



Impact of Diphenyl Diselenide on Acute Ethanol-Induced Disruption of Antioxidant Defense and Inflammatory Gene Expression in 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

Perturbation in antioxidant status which often leads to inflammation of liver cells and alteration in activities of purinergic enzymes are common outcomes of ethanol intoxication, this makes any compound that is able to prevent or repair the redox imbalances induced by alcohol intoxication a potential therapeutic measure. Hence, this study aims to assess the effect of diphenyl diselenide

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(DPDSe) on oxidative stress indicators, inflammatory genes and activities of purinergic enzymes in ethanol intoxicated male Wistar rats. 10mg/kg DPDSe was administered orally 30 minutes before and after a single dose of 13 ml/kg (28% ethanol solution) was given to the rats. Thereafter, the antioxidant status, activities of purinergic enzymes and expression of redox-sensitive genes in the rats were evaluated. It was observed that ethanol evoked high production of lipid peroxidation with concomitant decrease in thiol level, increased Nucleotidase and NTPDase activities, it also causes the downregulation of Nrf2 and upregulation of (NF-kB), however, pre- and post-treatment with DPDSe caused a reversal effects on the biochemical parameters and molecular parameters evaluated respectively. The reversal of ethanol-induced changes in biochemical parameters, expression of genes linked to inflammation and antioxidant status in the liver of acute ethanol intoxicated rats by DPDSe suggests that it has high prospect as a suitable therapeutic agent for hepatotoxicity linked with acute ethanol intoxication.

Keywords: Antioxidant; inflammation; ethanol; perturbation.

1. INTRODUCTION

Ethanol intoxication has complex effects on living cells. To explore the molecular events associated with ethanol intoxication, several studies have focused on the role of redox-sensitive genes, such as Nrf2 and NF-kB. These genes have been shown to be modulated by ethanol, contributing to its inflammatory effects [1,2]. Another mechanism by which ethanol induces toxicity is through the alteration of enzymes in the purinergic pathway. Enzymes such as 5'-nucleotidase and nucleoside triphosphate diphosphohydrolases (NTPDase), which are critical indicators of liver disease, are significantly affected by ethanol intoxication [3]. Research has documented that ethanol increases the activity of these enzymes in the platelet cell membrane, as they are sensitive to redox imbalances, with heightened activity observed during acute ethanol intoxication [4].

Although endogenous antioxidant systems provide some protection against oxidative damage, the excessive production of free radicals can overwhelm these systems, necessitating external sources of antioxidants. Exogenous antioxidants, such as flavonoids found in plants, have been shown to mitigate the effects of ethanol intoxication [5,6]. Specifically, studies have demonstrated the protective effects of quercetin and green tea extracts on diseases linked to ethanol intoxication by reducing lipid oxidative damage and enhancing antioxidant enzyme activity [6,7,8]. These findings confirm that oxidative stress is a key mechanism of ethanol intoxication [9,10], and the protective effects of phytochemicals are primarily due to their antioxidant capabilities. However, the use of plant-derived antioxidants poses challenges, including the potential for oxidation in the

presence of oxygen and contamination with metals, which can turn them into pro-oxidants [11].

To address these issues, synthetic antioxidants have been explored and have shown effectiveness in reducing oxidative stress-related pathologies [12,13]. For example, research into the antioxidative properties of organoselenium compounds has gained traction, as glutathione peroxidase (GPx), a potent endogenous enzymatic antioxidant, relies on selenocysteine at its active site for activity [14]. Diphenyl diselenide, one of the most studied organoselenium compounds, has demonstrated significant antioxidant properties [15,16] and has been used to alleviate diseases related to oxidative stress [15,17]. Studies have confirmed its ability to mimic glutathione peroxidase activity [18,19], helping to reduce hydrogen peroxide and lipid peroxides to water and corresponding alcohols, similar to the action of endogenous GPx.

