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Neuroprotective effects of resveratrol in a murine model of trimethyltin chloride-induced hippocampal injury

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Abstract

Objective: Trimethyltin chloride (TMT) is a neurotoxicant that induces neurodegeneration within the hippocampus. This study examined the therapeutic effects of resveratrol, a natural polyphenol, in a murine model of TMT-induced hippocampal damage.

Materials and methods: Forty NMRI mice were assigned to five experimental groups: control, control + resveratrol (40 mg/kg), TMT, TMT + resveratrol (10 mg/kg), and TMT + resveratrol (40 mg/kg). Hippocampal injury was established through a single intraperitoneal administration of TMT at a dose of 2.8 mg/kg. Resveratrol was orally administered daily for three weeks. The right-side hippocampus was used for biochemical analyses including malondialdehyde (MDA), tumor necrosis factor α (TNFα), glial fibrillary acidic protein (GFAP), and ionized calcium-binding adaptor (Iba1) levels, along with superoxide dismutase (SOD), catalase, and caspase 3 activities. The left-side hippocampus was processed for histological evaluation of CA1 neuronal density.

Results: The higher dose of resveratrol (40 mg/kg), in contrast to the lower dose (10 mg/kg), significantly attenuated TMT-induced neuronal loss within the CA1 area compared to the TMT group. It also caused a significant decrease in MDA levels and a significant enhancement of SOD and catalase activities relative to the TMT group. Furthermore, resveratrol (40 mg/kg) significantly reduced the TMT-induced elevations in caspase 3 activity and TNFα levels. It also significantly decreased the elevated GFAP levels. A decreasing trend in the Iba1 was noted in the TMT + resveratrol (40 mg/kg) group; however, it did not reach statistical significance.

Conclusion: The concordance between biochemical and histopathological data can support resveratrol neuroprotective efficacy, likely mediated by its antioxidant, anti-apoptotic, and anti-inflammatory mechanisms, underscoring its therapeutic potential in neurodegenerative disorders.

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Introduction

Trimethyltin chloride (TMT), an organometallic neurotoxin, elicits selective neurodegeneration within the central nervous system, with particular vulnerability observed in the hippocampal formation (Liu et al. 2021). The neuropathological manifestations of TMT intoxication -including cognitive impairment, aggressive behavior, and seizure-like activity- share remarkable similarity with clinical features of dementia, suggesting its utility as an experimental model of neurodegeneration (Geloso et al. 2011). At the cellular level, TMT neurotoxicity is mediated through multiple mechanisms including calcium dyshomeostasis, mitochondrial dysfunction, oxidative stress, and upregulation of amyloid precursor protein (APP) expression (Baciak et al. 2017). Furthermore, TMT exposure triggers neuroinflammatory cascades characterized by elevated pro-inflammatory cytokines and reactive nitrogen species. Prior investigations have reported that microglial activation elicited by TMT aggravates neuronal loss (Billingsley et al. 2006; Lee et al. 2016).

Resveratrol (3,4,5-trihydroxystilbene), a natural polyphenolic agent abundant in berries and grapes, has gained considerable attention as a promising therapeutic candidate owing to its pleiotropic biological activities (Meng et al. 2021). Beyond its well-documented cardioprotective and anticancer properties, resveratrol exhibits potent anti-inflammatory and antioxidant effects through modulation of multiple signaling pathways (Owjfard et al. 2024). Notably, recent evidence demonstrates its efficacy in mitigating metabolic and neurological disorders including amelioration of cognitive deficits in diabetic models through improvements in mitochondrial function and glucose metabolism (Aguilar-Garcia et al. 2024; Lotfi et al. 2020). These neuroprotective properties, coupled with its ability to cross the blood-brain barrier, position resveratrol as an attractive intervention for neurodegenerative conditions.

While the anti-inflammatory and antioxidant properties of resveratrol are well-documented, its specific multimodal mechanisms in the context of TMT-induced neurotoxic profile, characterized by selective hippocampal damage and robust glial activation, remain less explored. Through integrated biochemical and histological analyses, this study aims to elucidate whether resveratrol can concurrently ameliorate oxidative stress, attenuate apoptosis, suppress neuroinflammation, and modulate glial cell activation in the TMT-induced murine model of hippocampal neurodegeneration. The primary objective is to provide a comprehensive mechanistic insight into resveratrol pleiotropic actions, thereby clarifying its potential as a therapeutic candidate for targeting complex neurodegenerative pathways.

Materials and Methods

Animals

In this experimental study, forty adult male NMRI mice (weighing 22–27 g; aged 11–13 weeks) were obtained from the Center for Reproduction and Breeding of Laboratory Animals at the University of Tehran (Tehran, Iran). Animals were housed in groups of four per cage in transparent polypropylene cages under a controlled temperature of 22–24°C, a humidity of 45–50%, and a 12-hr light/dark cycle. All mice had *ad libitum* access to standard rodent chow and tap water. The experimental procedures were conducted in accordance with the guidelines of the U.S. National Institutes of Health (NIH) for the care and use of laboratory animals. Ethical approval for the study was obtained from the Ethics Committee of Shahed University (IR.SHAHED.REC.1403.009).

Experimental design

The study employed a single intraperitoneal (i.p.) injection of

trimethyltin chloride (TMT; 2.8 mg/kg, Merck, Germany) dissolved in 0.9% sodium chloride (NaCl) to induce hippocampal injury, based on established neurotoxicity protocols (Gao et al. 2023). Resveratrol (Sigma-Aldrich, USA) was administered orally at doses of 10 or 40 mg/kg/day, dissolved in 10% cremophor. The resveratrol dosages were chosen based on prior reports indicating potential dose-dependent neuroprotective effects, with 10 mg/kg representing an effective low dose that improves cognitive function (Moretti et al. 2021), and 40 mg/kg serving as a high dose exerting pronounced anti-inflammatory (He et al. 2025; Zhao et al. 2015) and antioxidant (Akosman et al. 2021) effects.

