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**Aqueous Rhizome Extract of *Zingiber officinale*: Assessing its Efficacy Against Arsenic-Induced Liver Damage in Wistar Rats.**

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<https://dx.doi.org/10.4314/sokjmls.v9i2.30>**Abstract**

The liver is especially vulnerable to toxins due to its role in metabolizing and clearing chemicals. Heavy metals like arsenic, found in contaminated water, food, and industrial processes, are well-documented hepatotoxic agents. Traditionally, medicinal plants like *Zingiber officinale* have been used to treat liver ailments. Known for its gastroprotective and hepatoprotective effects, *Zingiber officinale*, with its safety profile and ability to mitigate oxidative stress, is a promising candidate for preventing and treating hepatotoxicity. The aim of this study was to assess the effect of *Zingiber officinale* against arsenic trioxide-induced hepatotoxicity in Wistar rats. Thirty adult Wistar rats were randomly assigned into six groups (A-F). Group A served as control; Group B - 10 mg/kg As<sub>2</sub>O<sub>3</sub> only; Group C - 190 mg/kg body weight of *Zingiber officinale* stem extract and 10 mg/kg As<sub>2</sub>O<sub>3</sub>; Group D - 380 mg/kg body weight of *Zingiber officinale* stem extract and 10 mg/kg As<sub>2</sub>O<sub>3</sub>; Group E - 50 mg/kg body weight of standard drug (silymarin) and 10 mg/kg As<sub>2</sub>O<sub>3</sub>. Group F - 380 mg/kg body weight of *Zingiber officinale* stem extract. The administration lasted 28 days. Afterwards, the animals were anesthetized and sacrificed, and samples were taken for oxidative stress -related parameters, liver 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 ALT, AST, and total bilirubin, indicating liver damage. Histological analysis showed severe liver damage evidenced by vasodilation and congestion, zonal necrosis, and periportal infiltrates of inflammatory cells. 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 architecture with relatively normal liver histology. In conclusion, these findings suggest that *Zingiber officinale* possesses a protective effect against arsenic trioxide-induced hepatotoxicity, possibly through its antioxidant, anti-inflammatory, and hepatoprotective properties.

**Keywords:** *Liver, Hepatotoxicity, Arsenic trioxide, Zingiber officinale, Wistar rat.*

**Introduction**

Hepatotoxicity refers to liver damage caused by chemical substances. The liver, being a central organ for detoxification, is particularly vulnerable to toxins due to its role in metabolising and clearing chemicals from the body (Hinton *et al.*, 2017). When hepatotoxic substances are processed, they can cause cellular damage, leading to conditions such as hepatitis, fibrosis, and even liver failure (Abou Seif, 2016; Mohi-Ud-Din *et al.*, 2019; Berumen *et al.*, 2021). Symptoms of liver toxicity include jaundice, abdominal pain, fatigue, and elevated liver enzymes as measured by blood tests (Sivakrishnan and Pharm, 2019). Heavy metals, including arsenic, are well-documented hepatotoxic agents. Arsenic, in particular, can be found in contaminated water, certain foods, and industrial processes (Singh *et al.*, 2015). It is metabolized in the liver (Meyer *et al.*, 2014), producing reactive oxygen species and other intermediates that induce oxidative stress, leading to cellular damage and apoptosis (Hu *et al.*, 2020). Prolonged exposure to arsenic can

lead to chronic liver diseases, including cancer (Hu *et al.*, 2020; Palma-Lara *et al.*, 2020). The widespread issue of arsenic contamination in water supplies, especially in Lower-middle-income countries, has led to significant public health concern. Chronic arsenic exposure necessitates effective treatments to mitigate the risk and treat established liver damage. Medicinal plants have been used traditionally in various cultures to treat liver ailments (Muluye and Ayicheh, 2020). The rationale behind their use includes their antioxidant, anti-inflammatory, and immunomodulatory properties, which can protect against oxidative stress and assist in liver regeneration. *Zingiber officinale* is one such medicinal plant known for its gastroprotective and hepatoprotective effects (Yassin *et al.*, 2010). The rhizome of the *Zingiber officinale* plant contains bioactive compounds such as gingerols and shogaols (Yeh *et al.*, 2014; Mao *et al.*, 2019). These compounds have shown potential in neutralising ROS, modulating detoxification enzymes, and inhibiting inflammatory cytokines (Yassin *et al.*, 2010; Zhang and Tsao, 2016). Thus, *Zingiber officinale* holds promise as a protective and therapeutic agent in the context of liver diseases induced by heavy metals, including arsenic-induced hepatotoxicity. Considering its safety profile and the potential for mitigating oxidative stress, ginger is an attractive candidate for further research regarding its efficacy in the prevention and treatment of hepatotoxicity.

