International Journal of Zoology and Applied Biosciences
Volume 10, Issue 6, pp: 285-292, 2025
https://doi.org/10.55126/ijzab.2025.v10.i06.033
ISSN: 2455-9571
http://www.ijzab.com
Research Article

# AMELIORATIVE EFFECT OF *VITIS VINIFERA* L. EXTRACT AGAINST ALCOHOL INDUCED RENAL OXIDATIVE STRESS IN MALE ALBINO RATS

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**Article History:** Received 11th September 2025; Accepted 26th October 2025; Published 4th November 2025

## ABSTRACT

This study was conducted to assess the efficacy of successive *Vitis vinifera* extract in mitigating nephrotoxicity induced by alcohol in rats. The assessment involved examining kidney antioxidant levels and renal damage markers. Rats were categorized into four groups (n = 6 per group): normal control (NC), *Vitis vinifera* treated (Vvt.t), alcohol treated (Al.t), and alcohol plus *Vitis vinifera* treated (Al.t + Vvt.t). The alcohol-treated group received *Vitis vinifera* for 30 days, and renal antioxidant enzymes were analyzed. Results showed a significant reduction ($P < .001$) in renal antioxidant enzymes such as Superoxide dismutase, Catalase, Glutathione peroxidase, Glutathione, in the alcohol-treated group, while malondialdehyde levels and creatinine, urea, and uric acid levels were elevated. However, supplementation of *Vitis vinifera* extract to the alcohol-treated rats reversed these effects, bringing the antioxidant levels and renal markers back to normal. The study suggests that *Vitis vinifera* extract can help alleviate alcohol-induced nephrotoxicity, making it a potential regular nutrient for protecting renal cells.

**Keywords:** Alcohol, *Vitis vinifera*, Antioxidant enzymes, MDA, Urea, Creatinine.

## INTRODUCTION

Alcohol-related disorders present significant health challenges with widespread medical, social, and economic impacts. Prolonged alcohol consumption can lead to severe health issues such as alcoholic fatty liver, hyperglyceridemia, cirrhosis, cardiovascular disease, and pancreatitis (Sivaraj *et al*., 2010) inflammation. While the liver is the main organ involved in alcohol metabolism, other tissues like the kidney may also play a role in processing alcohol (Sekar *et al*., 2024). Free radicals are unstable chemical species characterized by the presence of one or more unpaired electrons, making them prone to causing damage to other molecules by extracting electrons from them in order to achieve stability. Reactive Oxygen Species (ROS), including superoxide anion, hydroxyl radical, and hydrogen peroxide, are highly reactive and potentially harmful transient chemical species formed in the body. These ROS play vital roles in energy supply, detoxification, chemical signaling, and immune function. The production of ROS in the human body is a continuous process regulated by endogenous enzymes like superoxide dismutase, glutathione peroxidase, and catalase. However, excessive ROS production, either due to external oxidant exposure or a failure in enzyme regulatory mechanisms, can lead to damage to cellular structures, DNA, lipids, and proteins. (Ahmed *et al*., 2000, Ajith *et al*., 2007). In rats exposed to alcohol, the oxidation of alcohol in the kidneys is enhanced, indicating a potential role of acetaldehyde in the harmful effects of alcohol on kidney health. Chronic

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alcohol intake can elevate blood pressure, increasing the risk of kidney damage (Heidland *et al*., 1985). Furthermore, the production of reactive oxygen species (ROS), partly stemming from acetaldehyde metabolism, may contribute to oxidative stress within kidney tissues (Rodrigo *et al*., 1988). Oxidative stress and ROS-induced toxicity are believed to be key mechanisms underlying the structural changes observed in the kidneys due to alcohol consumption (Rodrigo *et al*., 2002) and are crucial in the development of alcohol-related diseases (Zima *et al*., 2001).