While diphenyl diselenide has been applied in the management of various oxidative stress-related pathologies, its effects on acute ethanol intoxication in male Wistar rats are not well understood. Therefore, this study aims to investigate the potential influence of diphenyl diselenide on acute ethanol intoxication in the liver of male Wistar rats.

2. MATERIALS AND METHODS

2.1 Chemicals

Diphenyl diselenide, trichloroacetic acid (TCA), Dithiothreitol (DTT), Tris salt, dithio-bis-(2-nitrobenzoic acid) DTNB, ethanol and other chemicals were gotten from Sigma Chemical Co.

USA. Other chemicals were purchased from standard suppliers.

2.2 Experimental Animals

Male adult Wistar rats (120-150 g) were purchased, acclimatised at the Animal House of the Department of Biochemistry, The Federal University of Technology, Akure, Nigeria, for 2 weeks and used in the entire experiment according to standard guidelines of the Committee on Care and Use of Experimental Animal Resources.

2.3 Estimation of Ethanol Influence on Thiol Oxidation Induced by DPDS_e *In vitro*

The influence of ethanol on the *in vitro* activity of diphenyl diselenide (DPDS_e) induced thiol oxidation was carried out by measuring the formation of 2-nitro-5-thiobenzoic acid (TNB) at 412 nm.

2.4 Experimental Design (*In vivo*)

The study of DPDS_e influence on acute intoxication by ethanol after 6 hours of treatment was carried out. The rats were divided into five groups (n=6) and allowed to acclimatize for two weeks, after which group 1 (Control) was administered distilled water, group 2 was treated with 10 mg/kg DPDS_e only, group 3 induced with a single oral dose of 8 g/kg ethanol, group 4 was pretreated 30 minutes with 10 mg/kg DPDS_e before induction with a single oral dose of 10ml/kg of 28% ethanol solution, group 5 was post-treated with DPDS_e 30 minutes after a single oral dose of 8g/kg ethanol induction, the experiment was terminated 6 hours after the treatment with ethanol.

2.5 Lipid Peroxidation Assay

Lipid peroxidation was measured as thiobarbituric acid reactive substances (TBARS). TBARS were determined in tissue homogenates as previously described [20,21]. MDA values were determined using the absorbance coefficient ($1.56 \cdot 10^5$ /cm/mmol) of the MDA-TBA complex at 532 nm.

2.6 Thiol Oxidation

The thiol oxidation was determined in the presence of 50 mM Tris HCl pH 7.4 in both proteinized and deproteinized samples. The rate of thiol oxidation was evaluated by measuring

the disappearance of SH-group. The free SH-group was determined by Ellman [22].

2.7 5'-Nucleotidase and NTPDase like Activities

The 5'-Nucleotidase activity was determined in a reaction medium essentially as described by Heymann et al. [23]. The reaction was initiated by the addition of AMP and ATP to a final concentration of 2.0 mM for both enzymes (NTPDase and 5'-Nucleotidase) respectively. The assays were stopped by the addition of 250 μ l of 10% trichloroacetic acid (TCA). Inorganic phosphate was measured by the method of Fiske and SubbaRow [24]. Control experiments were carried to correct for non-enzymatic hydrolysis of the nucleotides. All samples were run in duplicate and Enzyme-specific activities are reported as nmol P_i released/min/mg of protein.

2.8 Gene Expression Analysis using Real-time Quantitative Polymerase Reaction

TRI Reagent (Zymo Research, USA) was used to extract total RNA from the tissues. 1 mg of RNA was used to make cDNA in a three-step reverse transcriptase reaction with the ProtoScript II First Strand cDNA Synthesis Kit (BioLabs, New England) at 65 °C for 5 min, 42 °C for 1 h, and 80 °C for 5 min. Table 1 lists the rat cDNA primers (Inqaba Biotec, Hatfield, SA) that were utilized for PCR. Solis BioDyne Reverse Transcriptase RT qPCR System and FIREPol[®] Master Mix (BioLabs, New England) were used to perform real-time quantitative PCR (RT-qPCR) according to the manufacturer's instructions. The following were the PCR conditions: 95 °C for 3 min, followed by 40 cycles of 95 °C for 15 s, 60 °C for 30 s, and 72 °C for 30 s. The relative quantity of cDNA was measured using the comparative cycle threshold (DDCT) method. The relative expression level of each gene was normalized using the β -actin gene.

