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DOSE-DEPENDENT NEUROPROTECTIVE EFFECTS OF RESVERATROL AND GSPE AGAINST COLD STRESS-INDUCED OXIDATIVE DAMAGE IN RAT BRAIN REGIONS

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Abstract: Chronic cold stress induces oxidative neurotoxicity through sustained HPA axis activation. The present study evaluated the duration-dependent effects of cold stress and the dose-optimized neuroprotective potential of polyphenols in Wistar rats. Animals were exposed to cold stress (5°C, 6 h/day) for 30 days, and LPO, MnSOD and serum cortisol levels were assessed in optimal exposure duration. A 15-day protocol produced significant oxidative stress with pronounced hippocampal vulnerability ($p < 0.05$) and no mortality. Trans-resveratrol and grape seed proanthocyanidin extract (GSPE) were administered at 25-100 mg/kg, individually and in combination. FTIR and UV-visible spectroscopy confirmed compound identities resveratrol (O–H stretching at 3200-3500 cm^{-1}; λ_max 215 and 305 nm) GSPE (λ_max ~280 nm). Cold stress increased LPO and cortisol in a duration dependent manner and reduced MnSOD activity, indicating impaired antioxidant defense. Polyphenol treatment showed a dose-dependent neuroprotective response, with maximal efficacy at 75 mg/kg. Higher doses (100 mg/kg) showed reduced effectiveness, consistent with hormesis. Combination treatment (50 mg/kg each) restored MnSOD activity and reduced LPO more than higher individual doses, indicating a synergy. These findings show moderate-dose polyphenol combinations attenuate cold stress–induced oxidative neurotoxicity validate a 15-day model for investigating stress-related neurodegenerative mechanisms.

Keywords: Cold stress, Grape-seed extract, Hippocampus, Lipid, Neuroprotection, Resveratrol.

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INTRODUCTION

Environmental stressors are key determinants of physiological dysregulation, with cold stress recognised as a significant inducer of neurochemical and oxidative imbalance (Rakesh *et al.,* 2021). An exposure to low ambient temperature activates adaptive and maladaptive responses mediated through the hypothalamic-pituitary-adrenal (HPA) axis. Finally, it results in an elevated glucocorticoids, particularly cortisol, and increased generation of reactive oxygen species (ROS). This disrupts cellular redox homeostasis and induces oxidative stress in the central nervous system (CNS), contributing to neuronal injury and functional impairment (Basha *et al.,* 2021; Merve *et al.,* 2024).

The brain is highly vulnerable to oxidative damage due to its high oxygen consumption, abundance of polyunsaturated fatty acids, and relatively limited antioxidant defences. Oxidative stress compromises blood–brain barrier (BBB) integrity, effectively promotes neuroinflammation, and accelerates neurodegeneration

(Kim *et al*., 2022). Cold stress preferentially affects metabolically active regions such as the cerebral cortex and hippocampus, leading to lipid peroxidation, mitochondrial dysfunction, and reduced antioxidant enzyme activity, including manganese superoxide dismutase (MnSOD) (Basha *et al*., 2021).

The polyphenols have emerged as multi-target neuroprotective agents capable of crossing the BBB and modulating oxidative stress, inflammation, autophagy, and mitochondrial function (Abdou *et al*., 2022; Mayer *et al*., 2024). They scavenge ROS, enhance endogenous antioxidant systems, and regulate transcription factors such as Nrf2 and SIRT1 (Vrankova *et al.,* 2026; Bas, 2026). Resveratrol promotes mitochondrial biogenesis via PGC-1α and modulates apoptotic and inflammatory pathways, while grape seed proanthocyanidin extract (GSPE) provides potent antioxidant and membrane-stabilizing effects (Abdou *et al*., 2022).

Although polyphenols are widely reported to mitigate the oxidative stress and neuroinflammation in neurodegenerative models (Fakhri *et al*., 2022; Mayer *et al*., 2024; Vrankova *et al.,* 2026), however, studies addressing chronic environmental stressors such as cold exposure remain limited. Hence, the present study investigates duration-dependent effects of chronic cold stress and dose-dependent neuroprotection by resveratrol and GSPE. Biochemical parameters including, serum cortisol, lipid peroxidation, and MnSOD activity, were assessed in the cerebral cortex and hippocampus. Compound integrity was confirmed using FTIR and UV-Visible spectroscopy. It is hypothesized that these polyphenols exert dose-dependent neuroprotection by attenuating oxidative stress and restoring antioxidant balance.