Research on plants has seen a surge globally, with a significant focus on the potential of medicinal plants utilized in traditional systems. *Vitis vinifera* (Linn.), a member of the Vitaceae family, is a popular fruit crop worldwide. Red Grape Seed Extract (RGSE) is abundant in polyphenols, anthocyanins, and proanthocyanins, commonly present in red wine and grapes. These compounds exhibit various biological activities, such as anti-inflammatory, cardioprotective, and anticancer properties (Zhihao *et al*., 2018), antidiabetic, antioxidant (Shanmuganayagam *et al*., 2012), antimicrobial (Oliveira *et al*., 2013), and anticarcinogenesis (Sharma *et al*., 2004) . According to research by Sivasankar *et al*., (2013). The extract derived from seeds has shown promise in protecting the liver from Nicotine-induced toxicity in rats. In red grapes, anthocyanins are the primary polyphenolics, while white grapes contain higher levels of flavan-3-ols, such as catchiness. The total phenolic content, which indicates the strength of dietary antioxidants, is higher in red grape varieties primarily due to the density of anthocyanins in the skin, which are absent in white grape skin. Scientists are currently focusing on understanding the health properties of these anthocyanins for human well-being, as highlighted in the work of Gross (2007). However, the nephroprotective effect of *Vitis vinifera* extract against alcohol-induced toxicity is not yet studied fully. Hence, in the present study we made an attempt to explore the nephro-protective effect of *Vitis vinifera* extract against alcohol-induced oxidative stress. The protective effects of *Vitis vinifera* extract have been monitored by assaying the antioxidant enzymes and MDA levels in alcohol ingested rats.

## MATERIAL AND METHODS

### Experiment Animals

Male Wistar albino rats, aged 3 months and weighing between 180 to 200 grams, were acquired from the Indian Institute of Science in Bangalore, Karnataka, India. The rats were placed in clean polypropylene cages with six rats per cage and were kept in a room with a controlled temperature of 27 ± 2°C and a 12-hour light-dark cycle. They were provided with standard pellet diet (Lipton Rat Feed, Ltd., Pune, Maharashtra, India) and had access to water ad libitum throughout the entire experimental period. All experiments were conducted in compliance with CPCSEA guidelines after receiving approval from the Institutional Animal Ethics Committee.

### Chemicals

All chemicals used in the current research were of analar Grade (AR) and sourced from reputable companies, including Sigma (St. Louis, MO, USA), Fischer (Pittsburgh, PA, USA), Merck (Mumbai, India), Ranbaxy (New Delhi, India), and Qualigens (Mumbai, India).

### Preparation Of Extract

Grapes, purchased as large bunches with red berries from a nearby store in Tirupati, were determined to be of the *Vitis vinifera* variety. The grape seeds and skin were separated from the fruit, and the pulp was crushed to extract the juice. This juice was then dried in the shade, powdered, and subjected to maceration with 70% alcohol for 72 hours at room temperature. After filtration, the solvent was removed through evaporation under reduced pressure using a rotary evaporator, resulting in a dry extract that was utilized for the research.

### Experimental design

The rats were divided into four groups and treated as described below. Group 1: Normal control (NC): This group of rats received vehicle solution (2% of Tween 80). Group 2: Alcohol treatment (Al.t): Rats received alcohol orally at a dose of (2 g/kg body weight orally for 30 days. Group 3: *Vitis vinifera* treatment (Vvt): Rats received ethanolic extract of *Vitis vinifera extract* (100 mg/kg body weight orally for 30 days). Group 4: Alcohol treated + *Vitis vinifera* extract treated (Al t+Vvt): These rats received nicotine at a dose of 2 g/kg body weight by subcutaneous injection and red grape extract 100 mg/kg body weight via orogastric tube for a period of 30 days. Rats were initially given alcohol followed by oral administration of *Vitis vinifera* extract within a 5-minute interval. After 24 hours, the animals were euthanized, and kidney tissues were extracted. The tissues were rinsed with ice-cold saline, flash-frozen in liquid nitrogen, and stored at -80°C for subsequent biochemical analysis.

### Biochemical Assays

The selected antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and the content of glutathione (GSH) and MDA (lipid peroxidation) levels were estimated by employing the methods of Misra and Fridovich (1972), Aebi (1984), Flohe and Gunzler (1984), Carlberg and Mannervik (1985), Theodorus *et al*., and Ohkawa *et al*., respectively. Non-protein nitrogen constituents were determined by the methods of Patton and Crouch (1977) for urea, Fossati *et al*., (1980) for uric acid and Bartels and Bohmer (1972) for creatinine.