2.9 Statistical Analysis

The results of replicate readings were pooled and expressed as mean \pm standard deviation (S.D). One-way Analysis of Variance (ANOVA) was used to analyze the results followed by Turkey's post hoc test, with levels of significance accepted at $p < 0.05$. All statistical analyses were carried out using the software Graph pad PRISM (V.5.0).

Table 1. Primer sequence for Real - time quantitative PCR

| S/N | Gene | Sequence |
|-----|---------|---|
| 1 | β-actin | Forward: CTCCCTGGAGAAGAGCTATGA Reverse: AGGAAGGAAGGCTGGAAGA |
| 2 | NFKB | Forward: AGACATCCTTCCGCAAATC Reverse: TAGGTCCATCCTGCCATAA |
| 3 | Nrf2 | Forward: ACGTGATGAGGATGGGAAAC Reverse: TATCTGGCTTCTTGCTCTTGG |

3. RESULTS

3.1 Influence of Acute Ethanol Intoxication and Diphenyl Diselenide on Biochemical Indices of Oxidation Stress

3.1.1 Influence of DPDS_e on ethanol-induced reduction in total thiol level *in vivo*

Fig. 1 shows that ethanol intoxication causes reduction in total thiol level by 2.3 times in relation to the control and that both pre-and post-DPDS_e treatment markedly ($p < 0.05$) reverse the ethanol-induced decrease in the *in vivo* thiol level.

3.1.2 Influence of DPDS_e on ethanol-induced lipid peroxidation

Fig. 2 shows that ethanol intoxication causes increase in lipid peroxidation by 1.5 times and DPDS_e pre-treatment markedly mitigates ethanol induced lipid peroxidation in ethanol intoxicated rats by 1.3 times while post-treatment has no significant effect on lipid peroxidation induced by ethanol intoxication.

3.1.3 Influence of DPDS_e on ethanol-induced reduction in non-protein thiol

Fig. 3 shows that ethanol intoxication causes reduction in non-protein thiol by 1.5 times and that both pre- and post- DPDS_e treatments markedly reverse the ethanol-induced decrease in the *in vivo* thiol level by 1.7 and 1.6 times respectively.

3.1.4 Influence of DPDS_e on ethanol-induced elevated NTPDase activity

Fig. 4 shows that ethanol intoxication causes elevation in NTPDase activity by 1.1 times in

relation to the control group and that both pre- and post- DPDS_e treatments markedly decrease the activity of the enzyme in ethanol induced group by 1.4 and 1.5 times respectively.

3.1.5 Influence of DPDS_e on ethanol-induced elevated Nucleotidase activity

Fig. 5 shows that ethanol intoxication causes elevation in Nucleotidase activity by 2.3 times in relation to the control group and that both pre- and post-DPDS_e treatments markedly decrease the activity of the enzyme in ethanol induced group by 1.9 and 2.1 times respectively.

3.2 Influence of Diphenyl Diselenide and Alcohol on Expression of Antioxidant and Pro-Inflammatory Genes

3.2.1 Influence of DPDS_e on ethanol-induced downregulation of Nrf2

Fig. 6 shows that ethanol intoxication causes a downregulation in the expression of Nrf2 by 0.8 times in relation to the control group and that post-treatment of the ethanol-induced animals with DPDS_e markedly upregulate the expression of the gene while the DPDS_e pre-treatment do not have any stimulatory effect on the expression of the gene.

