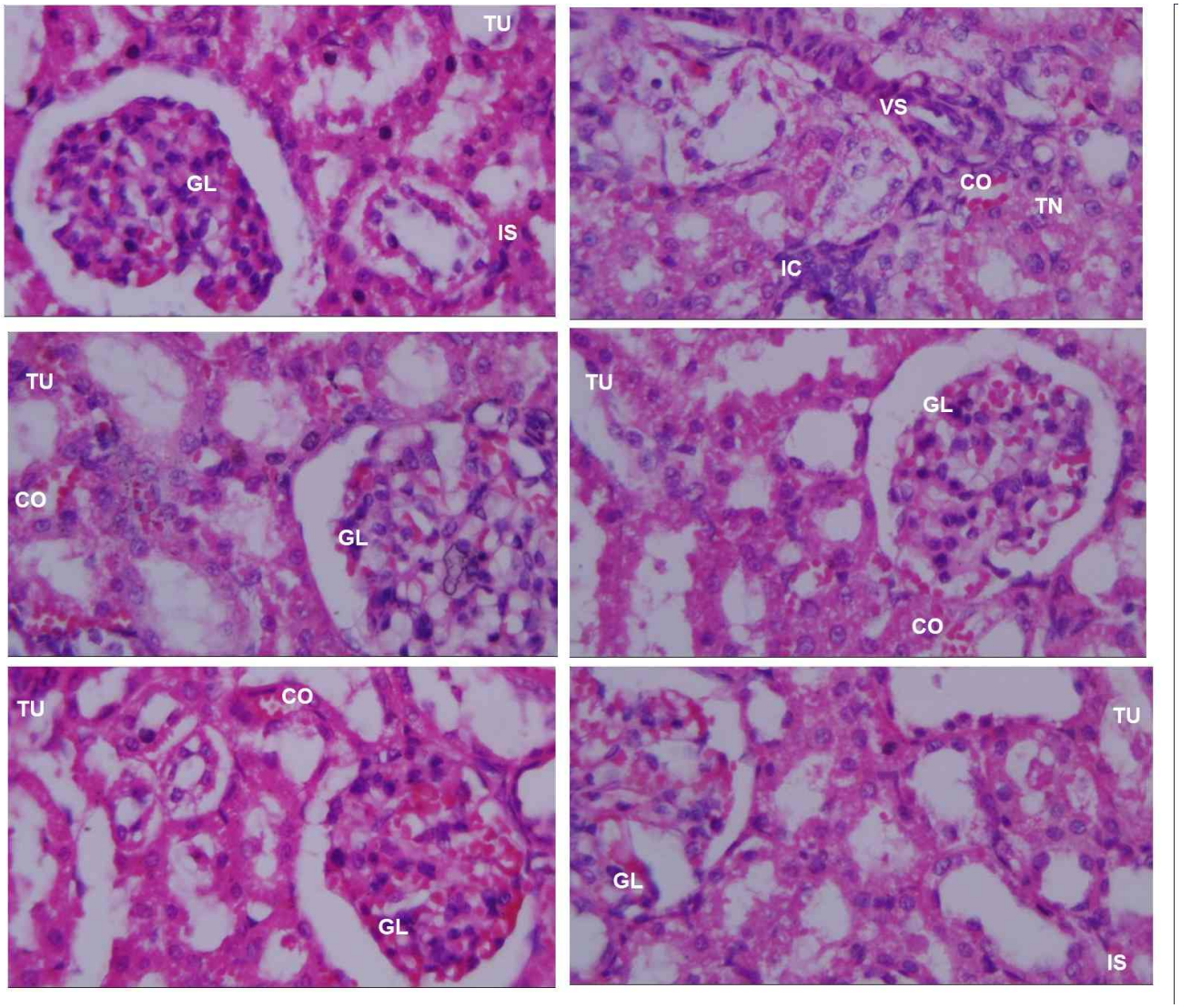

Figure 8: showing the kidney histology of **(A)** Control rats Composed of normal tissue architecture: tubules (TU), glomeruli (GL), interstitial space (IS); **(B)** Rat given 10 mg/kg body weight of Arsenic trioxide only showing: vascular stenosis (VS), interstitial congestion (CO), patchy tubular necrosis (TU), interstitial infiltrates of inflammatory cells (IC); **(C)** Rat given 190 mg/kg Zingiber officinale + 10 mg/kg body weight of Arsenic trioxide showing; normal architecture: tubules (TU), active interstitial congestion (CO), glomeruli (GL); **(D)** Rat kidney given 380 mg/kg of Zingiber officinale + 10 mg/kg body weight of Arsenic trioxide showing normal architecture: active interstitial congestion (CO), tubules (TU), glomeruli (GL); **(E)** Rat given 50 mg/kg of Silymarin + 10 mg/kg body weight of Arsenic trioxide showing: normal architecture: tubules (TU), active interstitial congestion (CO), glomeruli (GL); **(F)** Rat kidney given 380 mg/kg of Zingiber officinale only showing: normal architecture: tubules (TU), interstitial congestion (CO), glomeruli (GL).