MATERIALS AND METHODS

1. Experimental animals and Ethical approval

Adult male Wistar albino rats (180-220 g) were procured from Sri Venkateswara Enterprises, Bangalore, and housed under standard conditions (22 ± 2°C, 50-60% humidity, 12 h light-dark cycle) with pelleted diet and water *ad libitum*. All procedures followed CPCSEA guidelines and were approved by the Institutional Animal Ethics Committee (IAEC Approval No.: 402/GO/Re/01/CPCSEA/002).

2. Chemicals and Reagents

Trans-resveratrol (≥ 98% purity; from *Polygonum cuspidatum*; Decode Age, Bengaluru, Karnataka) and grape seed proanthocyanidin extract (GSPE) (>95% proanthocyanidins; Inlife Pharma, Hyderabad) were used. All other reagents were analytical grade from Sigma-Aldrich and SRL.

3. Cold exposure, Dose optimization and Treatment

Rats (n=6) were exposed to cold stress (5 ± 1°C, 6 h/day) for 5, 10, 15, or 30 days in a Colton BOD chamber; controls remained at ~24°C. Lipid peroxidation and serum cortisol identified 15-days as optimal. GSPE (water-soluble) and trans-resveratrol (suspended in 0.9% NaCl) were administered orally (25, 50, 75, 100 mg/kg; combination at equal doses) to cold-stressed rats for 15-days. Oxidative markers (lipid peroxidation) (Niehaus and Samuelsson 1968), serum cortisol [CLIA], and MnSOD (Misra and Fridovich, 1972) in the cerebral cortex and hippocampus determined the optimal dose.

4. Experimental design, Sample collection and Spectroscopic validation

Animals were randomly allocated into experimental groups (n = 6/group): normal control, cold-stress control, cold-stressed rats treated with trans-resveratrol (25, 50, 75 and 100 mg/kg), cold-stressed rats treated with GSPE (25, 50, 75 and 100 mg/kg), and the combination-treatment group at the optimized doses. The normal control group was maintained under standard laboratory conditions, whereas the cold-stress control group was exposed to 5 ± 1°C for 6 h/day for 15 days without polyphenol treatment. The resveratrol dose range (25–100 mg/kg body weight) was selected based on previously reported in-vivo evidence of antioxidant and neuroprotective activity (Xiao, 2015) and was further evaluated experimentally to establish a dose–response relationship. Lipid peroxidation, serum cortisol and MnSOD activity were used to identify the dose producing the optimal protective response. GSPE was used as a reference antioxidant treatment for comparison with trans-resveratrol.

At the end of the experimental period, animals were anaesthetized using sodium pentobarbital (40-60 mg/kg, intraperitoneally) in accordance with CPCSEA guidelines, and blood samples were collected via cardiac puncture under deep anaesthesia, followed by humane euthanasia using a CO_2 inhalation chamber with a controlled displacement rate of 20-30% of the chamber volume per minute. Brain tissues were rapidly excised on an ice-cold surface, and the cerebral cortex and hippocampus were carefully dissected, washed in chilled saline, and stored at −80 °C until further biochemical analysis. FTIR and UV-Visible spectral analyses were performed to confirm the structural integrity and purity of the compounds prior to experimental use, using ATR-FTIR (Bruker, Germany; 4000-400 cm^{-1}) and UV-Visible spectrophotometry (Shimadzu, Japan; 200-800 nm) with ethanol as solvent.

5. Statistical Analysis

Data were expressed as mean ± SEM. Statistical significance was determined using two-way ANOVA followed by Tukey's test ($p < 0.05$). Dose-response relationships were properly evaluated using quadratic regression.

RESULTS

1. Lipid Peroxidation

Cold stress induced a duration-dependent increase in lipid peroxidation in both brain regions. No significant change was observed at 5-days exposure, whereas significant elevations occurred at 10, 15, and 30 days ($p < 0.05$). Notably, the hippocampus consistently exhibited higher LPO levels than the cortex, particularly after prolonged exposure (Fig. 1A).