3.2.2 Influence of DPDS_e on ethanol-induced downregulation of Nrf2

Fig. 7 shows that ethanol intoxication causes an upregulation in the expression of NF-kB by 0.9 times in relation to the control group and that post-treatment of the ethanol-induced animals with DPDS_e markedly downregulated the expression of the gene by 2.3 times while the DPDS_e pre-treatment do not have any downregulatory effect on the expression of the gene.

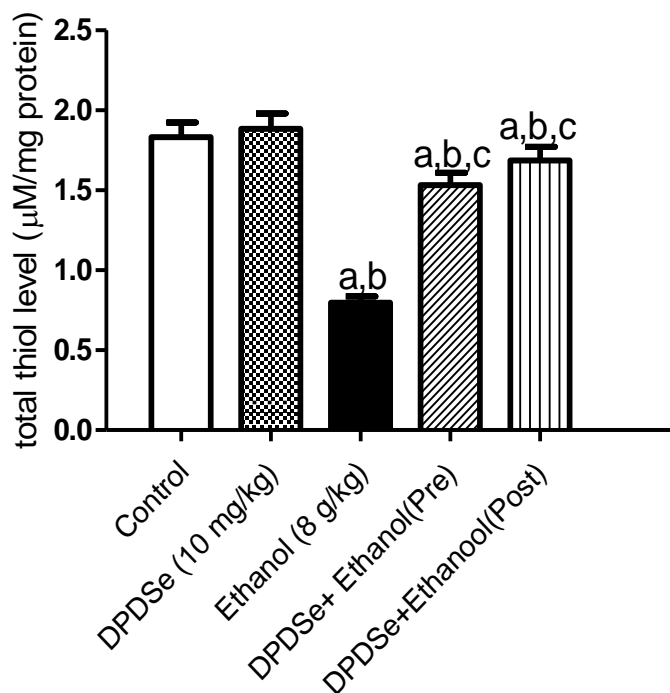


Fig. 1. Influence of DPDSe pre- and post-treatment on total thiol level in liver of acute ethanol-intoxicated male Wistar rats. ^a $p < 0.0001$ significant difference compared to control ^b $p < 0.0001$ significant difference compared to DPDSe ^c $p < 0.0001$ significant difference compared to ethanol

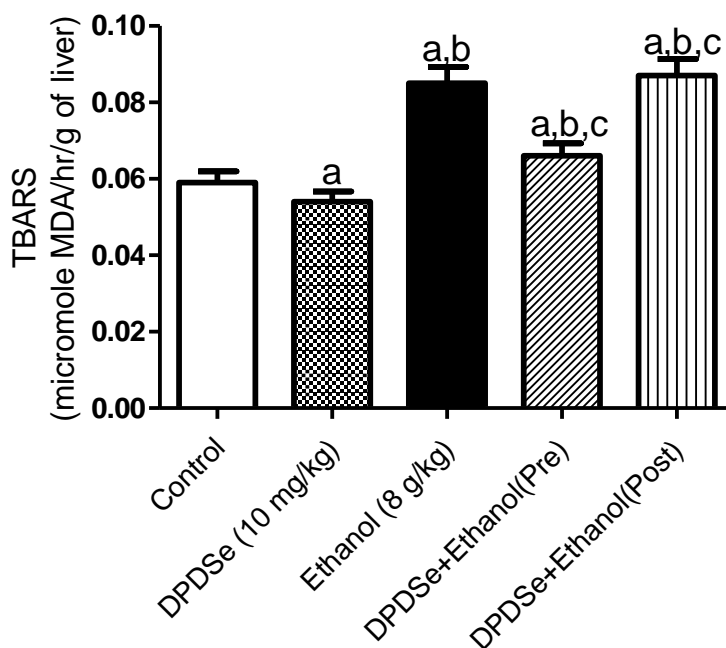


Fig. 2 Influence of DPDSe pre- and post-treatment on lipid peroxidation in liver of acute ethanol-intoxicated male Wistar rats. ^a $p < 0.0001$ significant difference compared to control ^b $p < 0.0001$ significant difference compared to DPDSe ^c $p < 0.0001$ significant difference compared to ethanol