Animal allocation to the five experimental groups (n=8 per group) was performed using a computer-generated random number sequence to ensure unbiased distribution. The experimental groups included:

1) Control group: Received a single i.p. administration of 0.9% NaCl, followed by daily oral gavage of the resveratrol vehicle (cremophor 10%) for 3 weeks.

2) Control + Resveratrol: Received a single i.p. injection of 0.9% NaCl, followed by oral administration of resveratrol at 40 mg/kg once daily for 3 weeks.

3) TMT group: Received a single i.p. administration of TMT (2.8 mg/kg), followed by daily oral gavage of the resveratrol vehicle (10% cremophor) for 3 weeks.

4) TMT + Resveratrol 10 mg/kg group: Received a single i.p. injection of TMT (2.8 mg/kg), followed by daily oral administration of resveratrol at 10 mg/kg for 3 weeks.

5) TMT + Resveratrol 40 mg/kg group: Received a single i.p. injection of TMT (2.8 mg/kg), followed by daily oral administration of resveratrol at 40 mg/kg for 3 weeks.

At the end of the experimental period, the animals were deeply anesthetized using a combination of ketamine (150 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). Adequate depth of anesthesia was verified by the absence of a withdrawal response to toe pinch stimulation. The mice were subsequently subjected to transcardial perfusion with approximately 20 mL of ice-cold 0.9% saline to remove circulating blood. After perfusion, the brains were carefully removed from the cranial cavity.

Preparation of hippocampal tissue homogenate and supernatant

For biochemical evaluations, the hippocampal tissue from the right hemisphere was carefully dissected and homogenized in ice-cold Tris buffer (150 mM, pH 7.4; 2% w/v) to optimize protein solubilization and preserve molecular integrity. The resulting homogenate was centrifuged at 7,000 rpm for 10 min at 4 °C to separate cellular debris. The clear supernatant was then collected and stored at −70 °C until further biochemical analyses were conducted. All biochemical analyses were conducted by investigators blinded to the group assignments.

Determination of total protein content in hippocampal tissue

Protein concentration in hippocampal homogenates was measured using the Bradford assay, a color-based analytical method that depends on the binding of Coomassie Brilliant Blue G-250 dye to proteins. In brief, 20 µL of each homogenate sample was added to 250 µL of Bradford reagent, allowed to stand for 5 min at room temperature, and then, analyzed at 595 nm with a microplate reader. The amount of protein in each sample was determined by comparison with a bovine serum albumin (BSA) standard curve.

Evaluation of oxidative stress and apoptotic activity in the hippocampus

To assess oxidative stress, lipid peroxidation—a hallmark of oxidative cellular injury—was quantified by measuring malondialdehyde (MDA) levels

using a commercial MDA assay kit (Cat. # Kiazist-001; Kiazist Co., Hamedan, Iran) (Abbasi et al. 2025).

In addition to lipid peroxidation analysis, the enzymatic activities of two critical antioxidant defense enzymes—superoxide dismutase (SOD) and catalase—were evaluated using commercially available assay kits specific for each enzyme: SOD assay kit (Cat. # Kiazist-003) and catalase assay kit (Cat. # Kiazist-004), both procured from Kiazist Co. (Hamedan, Iran) (Tayanloo-Beik et al. 2022).

To evaluate apoptotic activity within hippocampal tissue, caspase 3 activity was quantified in accordance with the method described by Fahanik-Babaei et al. (2019), using a colorimetric assay kit (Cat. # ab39401, Abcam, UK) (Fahanik-Babaei et al. 2019). This assay is grounded on the caspase 3–mediated cleavage of a specific chromogenic substrate, p-nitroaniline (pNA). Tissue lysates were incubated with a reaction buffer comprising sucrose, CHAPS (3-[(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate), HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), dithiothreitol (DTT), and ethylenediaminetetraacetic acid (EDTA), along with the caspase 3 substrate. Enzymatic hydrolysis of the substrate resulted in the release of pNA, the absorbance of which was quantified at 405 nm using a microplate reader (BioTek, USA). The level of its activity in each group is presented as the average optical density.

Quantification of hippocampal TNFα, GFAP, and Iba1 levels

The concentrations of tumor necrosis factor-alpha (TNFα), ionized calcium-binding adaptor molecule 1 (Iba1), and glial fibrillary acidic protein (GFAP) in the hippocampus were quantified utilizing the sandwich enzyme-linked immunosorbent assay (ELISA) method. TNFα (Cat. #sc-52746, Santa Cruz Biotechnology, USA), a key pro-inflammatory cytokine, was measured to assess the extent of neuroinflammatory signaling (Akbarizadeh-Mashkani et al. 2025). GFAP and Iba1, well-established markers of astrocyte and microglial activation respectively, were used to evaluate glial reactivity associated with neuroinflammation and injury response (Batlle et al. 2015). GFAP levels were determined using a specific ELISA kit (Cat. #MBS2515511, MyBioSource Inc., USA), while Iba1 quantification was performed using a corresponding kit (Cat. #MBS2709083, MyBioSource Inc., USA).

Absorbance readings were obtained at the appropriate wavelengths using a Synergy HT microplate reader (BioTek Instruments, USA), and protein levels were extrapolated using calibration curves prepared for each factor. All values were adjusted relative to the total protein content of the hippocampus and are expressed as pg/mg protein, ensuring reliable intergroup comparisons.

Histopathological assessment of hippocampus

To investigate morphological and cellular alterations in the hippocampus, tissue samples from the left hemisphere were fixed, embedded in paraffin, and sectioned coronally at a thickness of 5 µm. The sections were carefully selected based on stereotaxic coordinates ranging from 2.18 to 2.46 mm behind the bregma, targeting CA1 subregion of the hippocampus—an area particularly susceptible to excitotoxic and neurotoxic insults.