### Statistical Analysis

The data was analyzed using SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel software to determine the significance of both main effects (factors) and treatments, as well as their interactions. A

one-way analysis of variance (ANOVA) with Dunnett's multiple comparison test was utilized for comparison, with significance considered at $P < 0.001$.

## RESULTS AND DISCUSSION

In this study, we assessed the vital defense mechanism against oxidative stress caused by alcohol by analyzing the activities of antioxidant enzymes. Our research revealed a notable decrease in the activities of antioxidant enzymes including SOD, CAT, and GPx, as well as GSH content and MDA levels enhanced in rats subjected to alcohol treatment. Interestingly, the reduced activity of antioxidant enzymes induced by alcohol was effectively restored close to normal levels with the administration of *Vitis vinifera* extract. (Figure 1-5) The table 1 demonstrates that alcohol intake led to a notable increased in plasma creatinine, urea, and uric acid levels compared to the control group. However, when alcoholic rats were given *Vitis vinifera* extract, there was a significant decrease in these levels compared to the alcohol-only group. Interestingly, when compared to the control group, there were no significant differences in levels. Notably, treatment with *Vitis vinifera* extract restored plasma creatinine, urea, and uric acid levels to normal.

In the recent study, it was noticed a decline in SOD activity in the group treated with alcohol. Mallikarjuna *et al*. (2008) discovered that alcohol intake led to a reduction in SOD activity in the liver and kidney tissues of rats. Various research has also shown that alcohol consumption can diminish SOD activity in organs such as the liver, heart, brain, kidney, muscle, and serum (Husain *et al*., 2001). The decrease in SOD activity when exposed to alcohol could result in the accrual of O2 •, H2O2, or their byproducts. This escalation might stem from the heightened production of free radicals (Tan *et al*., 2018) and superoxide radicals, prompting the reduction in SOD activity as a response. Conversely, the introduction of *Vitis vinifera* extract to the alcohol-treated group exhibited an augmentation in SOD activity. These findings suggest that *Vitis vinifera* extract may effectively combat superoxide radicals induced by alcohol-related stress. The increase in SOD activity could be attributed to the presence of antioxidant bioactive compounds in *Vitis vinifera*. This extract contains flavonoids and phenols, two compounds recognized for their antioxidant properties which can effectively neutralize superoxide anion radicals (Weidner *et al*., 2013).

**Table 1.** Effects of *Vitis vinifera* extract on renal damage Markers of rat serum or plasma during chronic Alcohol administration.

| Renal damage markers mg/dl | Normal Control (NC) | Alcohol treated (Al.t) | *Vitis vinifera* treated (Bm.t) | Alcohol and *Vitis vinifera* treated (Al+Bm.t) |
|---|---|---|---|---|
| Albumin | 3.526±0.38 | 4.215±0.39* | 3.654± 0.51 | 3.546±0.50** |
| Creatine | 0.298±0.035 | 0.397±0.069* | 0.297±0.029 | 0.338±0.058** |
| Urea | 18.245±2.01 | 20.654±0.081* | 18.254±1.68 | 19.212±1.37** |
| Uric Acid | 1.194±0.22 | 2.014±0.33* | 1.189±0.21 | 1.542±0.24** |

Values are expressed as mean ± S.D of 6 animals. Alcoholic control is compared with normal. * Values are statistically significant at P* <0.001 when compared with normal. **Values are statistically significant at P** <0.001 when compared with Alcoholic control.