## Materials and Methods

**Plant Extract:** Fresh *Zingiber officinale* stems were obtained from a local farm and samples were taken to the herbarium (UBH-Z384) at the Department of Plant Biology and Biotechnology, University of Benin, Nigeria, for identification. The *Zingiber officinale* was thoroughly washed and cleaned after meticulously sorting to remove any damaged stems. To remove moisture, the *Zingiber officinale* was air-dried. Next, the dried *Zingiber officinale* was ground into a fine powder using a mechanical grinder. They then weighed 500 grams of the powder precisely using an electronic weighing balance and placed it in a one-litre beaker. Following the established procedure outlined by Joseph *et al.* (2010), the ground *Zingiber officinale* was prepared for aqueous extraction.

**Experimental Animals:** This study utilized Wistar rats obtained and bred within the Department of Anatomy's Animal House facilities at the University of Benin, Benin City, Edo State, Nigeria. A two-week acclimatization period was observed before the commencement of the experiment, during which the rats were fed Top feeds grower mash and had access to clean water. Approval for the study was granted by the Research Ethical Committee of the College of Medical Sciences, University of Benin, under reference number CMS/REC/2023/340.

**Experimental Design:** Thirty (30) adult Wistar rats weighing between 140 g and 196 g were randomly assigned into six (6) groups of five (5) rats each.

**Group A** Control Group.

**Group B** 10 mg/kg  $As_2O_3$  only.

**Group C** 190 mg/kg body weight of *Zingiber officinale* and 10 mg/kg  $As_2O_3$ .

**Group D** 380 mg/kg body weight of *Zingiber officinale* 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:** Following the 28-day treatment period, the rats were weighed and euthanized under chloroform anaesthesia. Blood samples were collected in EDTA anticoagulant sample bottles for biochemical analysis. The liver was harvested and promptly fixed in 10% formalin to prevent autolysis. Antioxidant enzyme activity, Liver enzyme function and Histological assessments were carried out.

**Biochemical analysis:** 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]. The liver function assessment was carried out as previously described by Lala *et al.* (2023).

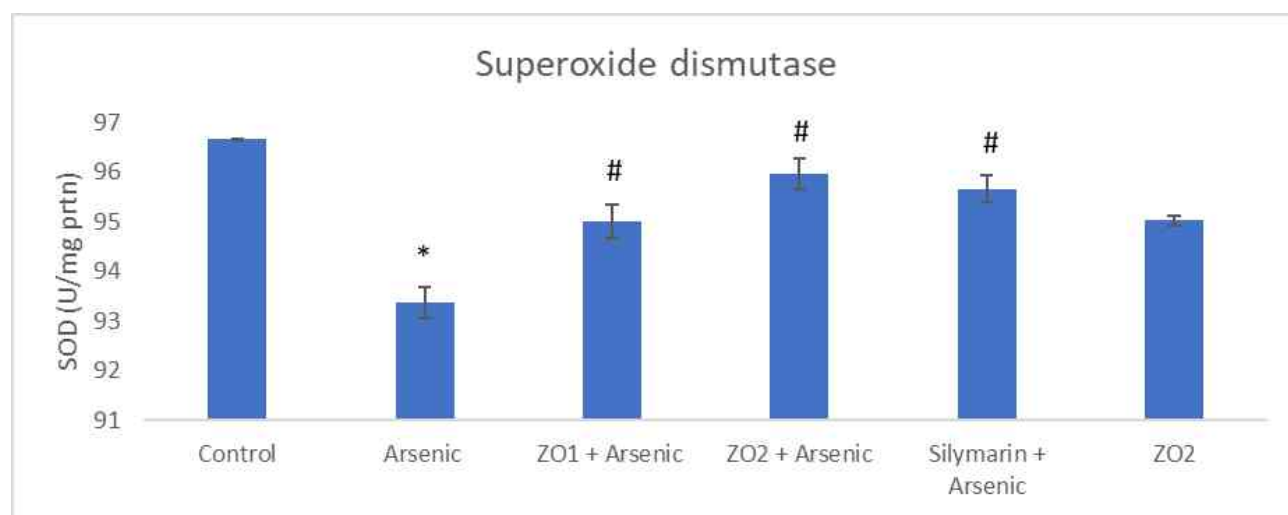
**Histological Assessments:** The harvested liver tissues were processed and routinely stained

using hematoxylin and eosin, according to the method previously reported by Drury and Wallington (1980).