Nissl staining was performed using Cresyl violet acetate solution (Cat. # C5042, Sigma-Aldrich, USA) to visualize neuronal somata. This method enabled clear delineation of neuronal morphology and facilitated the assessment of neuronal density, a critical indicator of neurodegenerative progression. Pyramidal neurons within the CA1 layer were identified based on their characteristic large, triangular somata, a clear nucleus

with a single distinct nucleolus, and abundant Nissl substance. For quantification, only neurons exhibiting intact cytoplasmic boundaries and distinct nucleoli were classified as morphologically viable. For consistency, neuronal quantification was carried out within a fixed 0.1 mm^2 area of the CA1 pyramidal layer across all specimens.

Digital images of stained sections were analyzed using ImageJ software (Version 1.53, NIH, USA). To eliminate observational bias, all histopathological evaluations were performed on coded slides assessed by a single investigator blinded to the experimental groups.

Data analysis

Data are presented as mean ± SEM and were processed in GraphPad Prism 9.5. Normality was examined using the Shapiro–Wilk test. Differences among groups were tested by one-way ANOVA with Tukey's post hoc procedure, and $p<0.05$ was considered statistically significant.

Results

Effects of resveratrol on oxidative stress biomarkers in the hippocampus

Three weeks following the intervention, significant alterations in hippocampal oxidative stress markers were observed across experimental groups. Administration of TMT led to a marked elevation in MDA levels—a key indicator of lipid peroxidation—compared to the control group ($p<0.001$). Similarly, mice co-treated with TMT and resveratrol at 10 mg/kg exhibited significantly higher MDA concentrations relative to the control ($p<0.001$). However, although the 10 mg/kg resveratrol dose did not produce a statistically significant reduction in MDA levels relative to the TMT-only group, 40 mg/kg resveratrol resulted in a significant attenuation of MDA accumulation in hippocampal tissue ($p=0.012$) (Figure 1a).
In contrast, SOD activity, a key antioxidant defense enzyme, was significantly diminished in the TMT group versus controls ($p<0.001$). Likewise, TMT-treated mice receiving 10 mg/kg resveratrol showed a substantial reduction in SOD activity compared to the control group ($p=0.0048$). While the 10 mg/kg dose did not significantly restore SOD activity relative to the TMT group, the higher dose of 40 mg/kg resveratrol elicited a significant enhancement in SOD levels ($p=0.031$) (Figure 1b).

Catalase activity followed a similar pattern. Exposure to TMT significantly suppressed catalase function in hippocampal tissue when compared to controls ($p<0.001$). Co-treatment with resveratrol at both 10 mg/kg and 40 mg/kg resulted in significantly lower catalase activity relative to the controls ($p=0.001$ and $p=0.036$, respectively). Nonetheless, both doses of resveratrol demonstrated a capacity to counteract TMT-induced catalase suppression: the 10 mg/kg dose significantly restored enzyme activity relative to the TMT group ($p=0.004$), while the 40 mg/kg dose produced an even more pronounced recovery ($p=0.002$) (Figure 1c).

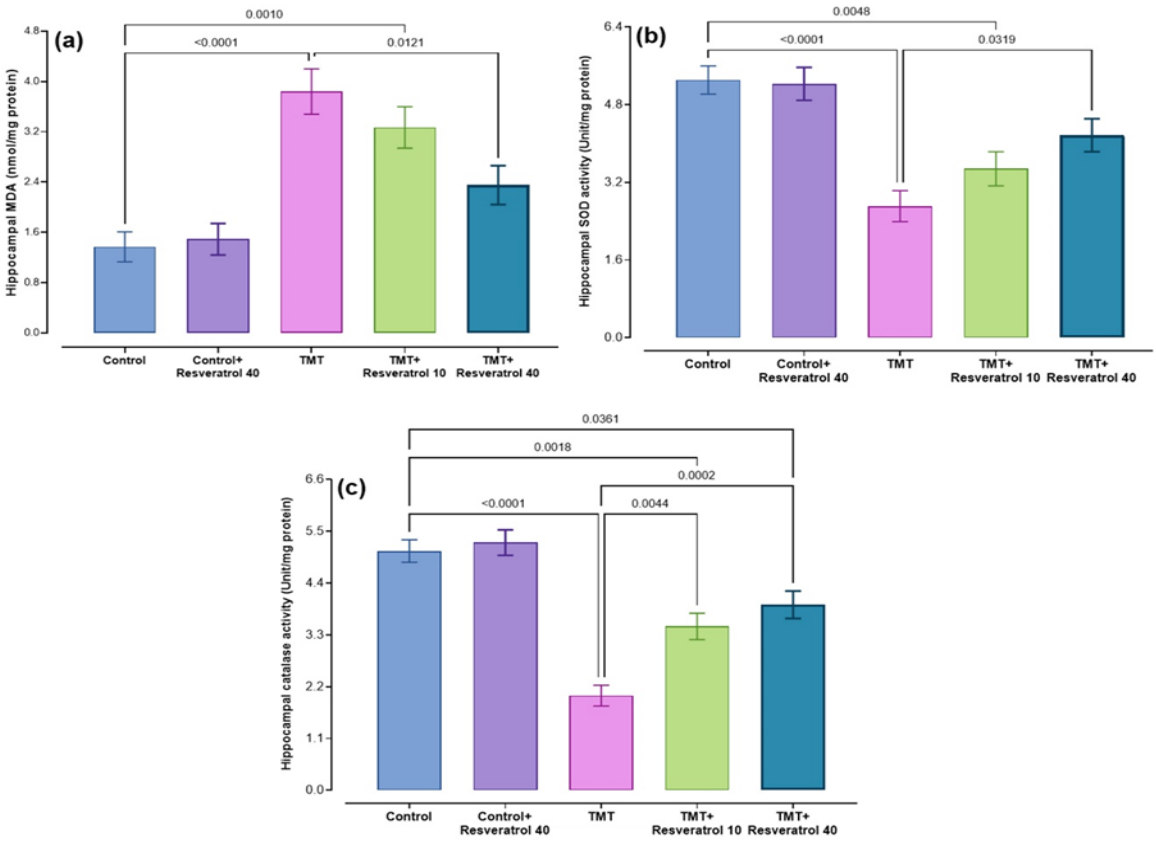

Figure 1. Quantitative data for oxidative stress-relevant factors such as lipid peroxidation index malondialdehyde (MDA) (a) and activity of antioxidants superoxide dismutase (SOD) (b) and catalase (c). Values are means ± SEM of n=8/group.

