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Research Paper

Galantamine Attenuates Aluminum Chloride-Induced Cytotoxicity and Modulates Tumor Necrosis Factor Expression in SH-SY5Y Cells

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ABSTRACT

Background: Neuroinflammation and oxidative stress are central to Alzheimer's disease pathogenesis. Aluminum chloride ($AlCl_3$) is a neurotoxicant utilized to model these pathological features, whereas galantamine, a clinically approved therapeutic, exhibits secondary anti-inflammatory properties. To evaluate the protective efficacy of galantamine against $AlCl_3$-induced cytotoxicity and its modulatory impact on tumor necrosis factor (TNF) gene expression in human neuroblastoma cells.

Methods: SH-SY5Y cells were exposed to varying concentrations of $AlCl_3$ or galantamine for 24 hours. For combination treatments, cells were pretreated with galantamine prior to $AlCl_3$ exposure. Cellular viability was evaluated using the MTT assay, and relative TNF mRNA expression was quantified via RT-qPCR.

Results: High-dose $AlCl_3$ (500 µg/mL) significantly decreased cell viability to 65% and upregulated TNF expression by 2.3-fold ($p<0.001$). Pretreatment with galantamine (100 µg/mL) partially restored cell viability (88–95%) and significantly suppressed the $AlCl_3$-induced TNF overexpression to 0.36-fold of control levels ($p<0.001$).

Conclusion: Galantamine confers neuroprotection against metal-induced cellular injury by downregulating pro-inflammatory signaling cascades. These findings highlight its potential therapeutic utility in mitigating neuroinflammation-driven neurodegenerative processes beyond its primary cholinergic action.

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Introduction

Alzheimer's disease (AD) represents a persistent neurodegenerative condition defined by a gradual deterioration of cognitive functions, which manifests as deficits in behavior, reasoning, learning, and memory [1]. The primary pathological signatures associated with AD encompass cholinergic deficits, oxidative damage, extracellular amyloid-beta (Aβ) aggregations, and intracellular tangles formed by hyperphosphorylated tau proteins [2]. While multiple theoretical frameworks including the neuroinflammatory, tau, Aβ cascade, and cholinergic hypotheses attempt to elucidate the origins of AD, the precise etiology continues to elude researchers [3].

In the realm of in vitro research, the human neuroblastoma cell line SH-SY5Y serves as a prominent model for investigating neurodegenerative conditions such as AD. Because these cells possess distinct neuronal traits and are capable of continuous proliferation, they provide an excellent platform for exploring the molecular basis of neurotoxicity [4]. To simulate AD-like cellular pathology, researchers frequently utilize aluminum chloride ($AlCl_3$), a potent neurotoxic agent known to trigger oxidative stress [5]. Exposure to $AlCl_3$ elevates reactive oxygen species (ROS) generation within neurons, subsequently driving plaque accumulation, neuroinflammation, and widespread neuronal injury [6].

Currently, galantamine is utilized clinically as an acetylcholinesterase (AChE) inhibitor to manage AD symptoms [7]. Beyond its primary mechanism, galantamine acts as an antioxidant by scavenging ROS, thereby mitigating oxidative neuronal injury and conferring neuroprotection. Furthermore, it suppresses the release of pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), primarily through interactions with the alpha-7 nicotinic acetylcholine receptor [8]. This robust anti-inflammatory action is largely driven by the upregulation of acetylcholine a neurotransmitter with established anti-inflammatory effects as well as the blockade of the NF-κB signaling cascade [9]. Consequently, this research was designed to assess how galantamine and $AlCl_3$ influence both cellular survival and TNF gene transcription in SH-SY5Y cells. Additionally, we sought to determine if galantamine pretreatment could shield these cells from $AlCl_3$-driven neurotoxicity by regulating TNF-linked inflammatory pathways.

Materials and Methods

SH-SY5Y Cell Line and Culture Conditions

The National Cell Bank of Iran supplied the human neuroblastoma cells used in this study. Cryopreserved vials were taken from liquid nitrogen and quickly defrosted using a water bath set to 37°C. Just before the ice melted entirely, the exterior of the vial was sanitized with 70% ethanol to ensure sterility during subsequent handling. The cells were then propagated in RPMI-1640 medium enriched with antibiotics and 10% fetal bovine serum (Gibco, U.K.). The culture flasks were kept in a 37°C incubator providing a humidified 5% CO_2 atmosphere, and passaging was performed whenever the cell monolayer reached 70% to 80% confluence.