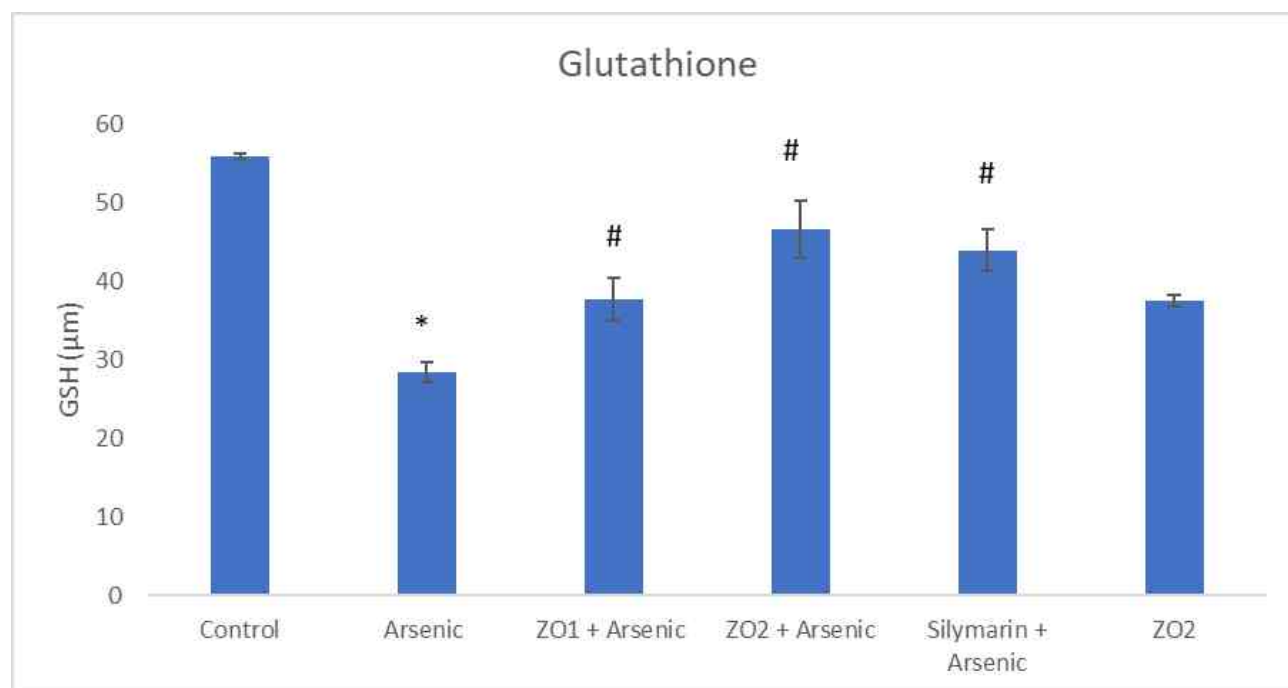
**Results**

**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

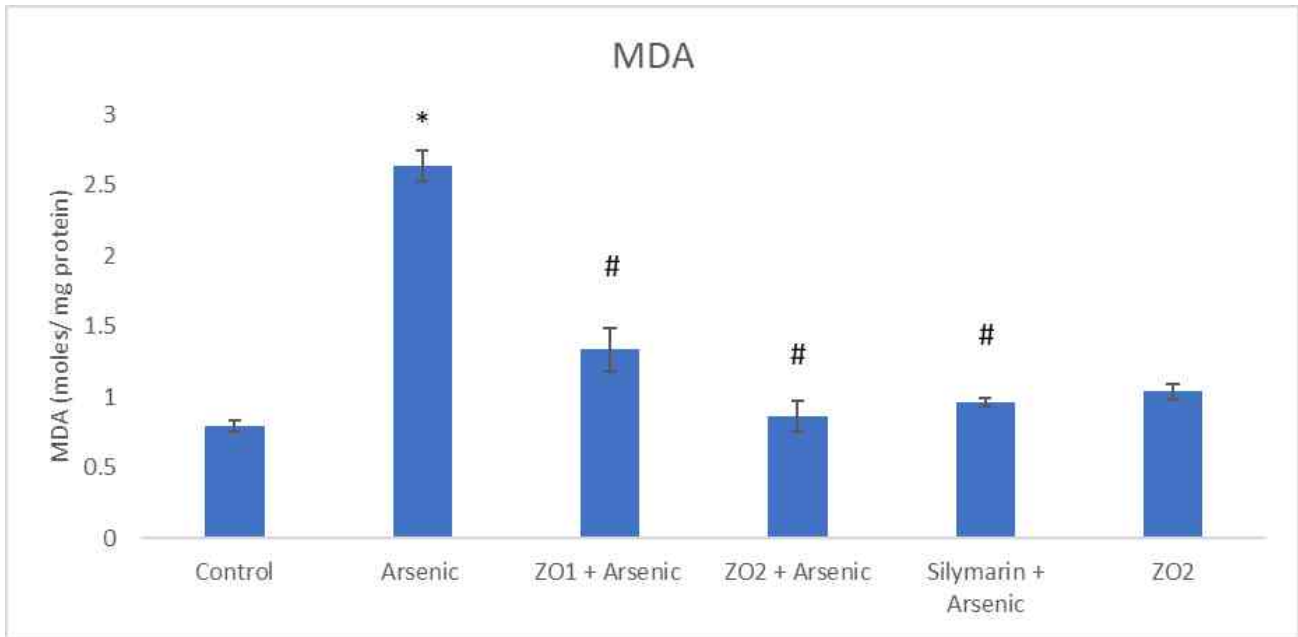
malondialdehyde concentration in Arsenic trioxide-only treated rats when compared to control. However, there was a significant increase ( $p < 0.05$ ) in superoxide and glutathione levels and a corresponding significant decrease ( $p < 0.05$ ) in malondialdehyde concentration in Arsenic trioxide rats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