Effects of resveratrol on apoptotic and neuroinflammatory markers in the hippocampus

TMT administration resulted in a significant upregulation of caspase 3 activity, a critical executor of apoptosis, when compared to the control mice ($p=0.0080$). Co-treatment with 10 mg/kg resveratrol did not significantly alter caspase 3 levels relative to either the control or TMT groups ($p>0.05$). However, a higher dose of resveratrol (40 mg/kg) significantly reduced caspase 3 activity in hippocampal tissue compared to the TMT group ($p=0.037$), indicating a dose-dependent anti-apoptotic effect (Figure 2a). In terms of neuroinflammatory response, TMT exposure markedly elevated hippocampal levels of TNFα, a pro-inflammatory cytokine, compared to controls ($p<0.001$). Mice treated with TMT and 10 mg/kg resveratrol also exhibited significantly increased TNFα levels relative to the control group ($p=0.002$). Nevertheless, while the lower dose of resveratrol did not significantly attenuate TNFα expression compared to the TMT-only group ($p>0.05$), the 40 mg/kg dose significantly suppressed TNFα levels in hippocampal tissue ($p=0.025$), demonstrating resveratrol anti-inflammatory efficacy at higher concentrations (Figure 2b).

Effects of resveratrol on astrocytic and microglial markers in the hippocampus

Three weeks post-TMT administration, a substantial elevation in hippocampal levels of GFAP was shown in TMT-treated mice relative to the controls ($p<0.001$). Similarly, resveratrol at both 10 and 40 mg/kg doses resulted in a marked increase in GFAP levels relative to controls ($p<0.001$ and $p=0.030$, respectively). However, while the 10 mg/kg dose did not significantly reduce GFAP levels when compared to the TMT-only rodents

($p>0.05$), administration of 40 mg/kg resveratrol markedly attenuated GFAP levels in hippocampal tissue ($p=0.007$), indicating a potential dose-dependent modulation of astrocyte activation (Figure 3a).

Hippocampal Iba1 was significantly elevated in the TMT group compared to controls ($p<0.001$). Both resveratrol-treated groups (10 mg/kg and 40 mg/kg) also exhibited elevated Iba1 levels compared to the control group ($p<0.001$ and $p=0.037$, respectively). However, neither dose of resveratrol produced a statistically meaningful decline in Iba1 expression relative to the TMT group ($p>0.05$) (Figure 3b).

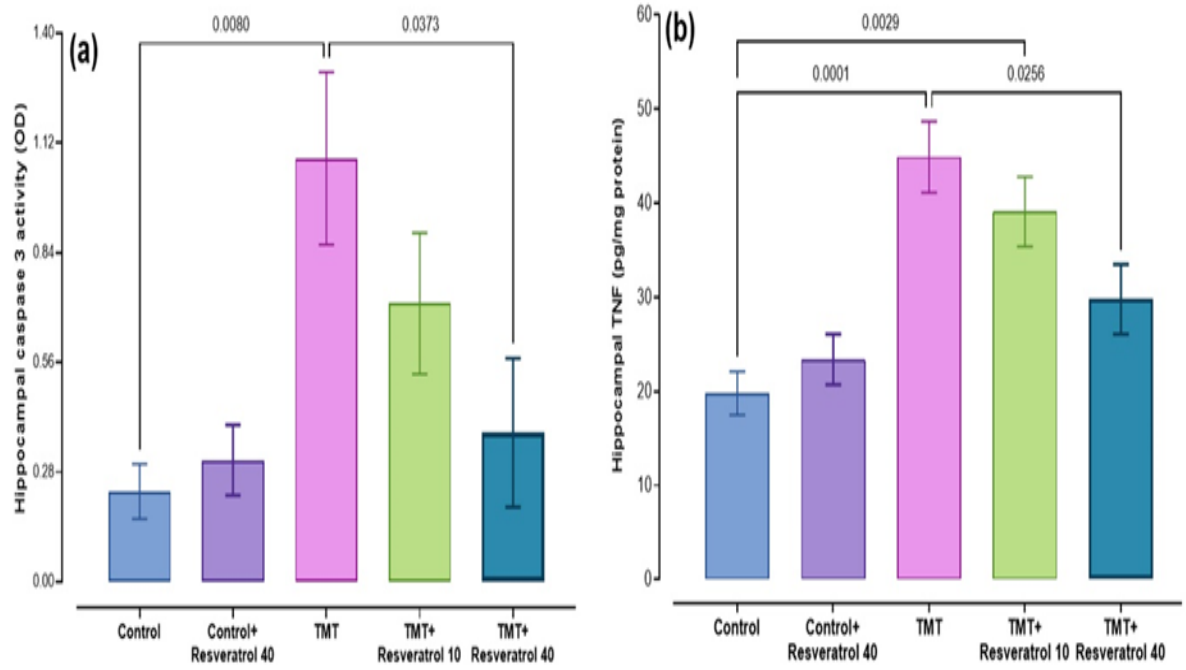

Figure 2. Quantitative data for apoptosis and inflammation-related markers including caspase-3 enzymatic activity (a) and TNFα levels (b). Values are means ± SEM with n=8/group.