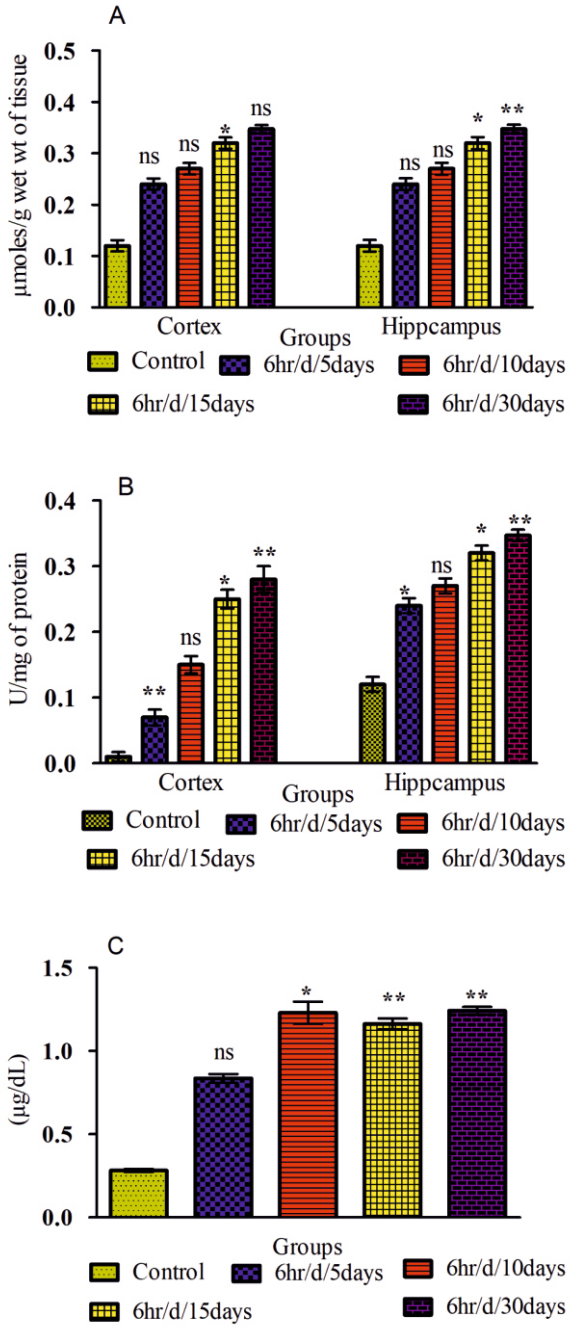

Fig. 1: Effects of cold stress (5 ± 0.5°C, 6 h/day) for 5, 10, 15, and 30 days on (A) lipid peroxidation, (B) superoxide dismutase, and (C) cortisol in rat cortex and hippocampus. Data are mean ± SEM (n = 6/group). *p < 0.05, **p < 0.01, ***p < 0.001; ns, non-significant versus controls (Tukey's post hoc test).

2. Superoxide dismutase (SOD) Activity

Cold stress induced a duration-dependent alteration in antioxidant defense, as evidenced by changes in SOD activity in both the cortex and hippocampus. No significant change was observed at 5 days of exposure; however, a significant decrease in SOD activity was recorded at 10, 15, and 30 days ($p < 0.05$), indicating compromised antioxidant capacity. The hippocampus exhibited a more pronounced reduction in SOD activity compared to the cortex, particularly with prolonged exposure duration. These findings suggest increased oxidative burden and reduced enzymatic defense under chronic cold stress conditions (Fig. 1B).

3. Serum cortisol

Serum cortisol levels increased in parallel with lipid peroxidation. Significant elevations were observed from day-10 onward ($p < 0.01$), indicating sustained HPA axis activation (Fig. 1C). A 15-day exposure produced consistent biochemical changes without mortality.

4. Dose-dependent Neuroprotection

Resveratrol and GSPE reduced lipid peroxidation and enhanced MnSOD activity in a dose-dependent manner (Figs. 2). Lower doses (25 mg/kg) provided partial protection. Maximal protection was observed at 50-75 mg/kg, while 100 mg/kg showed reduced efficacy consistent with hormesis. Combination treatment (50 mg/kg each) produced greater effects than individual treatments (Fig. 2E-F).