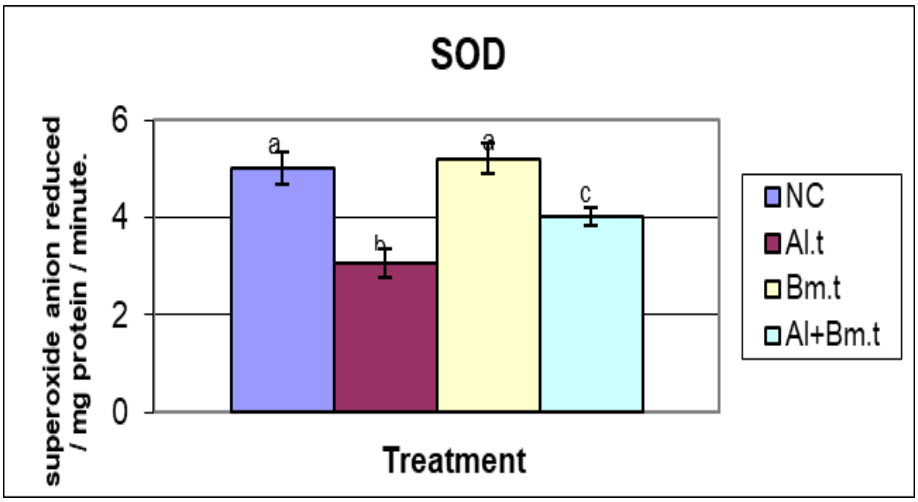


**Figure 1.** Effect of *Vitis vinifera* treatment (Vv.t), Alcohol (Al.t), and the combination (Al + Vv.t) on Kidney superoxide dismutase (SOD) activity. Values are significantly different ($^{b}P < 0.001$) compared with normal control (NC) and ($^{c}P < 0.001$) alcohol treated group.

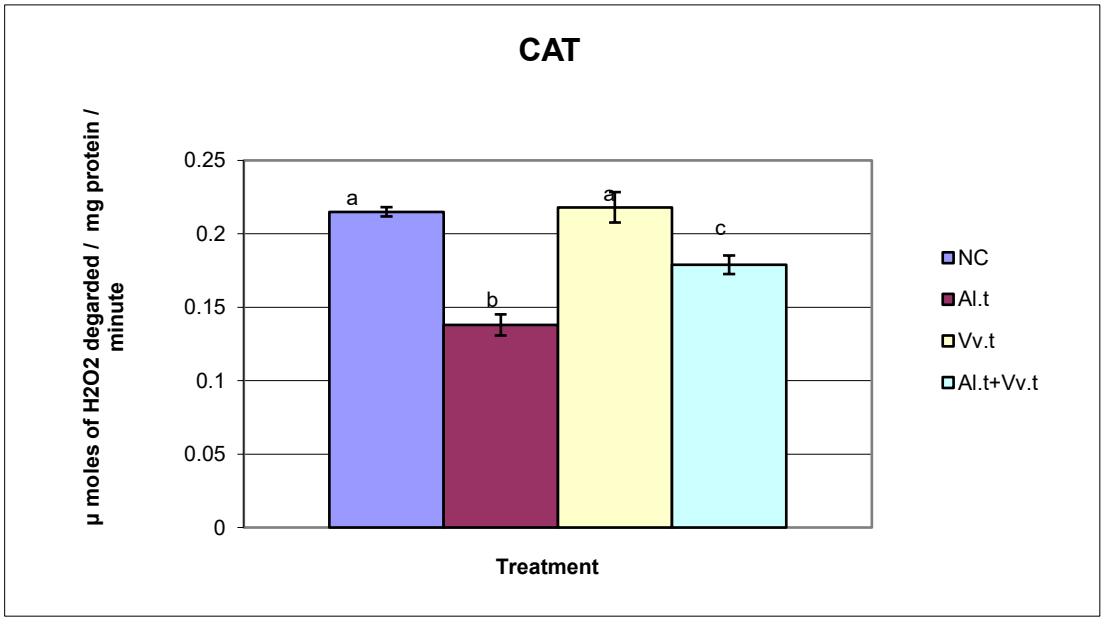


**Figure 2**. Effect of *Vitis vinifera* treatment (Vv.t), Alcohol (Al.t), and the combination (Al + Vv.t) on Kidney superoxide dismutase (SOD) activity. Values are significantly different ($^{b}P < 0.001$) compared with normal control (NC) and ($^{c}P < 0.001$) alcohol treated group.