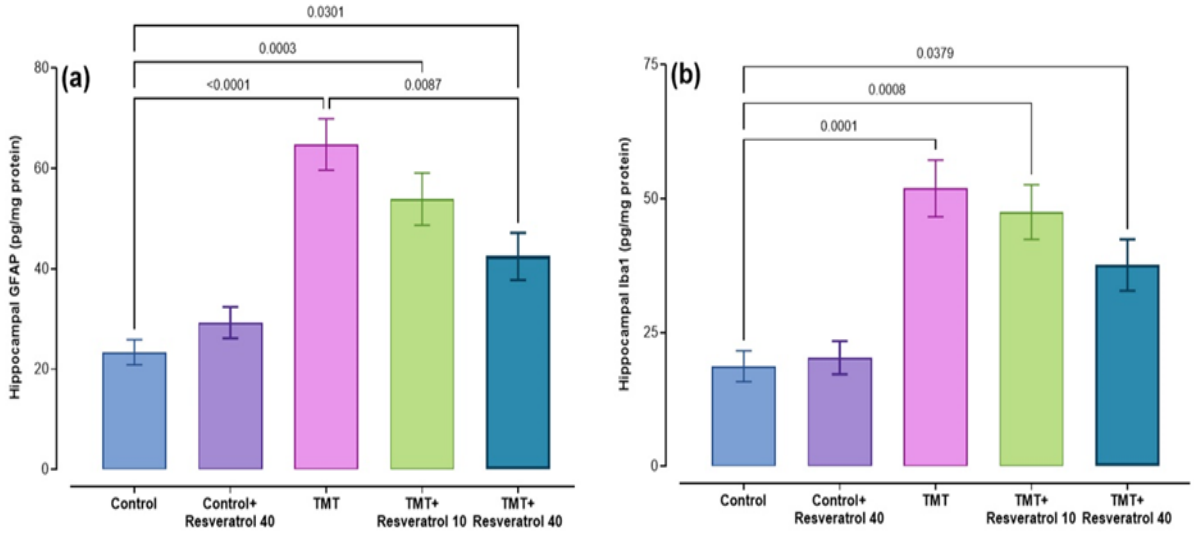

Figure 3. Quantitative data for glial activation markers including glial fibrillary acidic protein (GFAP) as a marker of astrocyte activation (a) and ionized calcium-binding adapter molecule 1 (Iba1) as a marker of microglial activation (b). Values are means ± SEM of n=8/group.

Effects of resveratrol on CA1 neuronal integrity

Histological evaluation of the CA1 subregion of the hippocampus showed a remarkable reduction in neuronal density in the TMT-exposed animals compared to the controls ($p<0.001$), indicating substantial neurodegeneration. Mice receiving 10 mg/kg resveratrol alongside TMT also exhibited significantly diminished neuronal density compared to controls ($p=0.012$). While resveratrol at the lower dose did not produce a notable improvement in neuronal survival compared to the TMT-only group ($p>0.05$), treatment with 40 mg/kg maintained neuronal density to a significant extent in the CA1 area ($p=0.005$) (Figure 4).

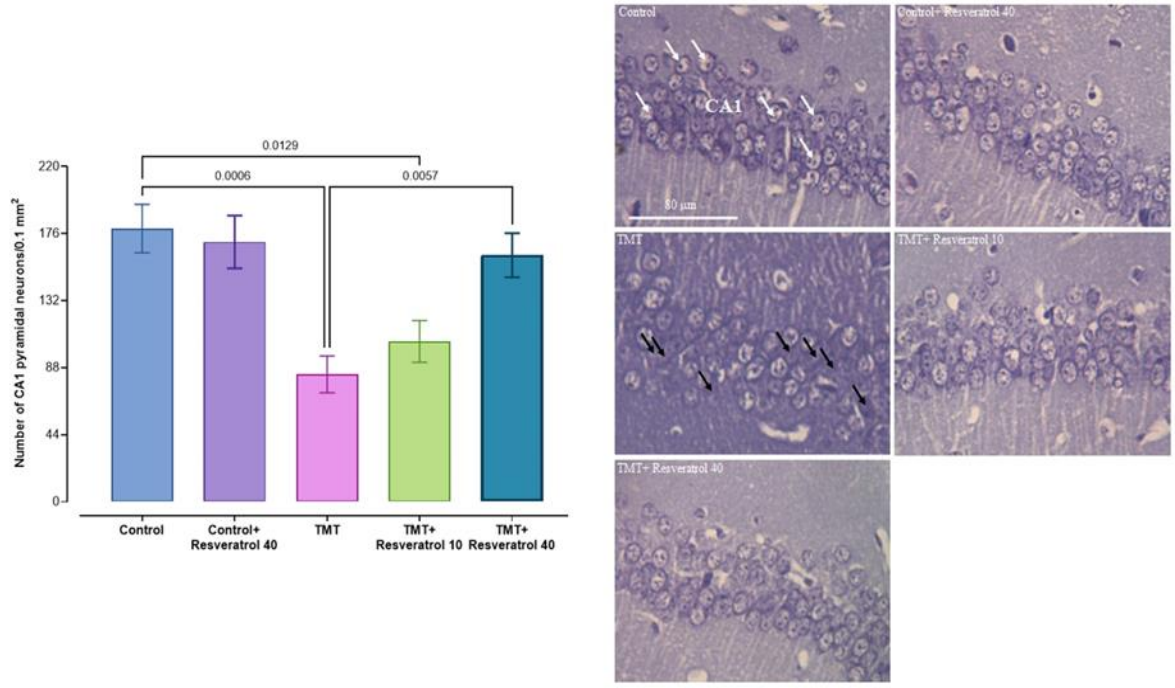

Figure 4. Neuronal integrity in the CA1 region of the hippocampus. Bar graph represents the density of surviving Nissl-stained neurons, accompanied by representative photomicrographs of coronal hippocampal sections. Within the micrographs, morphologically intact pyramidal neurons are indicated by white arrows, whereas degenerating pyramidal neurons are denoted by black arrows. Values are means ± SEM of n=8/group. Magnification = 200 X, scale bar = 80 µm.