5. FTIR Spectral confirmation

This analysis confirms that trans-resveratrol exhibited phenolic O–H stretching (3200-3500 cm^{-1}) and aromatic C=C stretching (1600-1500 cm^{-1}). Similarly, GSPE showed broad O–H stretching with C=C and C–O vibrations typical of proanthocyanidins (Fig. 3 and 4).

6. UV–Visible Spectral Analysis

The present spectral data verify that trans-resveratrol displayed absorption maxima at 215 nm ($\pi \rightarrow \pi^*$ transitions) and 305 nm (trans-stilbene) (Fig. 5a). GSPE exhibited a prominent peak at 280 nm characteristic of flavan-3-ols/ proanthocyanidins (Fig. 5b).

DISCUSSION

The results observed in this study establish three critical findings: First, chronic cold stress induces duration-dependent oxidative damage with selective hippocampal vulnerability, confirming environmental cold exposure as a reproducible model of stress-induced neurotoxicity (Fig. 1). Second, trans-resveratrol and GSPE demonstrate dose-optimized neuroprotection peaking at moderate concentrations (75 mg/kg), validating hormesis as a key therapeutic

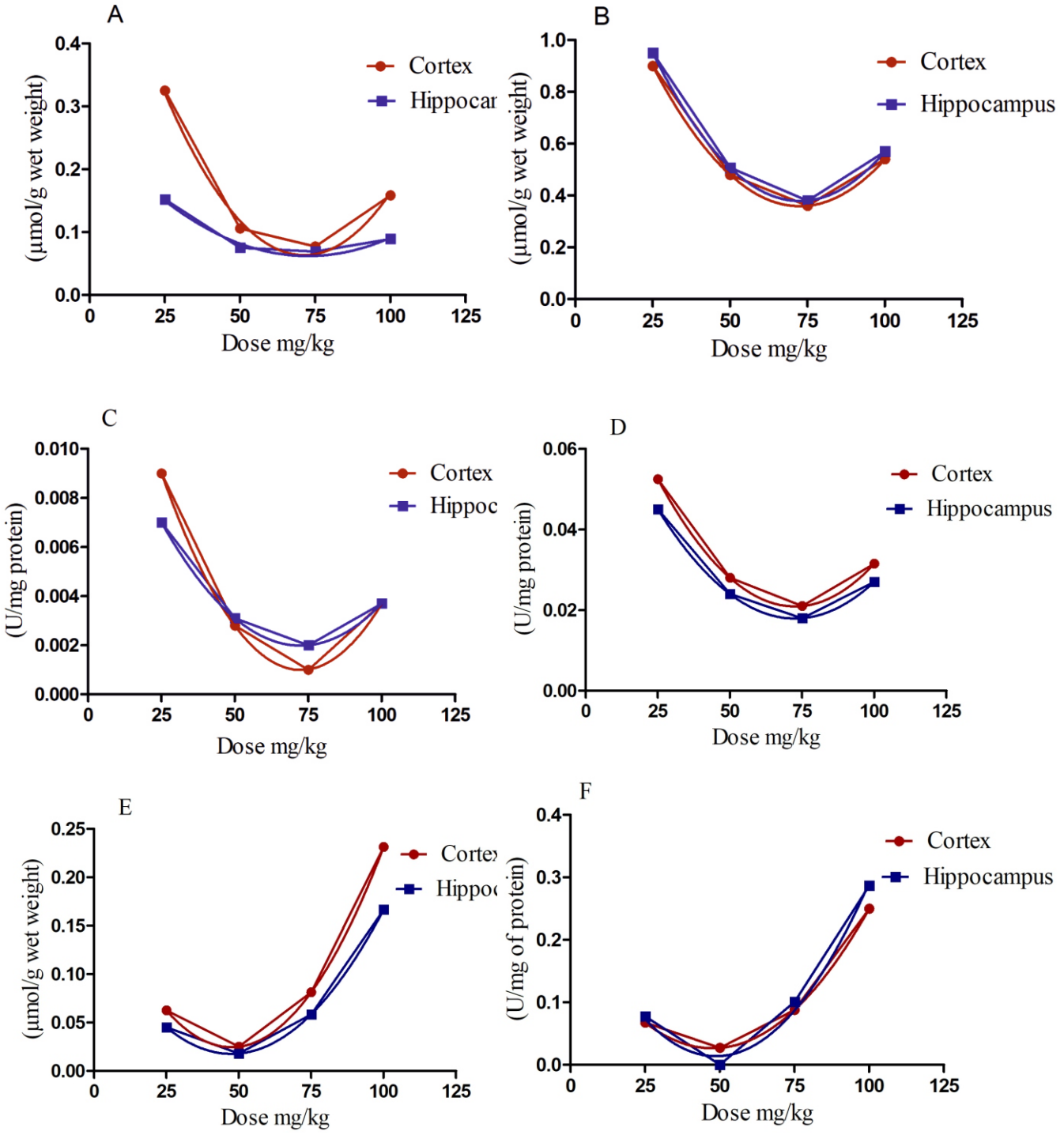