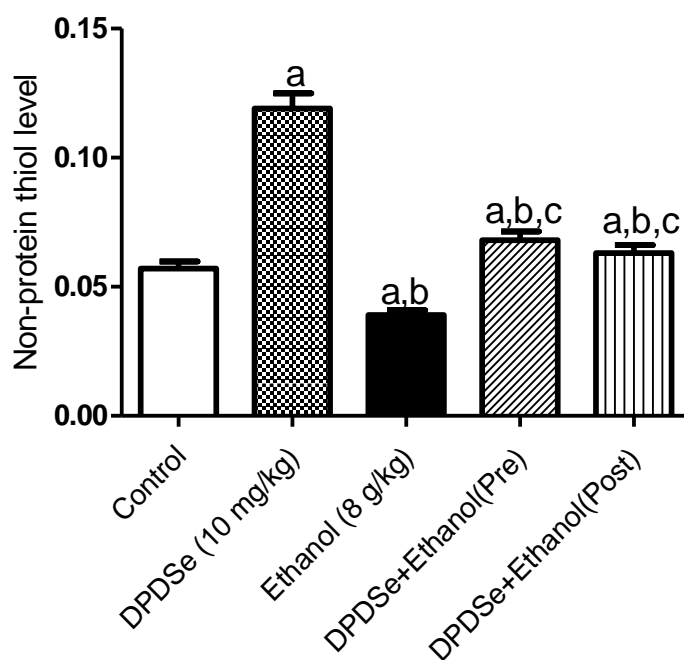


Fig. 3. Influence of DPDSe pre- and post- treatment on non-protein thiol level in liver of acute ethanol-intoxicated male Wistar rats. ^ap<0.0001 significant difference compared to control ^bp<0.0001 significant difference compared to DPDSe ^cp<0.0001 significant difference compared to ethanol

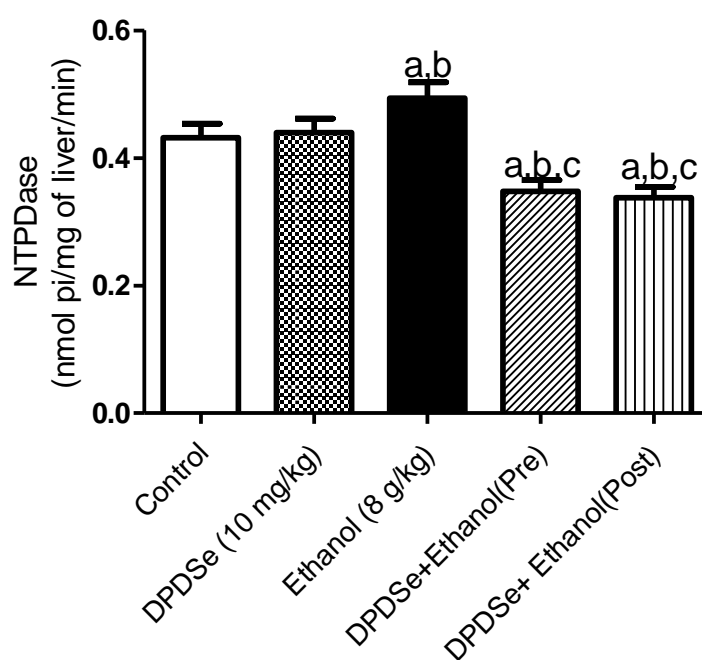


Fig. 4. Influence of DPDSe pre- and post- treatment on activity of NTPDase in liver of acute ethanol-intoxicated male Wistar rats. ^ap<0.0001 significant difference compared to control ^bp<0.0001 significant difference compared to DPDSe ^cp<0.0001 significant difference compared to ethanol