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



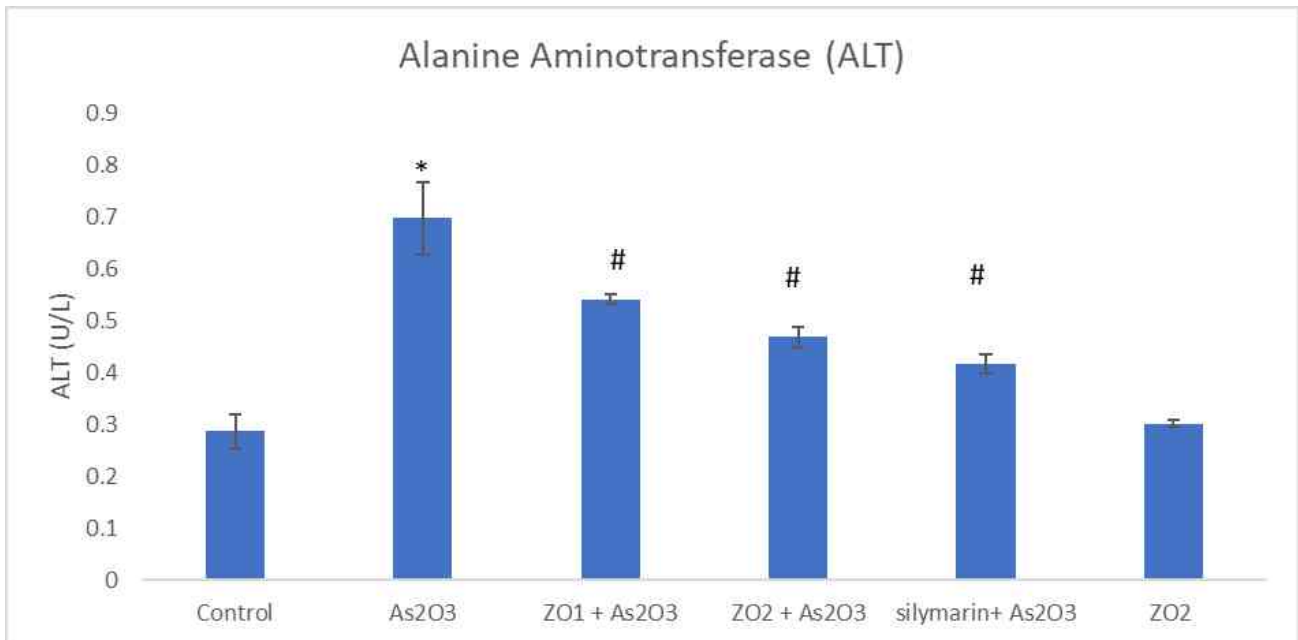
**Figure 2:** Chart showing Glutathione levels across the experimental groups. Values are given as mean  $\pm$  SEM. \*  $p < 0.05$  compared with the control group; #  $p < 0.05$  compared with the Arsenic only group.