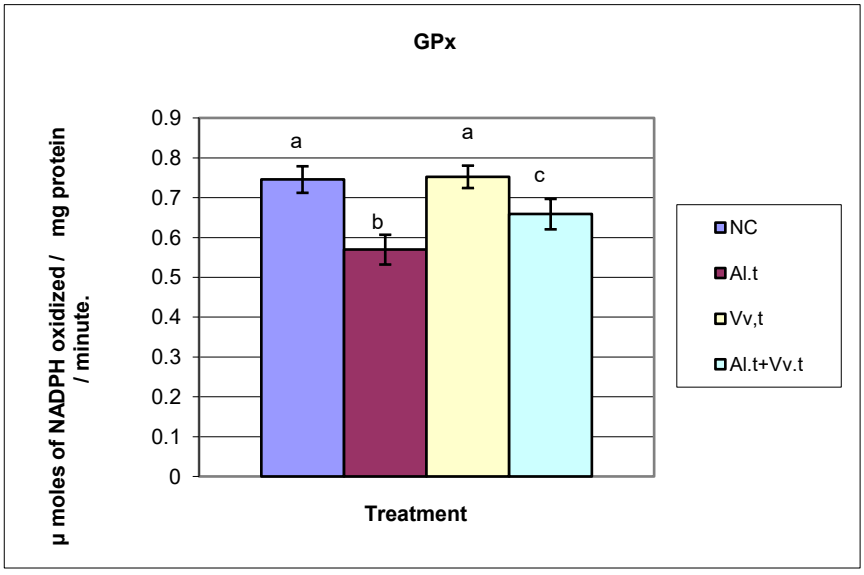


**Figure 3**. Effect of *Vitis vinifera* treatment (Vv.t), Alcohol (Al.t), and the combination (Al + Vv.t) on Kidney Glutathione peroxidase (GPx) activity. Values are significantly different ($^{b}P < 0.001$) compared with normal control (NC) and ($^{c}P < 0.001$) alcohol treated group.

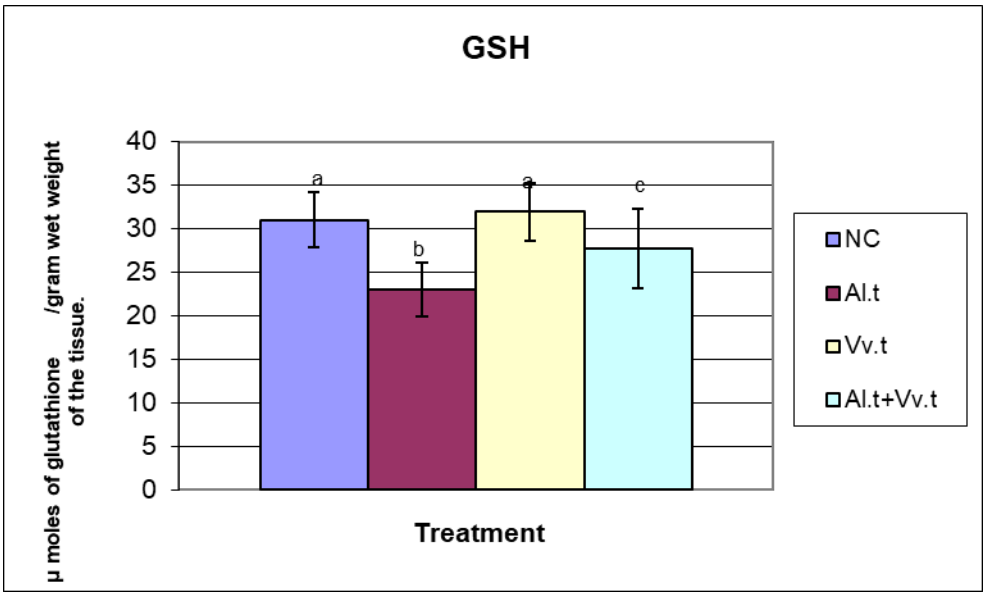


**Figure 4**. Effect of *Vitis vinifera* treatment (Vv.t), Alcohol (Al.t), and the combination (Al + Vv.t) on Kidney Glutathione level. Values are significantly different ($^{b}P < 0.001$) compared with normal control (NC) and ($^{c}P < 0.001$) alcohol treated group.