Discussion

Our results revealed that three weeks of oral administration of resveratrol dose-dependently attenuated TMT-induced hippocampal injury, potentially via modulating oxidative stress, apoptosis, neuroinflammation, and glial response.

Oxidative stress leads to neuronal damage and learning and memory impairment (Butterfield and Boyd-Kimball 2020). In this investigation, we observed that administration of TMT significantly increased MDA levels in the hippocampus, indicating increased lipid peroxidation. This observation is consistent with earlier studies showing that TMT induces oxidative damage in neural tissues (Song et al. 2021; Thong-Asa et al. 2020). Resveratrol (40 mg/kg) reduced MDA levels, suggesting its efficacy in mitigating peroxidation of lipid. This is consistent with studies indicating that resveratrol decreases MDA concentrations in the brain, thereby attenuating oxidative stress (Ates et al. 2007; Li et al. 2025). Furthermore, TMT exposure led to a marked decrease in the activities of key antioxidant enzymes in the hippocampus, which was consistent with prior studies (Rostami et al. 2022). SOD and catalase play a pivotal role in neutralizing reactive oxygen species (ROS), and their diminished activity reflects compromised antioxidant defense

mechanisms (Jomova et al. 2024). Resveratrol treatment at 40 mg/kg not only restored SOD activity but also enhanced catalase function beyond levels observed in the TMT group. These results corroborate findings from other studies where resveratrol administration increased the activities of SOD and catalase in a dose-dependent manner, highlighting its role in bolstering endogenous antioxidant defenses (Bai et al. 2024). The observed beneficial effects of resveratrol in the hippocampus underscore its therapeutic potential in counteracting oxidative damage associated with neurodegenerative conditions. By reducing lipid peroxidation and enhancing antioxidant enzyme activities, resveratrol may contribute to preserving neuronal integrity and function (Farkhakfar et al. 2023).

The observed elevation of caspase 3 activity following TMT administration underscores potent pro-apoptotic effects of TMT on hippocampal neurons. This aligns with prior research indicating that TMT induces neuronal apoptosis through mitochondrial dysfunction and oxidative stress pathways (Liu et al. 2023). Notably, co-treatment with resveratrol at 40 mg/kg significantly ameliorated caspase 3 activity, suggesting a dose-dependent neuroprotective effect. This finding is consistent with studies demonstrating resveratrol ability to inhibit caspase 3 activation and promote cell survival in various models of neuronal injury (Yildizhan et al. 2022). For instance, Ulakcsai et al. reported that resveratrol dose-dependently inhibited caspase 3 in primary mouse fibroblasts subjected to serum deprivation, highlighting its potential to mitigate apoptosis through regulation of the p38 MAPK pathway (Ulakcsai et al. 2015). Similarly, resveratrol protects hippocampal neurons from β-amyloid-induced neurotoxicity by caspase 3 inhibition, further supporting its role in combating neurodegenerative processes (Han et al. 2004). The lack of significant effect at the 10 mg/kg dose in our study, suggests that higher concentrations of resveratrol may be necessary to achieve therapeutic efficacy in mitigating TMT-induced apoptotic pathways. These findings underscore resveratrol potential as a neuroprotective agent, particularly at higher doses, in conditions characterized by heightened apoptotic activity.

The observed elevation of hippocampal TNFα levels following TMT exposure underscores the neuroinflammatory response associated with neurotoxic insults (Faryadras et al. 2025). While 10 mg/kg resveratrol did not significantly attenuate TNFα expression, a higher dose of 40 mg/kg effectively suppressed its levels, highlighting resveratrol dose-dependent anti-inflammatory properties. These findings align with prior studies demonstrating resveratrol capacity to mitigate neuroinflammation by downregulating pro-inflammatory cytokines such as TNFα and interleukin-1β in various models of brain injury. The efficacy of the higher resveratrol dose in reducing TNFα levels suggests its potential therapeutic role in modulating neuroinflammatory pathways, possibly through the suppression of NF-κB (Feng et al. 2016; Gatson et al. 2013; Zhang et al. 2010). This study contributes novel insights into the dose-dependent effects of resveratrol on TMT-induced neuroinflammation, emphasizing the importance of dosage in achieving optimal anti-inflammatory outcomes in neurotoxic conditions.

Our results elucidated the modulatory effects of resveratrol on glial activation within the hippocampus following TMT-induced neurotoxicity, highlighting both astrocytic and microglial responses. TMT exposure significantly elevated GFAP levels, indicative of reactive astrogliosis—a hallmark of neuroinflammatory processes. This was in line with a previous study (Taheri et al. 2024). While oral resveratrol at both doses resulted in increased GFAP levels compared to controls, only the higher dose significantly

attenuated GFAP levels. This dose-dependent attenuation suggests that higher concentrations of resveratrol may effectively mitigate astrocyte activation in the context of TMT-induced neurotoxicity. In a lipopolysaccharide-induced cognitive impairment mouse model, Zeini et al. indicated that resveratrol treatment suppresses hippocampal GFAP expression (Zeini et al. 2024).

In this study, Iba1, a marker for microglial activation, was significantly increased following TMT exposure. Resveratrol treatment at either doses did not produce a statistically significant reduction in Iba1 levels compared to the TMT group, indicating a limited effect on microglial activation under the conditions tested. However, previous studies have demonstrated that resveratrol can inhibit microglial activation under certain pathological conditions. For instance, Liao et al. indicated that resveratrol inhibits inflammation and microglial activation in a stroke model (Liao et al. 2023). Our findings provide new understanding of how resveratrol distinctly affects different types of glial cells in the hippocampus, highlighting its capacity to attenuate astrocyte activation at higher doses while exhibiting limited influence on microglial activation in this model. This emphasizes the intricate nature of glial responses to neurotoxic insults and the need for further research to delineate the mechanisms by which resveratrol modulates glial activity.