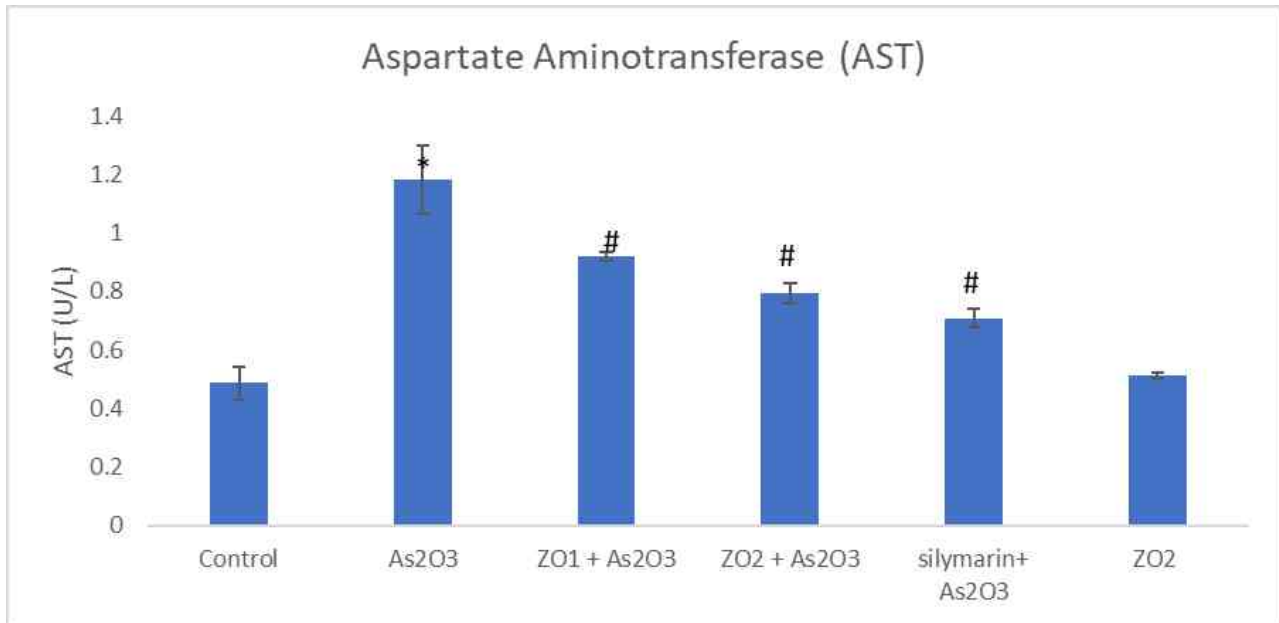
**Figure 3:** Chart showing Malondialdehyde concentration across the experimental groups. Values are given as mean  $\pm$  SEM. \*  $p < 0.05$  compared with the control group; #  $p < 0.05$  compared with the Arsenic only group.

**Effect of Treatment on Liver Function:** There was a significant increase ( $p < 0.05$ ) in ALT, AST, albumin, total bilirubin, and total protein levels in Arsenic trioxide-only treated rats when compared to control. However, there was a

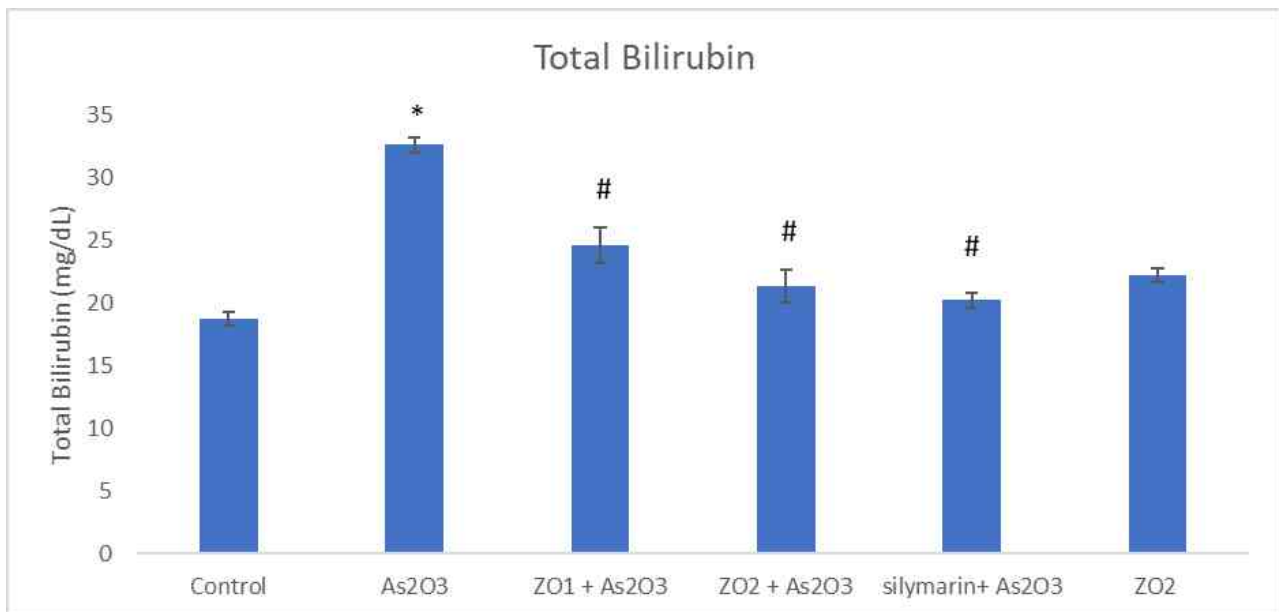
significant decrease ( $p < 0.05$ ) in ALT, AST, albumin, total bilirubin, and total protein levels in the Arsenic trioxide rats pretreated with *Zingiber officinale* and Silymarin.