Fig. 2: Dose-response effects of GSPE and RES on LPO and SOD activity in the cortex and hippocampus. (A) GSPE-LPO; (B) RES-LPO; (C) GSPE-SOD; (D) RES-SOD; (E) GSPE + RES–LPO; and (F) GSPE + RES–SOD. Blue circles and orange squares represent cortex and hippocampus, respectively. Values are means (n = 6/group); curves represent quadratic regression fits.

principle (Fig. 2 A-D). Third, their combination therapy (50 mg/kg each) produces synergistic antioxidant effects (Fig. 2E-F) surpassing individual high doses, identifying polyphenol cocktails as superior neuroprotective strategies (Mim *et al.*, 2026). Although 75 mg/kg produced the maximum individual response for both trans-resveratrol and GSPE, the combination treatment was evaluated at 50 mg/kg of each compound to determine whether combined administration at a moderate dose could provide enhanced protection while avoiding unnecessarily high individual doses. A detailed and explicit mechanistic interpretation is given in following sections.

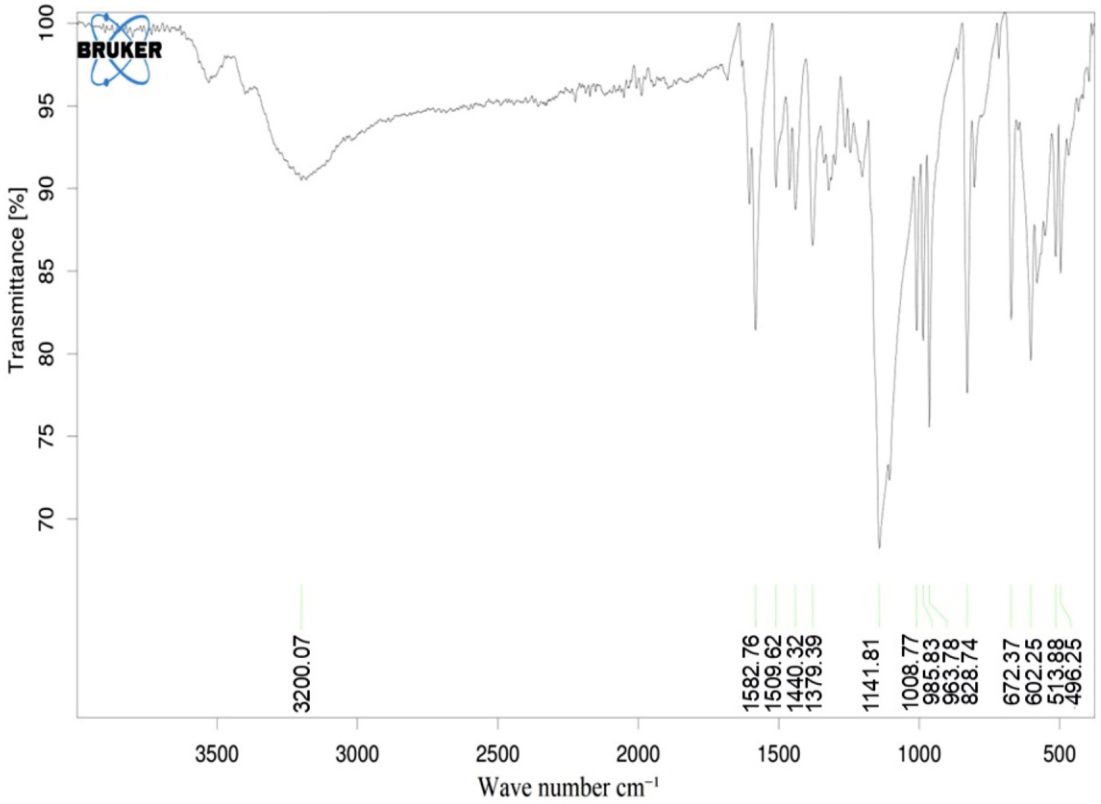

Fig. 3: Representing Fourier-transform infrared (FTIR) spectrum of Resveratrol (RES) illustrating its characteristic functional groups.