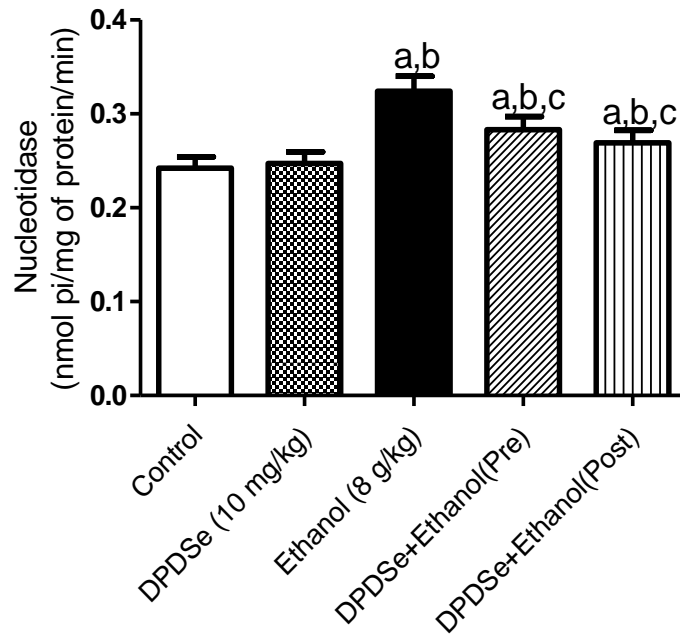


Fig. 5. Influence of DPDSe pre- and post- treatment on the activity of Nucleotidase in liver of acute ethanol-intoxicated male Wistar rats. ^ap<0.0001 significant difference compared to control ^bp<0.0001 significant difference compared to DPDSe ^cp<0.0001 significant difference compared to ethanol

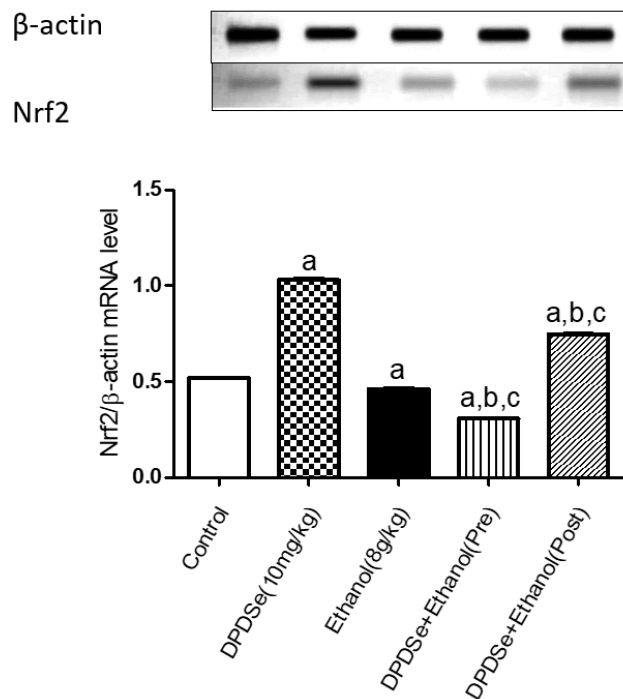


Fig. 6. Influence of DPDSe pre- and post- treatment on Nrf2 in liver of acute ethanol-intoxicated male Wistar rats. ^ap<0.0001 significant difference compared to control ^bp<0.0001 significant difference compared to DPDSe ^cp<0.0001 significant difference compared to ethanol