Discussion

Oxidative stress, a key factor in nephrotoxicity, is often induced by arsenic through the production of free radicals (Ozbek, 2012; Robles-Osorio *et al*., 2015). This stress arises from an imbalance between the generation of reactive oxygen species (ROS) and the cell's ability to repair damage and detoxify reactive molecules (Ozbek, 2012). This imbalance can result from increased ROS production, decreased antioxidant defenses, or both (Thangapandiyan *et al*., 2019). Antioxidants, including enzymes like Superoxide Dismutase (SOD) and Glutathione (GSH), play crucial roles in neutralizing free radicals and protecting cells (Krishnamurthy and Wadhwani, 2012). Malondialdehyde (MDA) is a stable marker of lipid peroxidation, indicating the levels of oxidative stress. Results from this study showed that rats exposed to Arsenic trioxide had significantly decreased SOD, and GSH with a corresponding increase in MDA concentrations following comparisons to control, thus corroborating earlier studies' reports that the nephrotoxic effects of Arsenic trioxide are mediated by oxidative stress via decreased antioxidant enzymes activity and increased lipid peroxidation (Robles-Osorio *et al*., 2015; Nahar *et al*., 2022; Zulfiqar and Ashraf, 2022). However, there was a significant increase in SOD and GSH, as well as a significant reduction in MDA levels of Arsenic trioxide exposed rats pre-treated with Ginger. This improvement in the antioxidant defense system could be attributed to the antioxidant property of *Zingiber officinale.*

Sodium, potassium, urea, and creatinine levels serve as key indicators of kidney function (Charles and Ferris, 2020). The kidneys play a vital role in regulating these substances in the body, with changes in their levels signaling potential kidney dysfunction. Sodium and potassium are electrolytes under tight kidney regulation (Ebert et al., 2021). Sodium is crucial for fluid balance, while potassium is essential for nerve and muscle function (Su et al., 2020). Abnormal levels of these electrolytes may indicate impaired kidney function. Urea is a byproduct of protein breakdown in the liver (Adeyomoye et al., 2022). The kidneys filter urea from the blood, excreting it in urine. Elevated urea levels, known as uremia, can occur in kidney disease when the kidneys fail to effectively eliminate urea (Faria and de Pinho, 2021). Increased urea levels can signal impaired kidney function. Creatinine, a waste product from muscle breakdown, is filtered by the kidneys and excreted in urine (Kreider and Stout, 2021). Elevated creatinine levels can indicate reduced kidney function, as the kidneys struggle to eliminate creatinine from the body. Creatinine levels are often used to estimate glomerular filtration rate (GFR), a key measure of kidney function (Shi et al., 2020). Results from the study showed that Arsenic trioxide exposed rats had significantly increased sodium, potassium, urea, and creatinine levels when compared to control; suggesting kidney dysfunction and impaired renal function, which are typical manifestations of nephrotoxicity. Arsenic trioxide is known to cause oxidative stress and damage to the kidneys, leading to the leakage of these electrolytes and waste products into the bloodstream. However, the significant decrease in sodium, potassium, urea, and creatinine levels in the group pre-treated with ginger suggests a protective effect against arsenic trioxide-induced nephrotoxicity. Ginger's potential nephroprotective properties, as indicated by the improvement in these markers, could be attributed to its antioxidant and anti-inflammatory properties.

Histological findings from this study suggest that arsenic trioxide induces severe kidney damage, as evidenced by vascular stenosis, tubular necrosis, and inflammatory cell infiltrates in the group exposed to arsenic trioxide only. Previous studies have reported arsenic trioxide's induction of severe kidney damage (Zheng *et al*., 2015; Orr and Bridges, 2017). However, findings from this study showed that pre-treatment with *Zingiber officinale* appears to protect against these detrimental effects, preserving normal kidney architecture. These results indicate the potential of *Zingiber officinale* as a nephroprotective agent against arsenic trioxide-induced nephrotoxicity.

Conclusion

Findings from this study demonstrate that *Zingiber officinale* possesses a protective effect against arsenic trioxide-induced nephrotoxicity, possibly through its antioxidant, anti-inflammatory, and reno-protective properties.

Recommendation

We recommend further research is warranted to elucidate the underlying mechanisms and to explore the potential clinical applications of *Zingiber officinale* as a nephroprotective agent.

Conflict of Interest

The authors declare no conflict of interest.

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