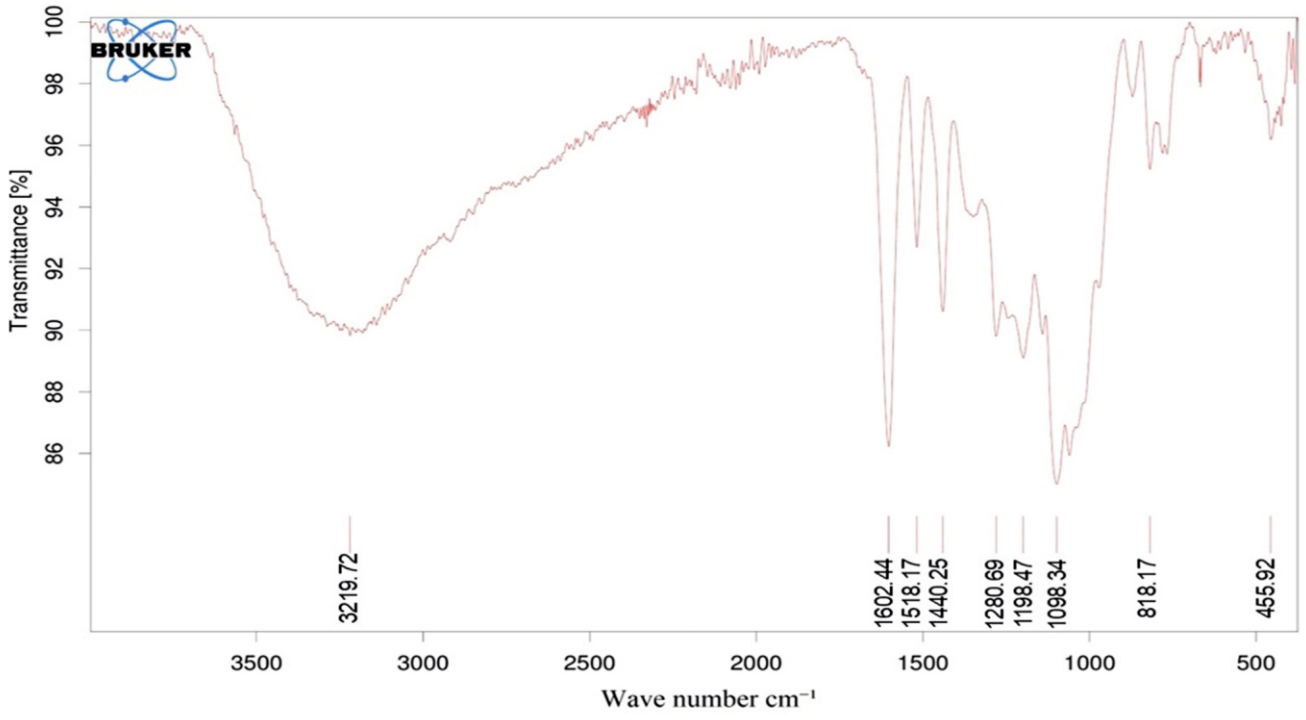

Fig. 4: Representing Fourier-transform infrared (FTIR) spectrum of Grape seed proanthocyanidin (GSPE) illustrating its characteristic functional groups.