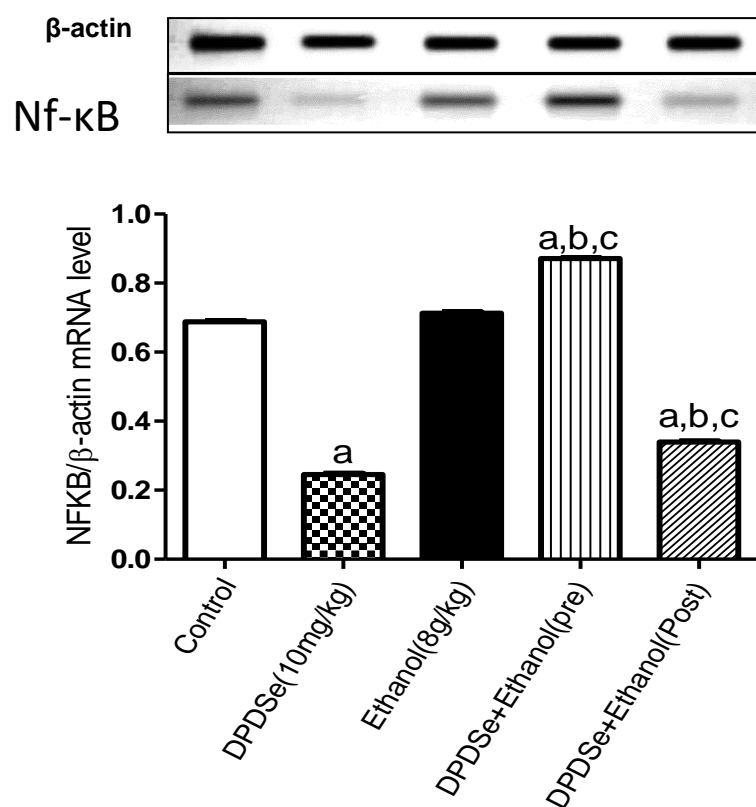


Fig. 7. Influence of DPDSe pre- and post- treatment on NFKB in liver of acute ethanol-intoxicated male Wistar rats. ^ap<0.0001 significant difference compared to control ^bp<0.0001 significant difference compared to DPDSe ^cp<0.0001 significant difference compared to ethanol

4. DISCUSSION

Redox imbalance is a hallmark of ethanol intoxication in the liver of male Wistar rats, and diphenyl diselenide (DPDSe) has been shown to improve antioxidant status, reverse altered activities of purinergic enzymes, and modulate the expression of redox-sensitive genes. When the redox balance shifts in favor of oxidants, macromolecules such as lipids, proteins, and DNA are vulnerable to oxidative damage, which is a key indicator of oxidative stress [25,26]. Lipid oxidative damage occurs when reactive oxygen species (ROS) abstract hydrogen from polyunsaturated fatty acids (PUFAs), leading to lipid peroxidation and subsequent cell membrane damage. This process releases malondialdehyde (MDA) and other reactive aldehydes, which form adducts with thiobarbituric acid (TBA). The MDA-TBA adduct can be measured spectrophotometrically at 532 nm to quantify the extent of lipid peroxidation. In this study, elevated thiobarbituric acid reactive

substances (TBARS) were observed in ethanol-treated animals, which were significantly reduced by DPDSe treatment. The high TBARS levels in the ethanol group indicate that lipid biomolecules were oxidatively damaged, while the reduction in TBARS in the DPDSe-treated group suggests that DPDSe either enhanced antioxidant defense or repaired oxidative damage by donating hydrogen to stabilize PUFAs.