**Figure 4:** Chart showing Alanine Aminotransferase levels across the experimental groups. Values are given as mean  $\pm$  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.

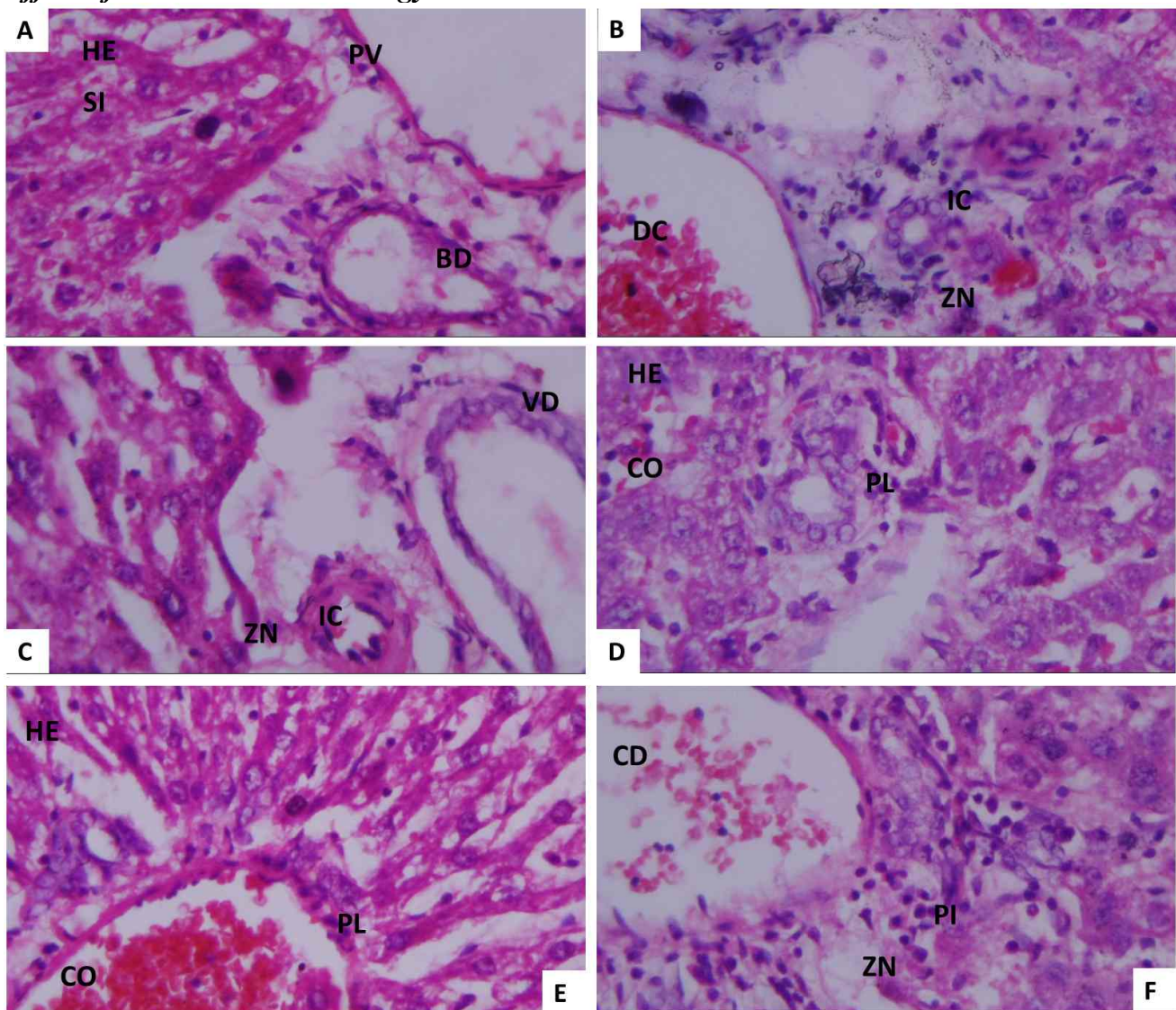


**Figure 5:** Chart showing Aspartate Aminotransferase (AST) levels across the experimental groups. Values are given as mean  $\pm$  SEM. \*  $p < 0.05$  compared with the control group; #  $p < 0.05$  compared with the Arsenic only group.



**Figure 6:** Chart showing Total bilirubin levels across the experimental groups. Values are given as mean  $\pm$  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:** Liver histology of (A) Control rats Composed of normal tissue architecture: hepatocytes (HE), sinusoids (SI), portal vein (PV), bile ducts (BD); (B) Rat given 10 mg/kg body weight of Arsenic trioxide only showing: vasodilatation and congestion (DC), zonal necrosis (ZN), periportal infiltrates of inflammatory cells (IC); (C) Rat given 190 mg/kg Zingiber officinale + 10 mg/kg body weight of Arsenic trioxide showing: vasodilatation (VD), zonal necrosis (ZN), periportal infiltrates of inflammatory cells (IC); (D) Rat kidney given 380 mg/kg of Zingiber officinale + 10 mg/kg body weight of Arsenic trioxide showing normal architecture: hepatocytes (HE), periportal lymphocyte mobilization (PL), active vascular congestion (CO); (E) Rat given 50 mg/kg of Silymarin + 10 mg/kg body weight of Arsenic trioxide showing: normal architecture: hepatocytes (HE), active portal congestion (CO), periportal lymphocyte mobilization (PL); (F) Rat kidney given 380 mg/kg of Zingiber officinale only showing: normal architecture: portal vascular congestion and dilation (CD), zonal necrosis (ZU), periportal infiltrates of inflammatory cells (PI).

## Discussion

Exposure of humans to arsenic trioxide results in its conversion to trivalent arsenic within the body. This trivalent arsenic binds to haemoglobin in the bloodstream and are subsequently transported to various organs through the circulatory system (San *et al.*, 2020). The primary site of metabolism for arsenic trioxide is the liver. However, when the liver's metabolic enzymes are insufficient or inhibited due to a high concentration of arsenic trioxide, this can lead to hepatic injury, (Hoonjan *et al.*, 2018). Therefore, the importance of developing treatment options to mitigate the adverse effects of hepatic injury cannot be overstated.