Preparation of Reagents

Aluminum chloride ($AlCl_3$) was obtained from THOMAS BAKER L.T.D. (India). Galantamine powder was purchased from China. MTT dye powder was obtained from Roth (Germany). RPMI-1640 medium powder was purchased from Capricorn Scientific (Germany). All reagents were prepared using sterile double-distilled water under aseptic conditions.

To formulate the aluminum chloride ($AlCl_3$) stock, 10 mg of the compound in powder form was solubilized in 20 mL of RPMI (Roswell Park Memorial Institute) medium lacking serum. This yielded a target concentration of 500 µg/mL. Prior to storage in a sterile environment for future application, the mixture was passed through a 0.22 µm filter membrane for sterilization.

For the galantamine stock, 10 mg of the active powder was first dissolved in dimethyl sulfoxide (DMSO). This mixture was subsequently expanded to a total volume of 5 mL using serum-free RPMI, producing a 2000 µg/mL final concentration. Similar to the $AlCl_3$, this solution was filtered through a 0.22 µm membrane. The maximum DMSO concentration in the final preparation was kept strictly at or below 0.1%.

MTT Cytotoxicity Assay

To determine cell survival, we employed the MTT colorimetric assay. Initially, 96-well plates were seeded with SH-SY5Y cells (5×10^3 cells/well) and left overnight to facilitate adherence. For individual toxicity assessments, the adhered cells were exposed to varying concentrations of either $AlCl_3$ (ranging from 15.8 to 500 µg/mL)) [10] or galantamine (3.125 to 100 µg/mL)) [11]. All experiments were performed in triplicate, with cells receiving no treatment acting as the baseline control.

After a 24-hour incubation period in a standard environment (37°C, 5% CO_2, and high humidity), cellular metabolism was evaluated by introducing the MTT reagent.

In the combination experiments, the cells first underwent a 24-hour pretreatment with galantamine, which was immediately followed by a 24-hour challenge with 500 µg/mL $AlCl_3$. Afterward, 0.5 mg/mL of MTT solution was applied to all wells. Following a 4-hour incubation at 37°C to permit formazan crystal development, the resulting crystals were solubilized. Finally, the optical density was recorded at 570 nm to quantify the proportion of viable cells.

Gene Expression Analysis

SH-SY5Y cells were cultured in flasks until approximately 80% confluence and were then assigned to the experimental groups. Cells were exposed for 48 hours to $AlCl_3$ at 31.25, 125, or 500 µg/mL; galantamine at 6.25, 25, or 100 µg/mL; or 500 µg/mL $AlCl_3$ in combination with galantamine at 6.25, 25, or 100 µg/mL. Untreated cells served as the calibrator control group.

The gene-expression workflow employed the FavorPrep™ Blood/Cultured Cell Total RNA Kit (catalog no. FABRK001-1; Favorgen, Korea), the AddScript cDNA Synthesis Kit (catalog no. 22701; Addbio, Korea), and the GoTaq® qPCR System (catalog no. A6001; Promega, USA). Gene-specific oligonucleotides were synthesized by Macrogen (Korea). The principal equipment included a dry microtube incubator (AE, UK), a Kern PFB balance (Kern & Sohn, Germany), a Microfuge IB centrifuge (Beckman Coulter, Germany), calibrated micropipettes (DARWELL, China), and an Mx3005P Stratagene Real-Time PCR System (Agilent Technologies, USA).

Total RNA was extracted from the treated SH-SY5Y cells using the FavorPrep™ kit according to the manufacturer's instructions. Briefly, harvested cell pellets were lysed with the supplied lysis buffer, the lysates were mixed with ethanol, and the mixtures were transferred to purification columns. After sequential washing and on-column DNase I treatment, purified RNA was eluted in RNase-free water and stored at −70°C until complementary DNA synthesis.

Complementary DNA (cDNA) was synthesized with the AddScript cDNA Synthesis Kit in a total reaction volume of 20 µL. Each reaction contained 10 µL of 2× reaction buffer, 2 µL of 10 mM dNTP mixture, 2 µL of oligo$(dT)_{20}$ or random-hexamer primer, 1 µL of AddScript enzyme solution, 4 µL of RNA template, and 1 µL of nuclease-free water. Reverse transcription was performed at 25°C for 10 minutes and 50°C for 60 minutes, followed by enzyme inactivation at 80°C for 5 minutes and a hold at 12°C until further use.

The primers were supplied in lyophilized form and reconstituted in nuclease-free distilled water to a stock concentration of 100 pM/µL (equivalent to 100 µM). Stock solutions were stored at −20°C, and 10 pM/µL (10 µM) working solutions were prepared for the amplification reactions.