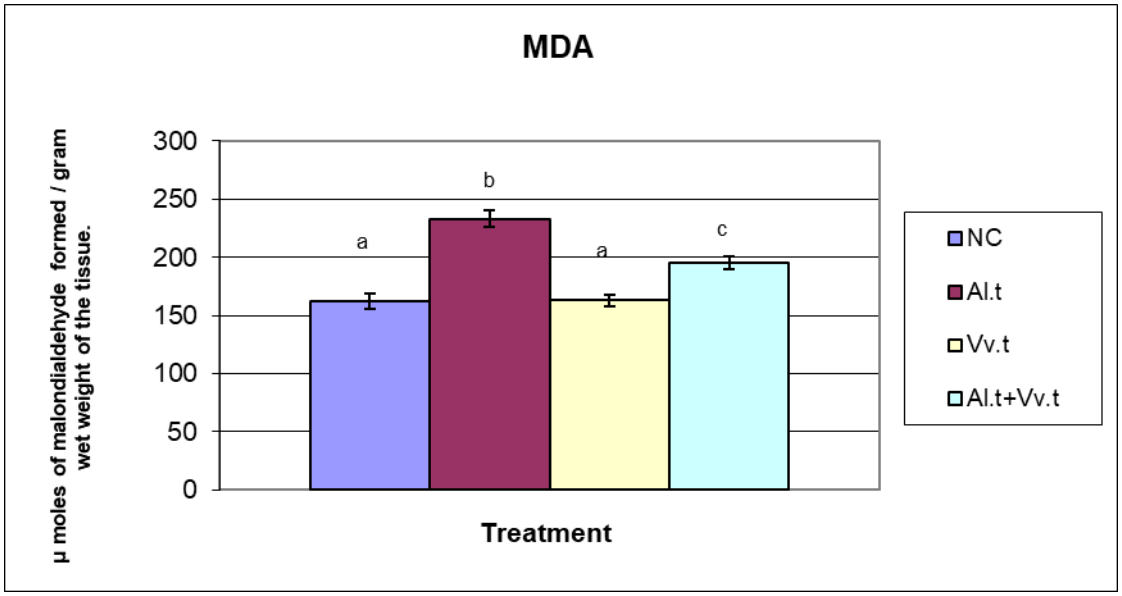


**Figure 5**. Effect of *Vitis vinifera* treatment (Vv.t), Alcohol (Al.t), and the combination (Al + Vv.t) on Kidney MDA level. Values are significantly different ($^{b}P < 0.001$) compared with normal control (NC) and ($^{c}P < 0.001$) alcohol treated group.

In this study, we found that the activity of the antioxidant enzyme catalase (CAT) was significantly reduced in rats that were exposed to alcohol compared to control rats. This decrease in CAT activity suggests that the ability to neutralize harmful hydrogen peroxide is compromised, leading to increased vulnerability to cellular damage from free radicals. The findings are consistent with previous research indicating that alcohol consumption can diminish the effectiveness of CAT (Praveen Kumar *et al*., 2022). Moreover, the simultaneous decrease in both superoxide dismutase (SOD) and CAT activities due to alcohol ingestion may result in the accumulation of oxygen and hydrogen peroxide, contributing to oxidative stress and triggering harmful reactions in the body (Somani *et al*., 2006). *Vitis vinifera*, a plant known for its ability to combat reactive oxygen species, has been shown to enhance the activities of these antioxidant enzymes. Supplementation with *Vitis vinifera* in alcohol-exposed rats appears to boost the activities of SOD and CAT, possibly due to its antioxidative properties that help eliminate free radicals. Therefore, the results suggest that *Vitis vinifera* could effectively mitigate alcohol-induced oxidative stress and maintain higher CAT activities in renal cells.