Exposure to arsenic is a well-established cause of liver damage (hepatotoxicity), and a key mechanism behind this injury is oxidative stress (Ozbek, 2012; Robles-Osorio *et al.*, 2015). Oxidative stress occurs when the body's production of harmful free radicals overwhelms its natural defenses. These free radicals can damage cells and tissues. An imbalance between the production of reactive oxygen species (ROS) and the cell's ability to detoxify and repair this damage is the root cause of oxidative stress (Ozbek, 2012). This imbalance can arise from two main factors: increased generation of ROS or decreased activity of antioxidant defenses (Thangapandiyam *et al.*, 2019). Antioxidants, such as enzymes like superoxide dismutase (SOD) and glutathione (GSH), play a critical role in neutralizing free radicals and protecting cells from oxidative damage (Krishnamurthy and Wadhvani, 2012). Measuring the levels of malondialdehyde (MDA), a stable marker of lipid peroxidation, allows for the assessment of the extent of oxidative stress.

Results from this study showed that rats exposed to arsenic trioxide had significantly decreased SOD, and GSH with a corresponding significant increase in MDA concentrations following comparisons to control, thus corroborating earlier studies' reports that the hepatotoxic effects of Arsenic trioxide are mediated by oxidative stress via decreased antioxidant enzymes activity and increased lipid peroxidation (Prakash and Kumar, 2016; Dugo *et al.*, 2017; Ahmad *et al.*, 2020).

However, there was a significant increase in SOD and GSH, as well as a significant reduction in MDA levels of Arsenic trioxide exposed rats pretreated with *Zingiber officinale*. This improvement in the antioxidant defense system could be attributed to the antioxidant property of *Zingiber officinale*. *Zingiber officinale* is renowned for its rich array of bioactive compounds, including gingerol, paradol, and shogaol, which have been extensively studied for their antioxidant properties (Yeh *et al.*, 2014; Mao *et al.*, 2019; Van *et al.*, 2024). These compounds possess the ability to scavenge free radicals and inhibit oxidative stress, thereby fortifying the body's natural defense mechanisms against oxidative damage.