In addition to measuring oxidative stress through lipid peroxidation and antioxidant capacity, assessing the activities of redox-responsive enzymes offers further insight. 5'-nucleotidase (5NT) and nucleoside triphosphate diphosphohydrolases (NTPDases) are crucial enzymes involved in nucleotide metabolism and are known to respond to oxidative stress. Their dysregulation can lead to various pathological conditions, making them targets for therapeutic interventions. Increased activities of these enzymes have been linked to ethanol-induced

oxidative stress, with serum 5NT levels being a marker of hepatobiliary disease [3]. Consistent with previous studies, this research demonstrated increased activities of 5'-nucleotidase and NTPDase in the liver of ethanol-intoxicated rats, likely due to elevated levels of NADH driving ATP production and, in turn, increasing purinergic enzyme activity. However, DPDS_e treatment reduced the activities of these enzymes in ethanol intoxicated rats, this reduction in activities of the enzyme by DPDS_e may be due to its antioxidant properties which limits the oxidative stress thereby stabilizing the structure of the purinergic enzymes which are membrane enzymes, hence, protecting their activities by reducing the altered enzyme activities that was heightened by oxidative stress.

To investigate the mechanism by which DPDS_e mitigates oxidative damage, the antioxidant capacity of untreated ethanol-intoxicated animals was compared with pre- and post-DPDS_e-treated animals by measuring reduced glutathione (GSH) levels. Since over 90% of non-protein thiols in rats are GSH [27], the observed decrease in thiol levels in ethanol-treated animals suggests that thiols were consumed in stabilizing ethanol-induced free radicals. This finding aligns with previous studies showing that thiol oxidation is a key event in ethanol intoxication [28]. Both pre- and post-DPDS_e treatments elevated thiol levels, indicating that DPDS_e either prevented thiol depletion or repaired oxidative damage by halting lipid peroxidation, thus sparing thiol groups. This confirms that ethanol intoxication is linked to oxidative stress and supports the antioxidant and hepatoprotective potential of DPDS_e in mitigating ethanol-induced liver damage.

Many endogenous antioxidants are gene products, and the protective effects of DPDS_e against ethanol-induced oxidative stress may also occur at the molecular level. To explore this, the expression of the antioxidant gene Nrf2 was evaluated. Nrf2 is crucial in regulating antioxidant defenses and responding to oxidative insults [29]. In ethanol-intoxicated rats, Nrf2 expression was downregulated, indicating that ethanol impairs the cell's endogenous defense system at the molecular level, consistent with previous reports [30]. However, DPDS_e treatment restored Nrf2 expression, showing that DPDS_e can modulate cellular defense systems compromised by ethanol intoxication at the molecular level by detablizing the Nrf2-Keap1

complex in the membrane so that Nrf2 can access the nucleus of the cell thereby influencing the transcription of genes that code for antioxidant enzymes such as catalase, superoxide dismutase.

To further understand the molecular effects of ethanol on inflammation, the expression of nuclear factor kappa B (NF-κB), a key component of the inflammatory pathway, was assessed. Ethanol intoxication upregulated NF-κB expression, while post-treatment with DPDS_e reduced its expression, highlighting the anti-inflammatory potential of DPDS_e.

Overall, this study demonstrates that DPDS_e significantly reduces oxidative stress markers such as TBARS, downregulates NF-κB expression, increases total and non-protein thiol levels, and upregulates Nrf2 expression in the liver of ethanol-intoxicated rats. These findings confirm DPDS_e's potent antioxidant and anti-inflammatory properties, effectively reversing ethanol-induced oxidative damage.

5. CONCLUSION

Acute ethanol exposure remains a challenge due to its well-documented toxicity. This study reveals several toxic mechanisms of ethanol, including thiol oxidation, lipid peroxidation, downregulation of the antioxidant gene Nrf2, and upregulation of inflammatory pathways via NF-κB. Diphenyl diselenide (DPDS_e) has emerged as a promising agent for mitigating toxic effects of ethanol at various mechanisms studied. It effectively reverses ethanol-induced oxidative stress by modulating redox-sensitive transcription factors such as Nrf2 and NF-κB, reducing oxidative stress markers like TBARS, and enhancing antioxidant capacity by preserving non-protein and total thiol levels. Additionally, DPDS_e ameliorates the effects of ethanol intoxication on purinergic enzymes, further supporting its potential as a therapeutic agent in managing the oxidative damage and inflammation associated with acute ethanol intoxication.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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