The neuroprotective effect of resveratrol has previously been associated with its modulation of apoptotic pathways, particularly through regulation of Bax and Bcl-2 expression. In a TMT-induced neurotoxicity model, resveratrol improved working, reference, and spatial memory impairments, which correlated with reduced hippocampal cell death (Nezhad et al. 2023). However, this study primarily focused on intrinsic mitochondrial apoptosis. In contrast, our study investigated a broader range of mechanisms including oxidative stress, neuroinflammation, astrocyte and microglial activation, and downstream caspase 3 activity. This comprehensive approach provides novel insight into the multifaceted protective actions of resveratrol against TMT-induced hippocampal damage.

This study has some limitations that should be considered. First, the absence of behavioral data, while a conscious choice to focus resources on a detailed mechanistic profile, limits the direct correlation of our biochemical and histological findings with functional recovery. Second, our investigation was confined to a specific treatment window and dosage; the long-term neuroprotective effects of resveratrol, along with a comprehensive dose-response analysis and exploration of alternative administration routes, remain to be determined. Addressing these aspects in future work will be critical for optimizing resveratrol therapeutic potential.

This study demonstrates that resveratrol provides significant, dose-dependent neuroprotection in a murine hippocampal neurodegeneration model induced by TMT. The higher dose (40 mg/kg) was effective in mitigating neuronal loss, potentially through a multimodal action that concurrently enhanced antioxidant defenses, suppressed apoptosis, and attenuated neuroinflammation, with a pronounced effect on astrocytic reactivity. The concordance between histological preservation and the amelioration of these core pathological pathways strongly supports the therapeutic potential of resveratrol for conditions involving hippocampal damage. Future studies elucidating its long-term functional benefits and precise molecular targets are justified to advance its clinical translation.

Conflicts of interest

Nothing to declare.

Funding

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Ethical Considerations

The experimental procedures were conducted in accordance with the guidelines of the National Institutes of Health (NIH) for the care and use of laboratory animals.

Code of Ethics

IR.SHAHED.REC.1403.009

Authors' Contributions

Mohadeseh Mokhtarzadeh-Bazargani performed experiments, helped in data analysis and manuscript writing; Saeid Iranzadeh analyzed data and wrote the initial manuscript; Mehrdad Roghani conceived, designed, funded, and supervised the study, analysed data, and wrote the final manuscript. All authors approved the final manuscript for submission and publication.

Abbreviations

CA1, Cornu Ammonis 1; GFAP, Glial fibrillary acidic protein; Iba1, Ionized calcium-binding adaptor 1; MDA, Malondialdehyde; SOD, Superoxide dismutase; TMT, Trimethyltin; TNF-α, Tumor necrosis factor-alpha

References

Abbasi E, Mirzaei F, Mashayekhi S, et al. (2025) Effects of opium on hippocampal-dependent memory, antioxidant enzyme levels, oxidative stress markers, and histopathological changes of rat hippocampus. Biochem Biophys Rep 42:101993

Aguilar-Garcia IG, Alpirez J, Castañeda-Arellano R, et al. (2024) Resveratrol and Exercise Produce Recovered Ankle and Metatarsus Joint Movements after Penetrating Lesion in Hippocampus in Male Rats. Brain Sci 14(10):980

Akbarizadeh-Mashkani MH, Afshinmajd S, Iranzadeh S, Roghani M (2025) Involvement of synaptophysin and microtubule-associated protein 2 in the neuroprotective effect of berberine in an amyloid β-induced rat model of Alzheimer's disease. Avicenna J Phytomed 15(6):1741–1754

Akosman MS, Türkmen R, Demirel HH (2021) Investigation of the protective effect of resveratrol in an MK-801-induced mouse model of schizophrenia. Environ Sci Pollut Res Int 28(46):65872–65884

Ates O, Cayli S, Altinoz E, et al. (2007) Neuroprotection by resveratrol against traumatic brain injury in rats. Mol Cell Biochem 294(1-2):137–44

Baciak L, Gasparova Z, Liptaj T, Juranek I (2017) In vivo magnetic resonance approach to trimethyltin induced neurodegeneration in rats. Brain Res 1673:111–116

Bai Y, Sui R, Zhang L, Bai B, Zhu Y, Jiang H (2024) Resveratrol Improves Cognitive Function in Post-stroke Depression Rats by Repressing Inflammatory Reactions and Oxidative Stress via the Nrf2/HO-1 Pathway. Neuroscience 541:50–63

Batlle M, Ferri L, Andrade C, et al. (2015) Astroglia-Microglia Cross Talk during Neurodegeneration in the Rat Hippocampus. Biomed Res Int 2015(1):102419

Billingsley M, Yun J, Reese B, Davidson C, Buck-Koehntop B, Veglia G (2006) Functional and structural properties of stannin: roles in cellular growth, selective toxicity, and mitochondrial responses to injury. J Cell Biochem 98(2):243–250

Butterfield DA, Boyd-Kimball D (2020) Mitochondrial Oxidative and Nitrosative Stress and Alzheimer Disease. Antioxidants (Basel) 9(9):818

Fahanik-Babaei J, Baluchnejadmojarad T, Nikbakht F, Roghani M (2019) Trigonelline protects hippocampus against intracerebral Aβ (1–40) as a model of Alzheimer's disease in the rat: Insights into underlying mechanisms. Metab Brain Dis 34:191–201

Farkhakfar A, Hassanpour S, Zendehdel M (2023) Resveratrol plays neuroprotective role on ketamine-induced schizophrenia-like behaviors and oxidative damage in mice. Neurosci Lett 813:137436 doi:10.1016/j.neulet.2023.137436

Faryadras K, Golchoobian R, Iranzadeh S, Roghani M (2025) Promising neuroprotective potential of naringenin against trimethyltin-induced cognitive

deficits and hippocampal neurodegeneration in rats. Front Neurosci 19:1567236 doi:10.3389/fnins.2025.1567236