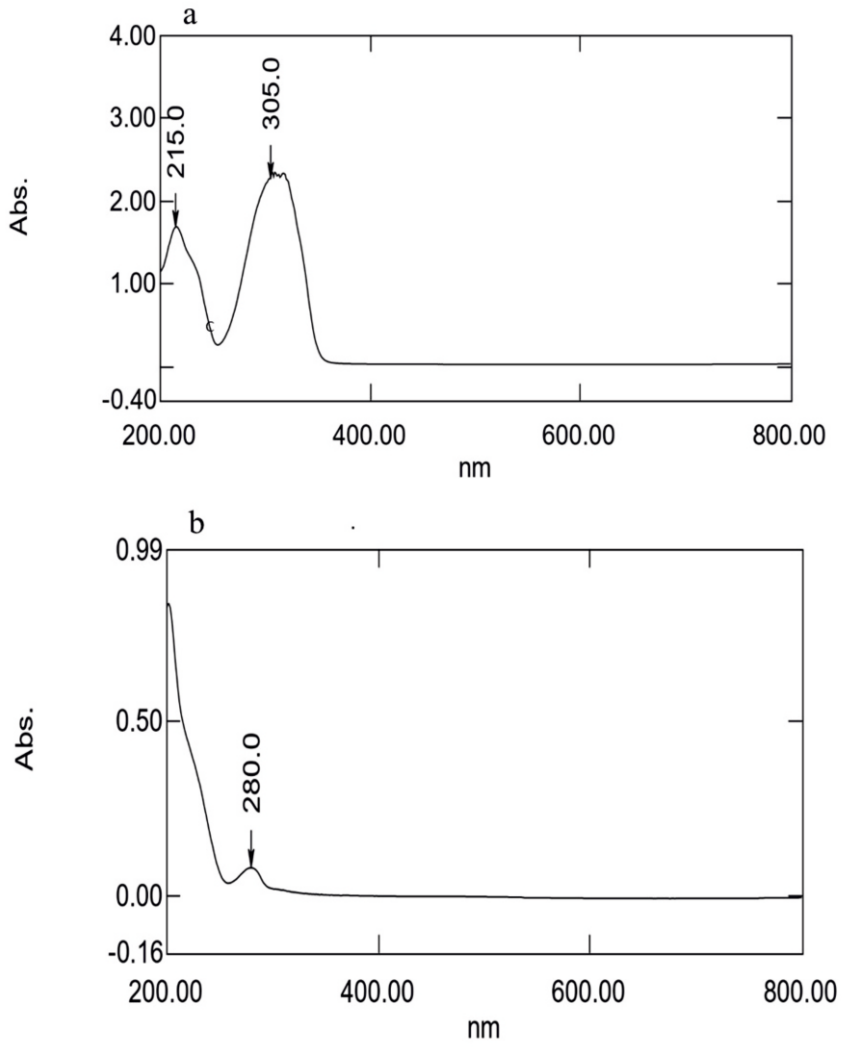

Fig. 5: UV-Vis absorption spectra of (a) Resveratrol (RES) and (b) Grape Seed Proanthocyanidin Extract (GSPE) showing their characteristic absorption profiles.

1. Duration-dependent oxidative damage from chronic cold stress

The present investigation clearly demonstrates that chronic intermittent cold stress (5°C, 6 h/day) induces progressive lipid peroxidation (LPO) in the cerebral cortex and hippocampus, with the hippocampus exhibiting greater vulnerability due to its high metabolic demand. This finding aligns with established literature documenting cold-induced reactive oxygen species (ROS) overproduction, mitochondrial dysfunction, and lipid membrane damage in neural tissues (Şahin and Gümüşlü, 2004; Girotti, 2015; Falla *et al.,* 2026). The non-significant LPO rise at day-5 (Fig. 1A) followed by significant increases at 10-30 days indicates a temporal transition from initial adaptive antioxidant responses to maladaptive oxidative overwhelm. This shift is further substantiated by the observed decline in SOD activity from day-10 onward, reflecting progressive impairment of endogenous antioxidant defense mechanisms. The reduction in SOD activity (fig.1B), particularly in the hippocampus, suggests diminished dismutation of superoxide radicals and consequent amplification of oxidative damage. Such enzymatic exhaustion is characteristic of sustained HPA axis activation, glucocorticoid-mediated ROS over-production, and mitochondrial dysfunction, ultimately leading to enhanced lipid membrane peroxidation and neuronal vulnerability (McEwen, 2007; Rakesh *et al*., 2021).