In the recent study, it was observed that the activity of GSH-Px decreased notably in rats exposed to alcohol, potentially disrupting the balance of glutathione within renal cells and leading to kidney damage. This decline indicated impaired elimination of $H_2O_2$ and lipid peroxides. The decrease in GPx activity could result from either enzyme inactivation by free radicals (Pigeolet *et al*., 1990) or the depletion of essential co-substrates, such as GSH and NADPH, in alcohol-treated rats (Kode *et al*., 2004). Interestingly, treatment with *Vitis vinifera* extract was able to restore the diminished renal GPx activity to control levels. Moreover, the combined treatment of alcohol and *Vitis vinifera* led to a significant increase in GSH-Px activity, suggesting that *Vitis vinifera* may have an inhibitory or scavenging effect on free radicals within the renal tissue of rats. Additionally, *Vitis vinifera* contains antioxidant compounds like flavonoids, which could play a role in bolstering the antioxidant defense mechanism and shielding kidney tissue from the damage caused by alcohol-induced free radicals. Glutathione (GSH) is a crucial non-enzymatic antioxidant and the most abundant non-protein thiol in cells, playing essential roles in free radical metabolism. It serves as a key component in the body's defense against oxidative stress (Deneke *et al*., 1989). In a recent investigation, the GSH levels were found to be reduced in the kidneys of rats exposed to alcohol when compared to control rats. This decline in GSH may be attributed to elevated levels of lipid oxidation products, leading to a decreased availability of NADPH necessary for the activity of glutathione reductase (GR) in converting oxidized glutathione to GSH (Sarkar *et al*., 1995). This imbalance could result from the increased generation of reactive oxygen species (ROS) surpassing the capacity to replenish GSH during prolonged ethanol exposure. Interestingly, administration of *Vitis vinifera*, specifically red grape seed extract, was found to elevate glutathione levels in the kidney, as demonstrated in a study involving rats induced with nicotine (Sivasankar *et al*., 2013).

In the recent research, it was observed that alcohol consumption led to increased MDA levels in rats. Chronic alcohol intake is known to elevate MDA levels, indicating significant lipid peroxidation in the liver, heart, and kidneys of rats (Ostrowska *et al*., 2004). The unstable reactive oxygen species (ROS) produced during alcohol metabolism can interact with membrane lipids, ultimately resulting in lipid peroxidation. However, in our study, we found that administering *Vitis vinifera* seed ethanolic extract to the alcohol-exposed rats resulted in a reduction of MDA levels in kidney homogenates. A previous study demonstrated that the red grape seed extract from *Vitis vinifera* Burgund mare variety could decrease oxidative stress in diabetic rats, as shown by the decrease in levels of TBARS (Chis *et al*., 2009). In a recent study, researchers examined the impact of *Vitis vinifera* on kidney function by measuring levels of plasma creatinine, urea, and uric acid. The findings showed that administering *Vitis vinifera* extract to alcoholic rats resulted in a decrease and normalization of these plasma levels. Additionally, a study by Swaroopa *et al*. (2012) found that the ethanol extract of *Vitis vinifera* provided significant protection against nephrotoxicity in mice, as evidenced by lower serum urea and creatinine levels in those pre-treated with *Vitis vinifera* extract. The study concluded that *Vitis vinifera* extract effectively prevented increases in serum creatinine and urea levels, likely due to the presence of phenols, saponins, and flavonoids in the extract, which are believed to possess antioxidant properties and contribute to nephroprotective effects.

## CONCLUSION

The findings indicate that alcohol consumption leads to nephro-toxicity by reducing antioxidant levels, increasing lipid peroxidation, and harming renal cells. Fortunately, supplementation with *Vitis vinifera* can reverse these negative effects. This suggests that *Vitis vinifera* may serve as a protective nutrient and antioxidant supplement to safeguard the kidneys against alcohol-induced oxidative harm.

## ACKNOWLEDGMENT

The authors express sincere thanks to the head of the Department of Zoology, Government Degree College, Badangpet - 500 058, Telangana for the facilities provided to carry out this research work.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest

## ETHICS APPROVAL

All experiments were conducted in compliance with CPCSEA guidelines after receiving approval from the Institutional Animal Ethics Committee.

**FUNDING**

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

**AI TOOL DECLARATION**

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

**DATA AVAILABILITY**

Data will be available on request

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