Feng Y, Cui Y, Gao JL, et al. (2016) Resveratrol attenuates neuronal autophagy and inflammatory injury by inhibiting the TLR4/NF-κB signaling pathway in experimental traumatic brain injury. Int J Mol Med 37(4):921–30 doi:10.3892/ijmm.2016.2495

Gao Y, Liao W, Zhang R, et al. (2023) PK2/PKRs pathway is involved in the protective effect of artemisinin against trimethyltin chloride-induced hippocampal injury. Toxicology 486:153432 doi:10.1016/j.tox.2023.153432

Gatson JW, Liu MM, Abdelfattah K, et al. (2013) Resveratrol decreases inflammation in the brain of mice with mild traumatic brain injury. J Trauma Acute Care Surg 74(2):470–4; discussion 474–5

Geloso MC, Corvino V, Michetti F (2011) Trimethyltin-induced hippocampal degeneration as a tool to investigate neurodegenerative processes. Neurochem Int 58(7):729–738

Han YS, Zheng WH, Bastianetto S, Chabot JG, Quirion R (2004) Neuroprotective effects of resveratrol against beta-amyloid-induced neurotoxicity in rat hippocampal neurons: involvement of protein kinase C. Br J Pharmacol 141(6):997–1005

He X, Cao Z, Chen X, et al. (2025) Resveratrol Alleviates the Prenatally Intermittent Hypoxia-Induced Cognitive Impairment in Male Offspring Mice Through Modulating the SIRT1/HIF-1α Pathway. Brain Behav 15(3):e70413

Jomova K, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M (2024) Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. Arch Toxicol 98(5):1323–1367

Lee S, Yang M, Kim J, et al. (2016) Trimethyltin-induced hippocampal neurodegeneration: A mechanism-based review. Brain Res Bull 125:187–199

Li C, Ge H, Huang J, et al. (2025) Resveratrol alleviates depression-like behaviors by inhibiting ferroptosis via AKT/NRF2 pathway. Brain Res Bull 220:111136

Liao H, Huang J, Liu J, et al. (2023) Resveratrol Inhibits Activation of Microglia after Stroke through Triggering Translocation of Smo to Primary Cilia. J Pers Med 13(2)

Liu Z, Lv J, Zhang Z, et al. (2021) The main mechanisms of trimethyltin chloride-induced neurotoxicity: Energy metabolism disorder and peroxidation damage. Toxicol Lett 345:67–76

Liu Z, Wang L, Wang Y, et al. (2023) Quantitative proteomics reveals the neurotoxicity of trimethyltin chloride on mitochondria in the hippocampus of mice. Neurotoxicology 99:162–176

Lotfi K, Nouri M, Askari G (2020) The effect of resveratrol supplementation on improving non-alcoholic fatty liver: a review on randomized clinical trials. Clin Exc 9(4):11–22

Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J (2021) Anti-inflammatory action and mechanisms of resveratrol. Molecules 26(1):229

Moretti RL, Dias EN, Kiel SG, et al. (2021) Behavioral and morphological effects of resveratrol and curcumin in rats submitted to doxorubicin-induced cognitive impairment. Res Vet Sci 140:242–250

Nezhad MH, Ortegoli Z, Baazm M (2023) Effect of Resveratrol on Hippocampal Injury Induced by Trimethyltin Chloride in Rats. J Mazandaran Univ Med Sci 33(1):287–294

Owjfard M, Rahimian Z, Ghaderpanah R, et al. (2024) Therapeutic effects of intranasal administration of resveratrol on the rat model of brain ischemia. Heliyon 10(12)

Rostami A, Taleahmad F, Haddadzadeh-Niri N, et al. (2022) Sinomenine Attenuates Trimethyltin-Induced Cognitive Decline via Targeting Hippocampal Oxidative Stress and Neuroinflammation. J Mol Neurosci 72(8):1609–1621

Song W-J, Yun J-H, Jeong M-S, et al. (2021) Inhibitors of lipoxygenase and cyclooxygenase-2 attenuate trimethyltin-induced neurotoxicity through regulating oxidative stress and pro-inflammatory cytokines in human neuroblastoma SH-SY5Y Cells. Brain Sci 11(9):1116

Taheri M, Roghani M, Sedaghat R (2024) Metformin Mitigates Trimethyltin-Induced Cognition Impairment and Hippocampal

Neurodegeneration. Cell Mol Neurobiol 44(1):70

Tayanloo-Beik A, Kiasalari Z, Roghani M (2022) Paeonol ameliorates cognitive deficits in streptozotocin murine model of sporadic Alzheimer's disease via attenuation of oxidative stress, inflammation, and mitochondrial dysfunction. J Mol Neurosci 72(2):336–348

Thong-Asa W, Prasartsri S, Klomkleaw N, Thongwan N (2020) The neuroprotective effect of betanin in trimethyltin-induced neurodegeneration in mice. Metab Brain Dis 35:1395–1405

Ulakcsai Z, Bagaméry F, Vincze I, Szökő É, Tábi T (2015) Protective effect of resveratrol against caspase 3 activation in primary mouse fibroblasts. Croat Med J 56(2):78–84

Yildizhan K, Çinar R, Naziroğlu M (2022) The involvement of TRPM2 on the MPP(+)-induced oxidative neurotoxicity and apoptosis in hippocampal neurons from neonatal mice: protective role of resveratrol. Neurol Res 44(7):636–644

Zeini S, Davoodian N, Kazemi H, et al. (2024) Resveratrol prevents cognitive impairment and hippocampal inflammatory response induced by lipopolysaccharide in a mouse model of chronic neuroinflammation. Physiol Behav 278:114508

Zhang F, Liu J, Shi JS (2010) Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation. Eur J Pharmacol 636(1-3):1–7

Zhao HF, Li N, Wang Q, Cheng XJ, Li XM, Liu TT (2015) Resveratrol decreases the insoluble Aβ1-42 level in hippocampus and protects the integrity of the blood-brain barrier in AD rats. Neuroscience 310:641–9