2. HPA Axis hyperactivation and Neuroendocrine-oxidative crosstalk

A key observation is the parallel elevation of serum cortisol mirroring lipid peroxidation (LPO) patterns, establishing a direct neuroendocrine-oxidative stress nexus. This investigation validates sustained HPA axis hyperactivity-via the CRH/ACTH/cortisol cascade-as the primary mediator linking environmental cold

exposure to CNS oxidative pathology (McEwen, 2007). Excess cortisol impairs neuronal antioxidant defenses (notably through downregulation of MnSOD) and promotes ROS generation via xanthine oxidase activation, thereby creating a self-amplifying oxidative cycle. This is consistent with the present findings of reduced SOD activity under prolonged cold stress, reinforcing the role of glucocorticoid-mediated suppression of antioxidant enzymes in driving oxidative neurotoxicity. Furthermore, the 15-day exposure protocol induces robust biochemical alterations without mortality, representing an optimal experimental window that balances patho-physiological relevance with animal welfare-a critical advantage over acute stress models associated with non-specific lethality (Basha *et al.,* 2021).

3. Dose-optimized polyphenol neuroprotection

The current findings reveal trans-resveratrol and GSPE exert dose-dependent neuroprotection, peaking at 75 mg/kg with efficacy decline at 100 mg/kg-classic hormesis where moderate polyphenol doses activate adaptive stress responses (Nrf2/SIRT1/PGC-1α pathways) (Jha 2025; Vrankova *et al.,* 2026; Bas, 2026) while excessive concentrations induce pro-oxidant effects via redox cycling (Calabrese *et al.,* 2010; Bagchi *et al.,* 2010; Mayer *et al.,* 2024). Significantly, combination therapy (50 mg/kg each) surpassed individual high doses, confirming synergistic antioxidant interactions through complementary mechanisms (Fig. 2): resveratrol's PGC-1α-mediated mitochondrial biogenesis along with GSPE's potent membrane stabilization and direct ROS scavenging (Bagchi *et al.,* 2000; Baur and Sinclair, 2006; Lucarini *et al.,* 2019; Abdou *et al.,* 2022).

4. FTIR/UV-visible validation strengthens methodological rigor

Spectral confirmation of characteristic resveratrol (O–H: 3200–3500 cm^{-1}; λ_max: 215/305 nm, stilbene) (Camont *et al.,* 2009) and GSPE (broad O–H; λ_max: 280 nm, flavan-3-ols) fingerprints eliminates formulation artifacts and auto-oxidation concerns, ensuring observed neuroprotection reflects true compound bioactivity (Fig. 3) (Adhikary *et al.,* 2025*)*. This rigorous validation perfectly distinguishes the present work from studies lacking compound characterization, enhancing translational confidence.

5. Limitations of the study

The present study has several limitations that should be considered when interpreting the findings. First, only adult male Wistar rats were used; therefore, the findings may not fully represent sex-specific responses to chronic cold stress or polyphenol treatment. Second, the study primarily evaluated biochemical indicators of oxidative stress and antioxidant defence, including lipid peroxidation and MnSOD activity. It did not include a vast molecular, histopathological or behavioural assessment to establish clearcut underlying neuroprotective mechanisms. Third, although the dose–response design identified 75 mg/kg as the most effective dose under the present experimental conditions, the findings cannot be directly extrapolated to humans because of differences in resveratrol bioavailability, metabolism and pharmacokinetics. Finally, the study duration was limited to 15 days and therefore does not establish the effects of prolonged or chronic resveratrol/ GSPE administration. Future studies incorporating both the sexes, larger sample sizes, extended treatment periods, histopathological and molecular endpoints, pharmacokinetic assessment etc. would strengthen the mechanistic and translational relevance of these findings.

CONCLUSIONS

The findings of the present study establish that chronic cold stress induces duration-dependent oxidative damage with pronounced hippocampal vulnerability, and further demonstrate that trans-resveratrol and GSPE confer dose-optimised neuroprotection, with moderate dosing showing maximal efficacy. It must be noted that combination treatment produced enhanced antioxidant effects compared to individual administration, highlighting the therapeutic potential of polyphenol-based effective combination strategies in stress-induced neurotoxicity. The use of only male Wistar rats in the present study was intended to minimise hormonal variability associated with the oestrous cycle, thereby ensuring experimental consistency in assessing stress-induced oxidative responses and antioxidant efficacy. Future investigations incorporating female cohorts are warranted to evaluate the potential sex-specific differences, particularly in the context of oestrogen-mediated neuroprotection. Overall, the study provides a standardised and reproducible experimental framework, with the 15-day cold stress model offering a reliable platform for evaluating polyphenol-mediated neuroprotection and for subsequent mechanistic and translational investigations in stress-associated neurodegenerative conditions.

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CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

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