Liver enzymes play a crucial role in maintaining overall health by participating in various metabolic processes essential for the body's proper functioning (Jackson, 2017). Their activity levels serve as critical indicators of liver function (Contreras-Zentella and Hernández-Muñoz, 2016). Arsenic trioxide induces hepatotoxicity by disrupting liver function, affecting key biomarkers such as ALT, AST, albumin, bilirubin, and protein (Ozoani *et al.*, 2024). ALT and AST, primarily found in liver cells, play roles in amino acid metabolism (Ndrepepa, 2021). Exposure to arsenic trioxide can cause liver cell damage, releasing ALT and AST into the bloodstream (Liu *et al.*, 2021). Elevated levels of these enzymes in the blood indicate liver cell injury, a hallmark of hepatotoxicity. Arsenic trioxide can also interfere with bilirubin metabolism and excretion by the liver, leading to an accumulation of bilirubin in the blood (Creeden *et al.*, 2021). Elevated levels of total bilirubin can result in jaundice, a common symptom of liver dysfunction (Fargo *et al.*, 2017).

This study showed that arsenic trioxide significantly increased the activity levels of key liver enzymes, including ALT, AST, and total bilirubin, in rats exposed to arsenic trioxide only when compared to control. These elevated enzyme levels often indicate liver injury, suggesting that arsenic trioxide exposure disrupts the liver's normal functioning (Contreras-Zentella and Hernández-Muñoz,



2016). However, there was a significant decrease in the enzyme activity levels of Arsenic trioxide rats pre-treated with *Zingiber officinale* when compared to arsenic trioxide-only. *Zingiber officinale* has been reported to possess potent properties that may stimulate the activity of detoxification enzymes (Ahd *et al.*, 2019; Akbari *et al.*, 2019), aiding in the elimination of arsenic trioxide.

The histological assessment of liver tissues from the different treatment groups revealed varying degrees of liver damage and protection, illustrating the effects of arsenic trioxide and the protective properties of *Zingiber officinale*. Rats administered 10 mg/kg body weight of arsenic trioxide exhibited significant liver damage, characterized by vasodilatation and congestion, zonal necrosis, and periportal infiltrates of inflammatory cells. Arsenic trioxide is widely recognized for its hepatotoxic properties, causing extensive liver damage primarily through oxidative stress and inflammation (Ozbek, 2012; Robles-Osorio *et al.*, 2015). This aligns with numerous studies that have highlighted arsenic's ability to generate reactive oxygen species (ROS), which disrupt cellular function and induce liver toxicity. The mechanisms underlying arsenic trioxide's hepatotoxicity include ROS generation, mitochondrial dysfunction, and the induction of apoptosis, all of which contribute to significant liver damage (Wang *et al.*, 2019; Renu *et al.*, 2020; Prakash *et al.*, 2022).

However, Arsenic trioxide-exposed rats pre-treated with *Zingiber officinale* showed significant amelioration of arsenic-induced liver damage. At a dose of 190 mg/kg, *Zingiber officinale* showed some pathological changes, including vasodilatation, zonal necrosis, and periportal infiltration of inflammatory cells, but these were less severe compared to the arsenic trioxide-only group. This suggests that *Zingiber officinale* at 190 mg/kg provides partial hepatoprotection against arsenic-induced damage, likely due to its antioxidant properties. Previous studies support ginger's role in mitigating oxidative stress and inflammation in various models of toxicity (). At a higher dose of 380 mg/kg, *Zingiber officinale* significantly

ameliorated arsenic-induced liver damage, indicating a dose-dependent protective effect. This was evident from the normal liver architecture observed, including well-preserved hepatocytes, periportal lymphocyte mobilization, and active vascular congestion. These findings suggest that the bioactive compounds in ginger are effective in higher concentrations for combating arsenic toxicity. Prior studies have demonstrated *Zingiber officinale*'s potential to mitigate liver damage caused by various toxins (Askari *et al.*, 2020; Alsahli *et al.*, 2021), with its bioactive components such as gingerols and shogaols exhibiting strong antioxidant and anti-inflammatory activities (Yeh *et al.*, 2014; Mao *et al.*, 2019; Van *et al.*, 2024), consistent with the protective effects observed in this study.

### 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 hepatoprotective agent.

### Conflict of Interest

The authors declare no conflict of interest.

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