For human TNF (transcript NM_000594), the forward primer was 5′-CTCTTCTGCCTGCTGCACTTTG-3′, and the reverse primer was 5′-ATGGGCTACAGGCTTGTCACTC-3′, yielding a 135-bp amplicon; these sequences correspond to the OriGene TNF qPCR primer pair, catalog no. HP200561 [12]. For human GAPDH, the forward primer was 5′-GGAGTCAACGGATTTGGT-3′ and the reverse primer was 5′-GTGATGGGATTTCCATTGAT-3′, yielding a 206-bp amplicon [13].

Quantitative real-time PCR was performed with the GoTaq® qPCR System. Reagents, cDNA templates, and primers were thawed on ice and mixed gently before use. Each 20-µL reaction was prepared on ice and contained 10 µL of 2× GoTaq qPCR Master Mix, 2 µL of 10 µM forward-primer working solution, 2 µL of 10 µM reverse-primer working solution, 2 µL of cDNA template, and 4 µL of nuclease-free distilled water. Reactions were transferred immediately to the Mx3005P instrument. The thermal program consisted of initial denaturation at 95°C for 5 minutes; 40 cycles of denaturation at 95°C for 10 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds; and a final extension at 72°C for 2 minutes.

TNF transcript abundance was measured using fluorescent dye-based real-time PCR, with GAPDH serving as the endogenous reference gene. Relative expression was calculated using the $2^{-}\Delta\Delta Ct$ method, with the untreated group used as the calibrator. All experimental conditions were assessed in biological duplicate.

Statistical Analysis

Data were presented as mean ± SEM. Statistical analysis was conducted utilizing one-way ANOVA, succeeded by Tukey's post hoc test, employing GraphPad Prism software. A p-value of less than 0.05 ($p < 0.05$) was deemed to be statistically significant.

Results

MTT Cytotoxicity Assay

The viability of SH-SY5Y cells was evaluated following exposure to different concentrations of galantamine. Treatment with low to moderate concentrations of galantamine (3.125–6.25 µg/mL) maintained cell viability close to control values (>97%). Mild reductions in viability were observed at concentrations of 12.5–50 µg/mL. However, the highest concentration tested (100 µg/mL) significantly reduced cell viability to approximately 75% of control values ($p < 0.001$), corresponding to a 25% decrease in cellular survival (Figure 1A). Exposure of SH-SY5Y cells to $AlCl_3$ (15.8–500 µg/mL) resulted in a decrease in cell viability that was dependent on the concentration used. Notable reductions were noted at concentrations of 62.5 µg/mL and higher. The maximum quantity that was tested, which was 500 µg/mL, had a substantial impact on cell viability, reducing it to around 65% of the control values ($p < 0.001$). This means that the metabolic activity of the cells was decreased by 35% when compared to the cells that were not treated (Figure 1B). Pretreatment with galantamine for twenty-four hours prior to exposure to AlCl3 (500 µg/mL) resulted in an increase in cell viability that was around eighty-eight to ninety-five percent of the control values in the combined treatment model. This corresponded to an absolute increase of 23–30% in viability compared with the $AlCl_3$-treated group (65% viability). However, these improvements did not reach statistical significance ($p > 0.05$) (Figure 1C).

Gene Expression Analysis

Relative TNF gene expression was quantified by RT-qPCR using GAPDH as the housekeeping gene. Treatment with galantamine alone affected the expression of the TNF gene ($p < 0.001$, ANOVA). Low and moderate concentrations (6.25 and 25 µg/mL) slightly reduced the expression of the TNF gene 0.92-fold of control levels. In contrast, treatment with 100 µg/mL galantamine significantly increased the expression of the TNF gene to approximately 2.25-fold (225%) of control values ($p < 0.001$) (Figure 2A). Exposure to $AlCl_3$ significantly altered the expression of the TNF gene in a concentration-dependent manner ($p < 0.001$, ANOVA). The highest concentration (500 µg/mL) increased the expression of the TNF gene to approximately 2.3-fold of control levels ($p < 0.001$). Conversely, treatment with 125 µg/mL $AlCl_3$ reduced the expression of the TNF gene to approximately 0.65-fold of control values ($p < 0.05$) (Figure 2B). In the combination treatment model, pretreatment with galantamine modulated the expression of the TNF gene following exposure to $AlCl_3$ ($p < 0.001$, ANOVA). Notably, the combination of $AlCl_3$ (500 µg/mL) and galantamine (100 µg/mL) significantly reduced the expression of the TNF gene to approximately 0.36-fold (36%) of control values ($p < 0.001$). This represented reduction in expression compared with the 2.3-fold increase observed in cells treated with $AlCl_3$ (500 µg/mL) alone (Figure 2C).

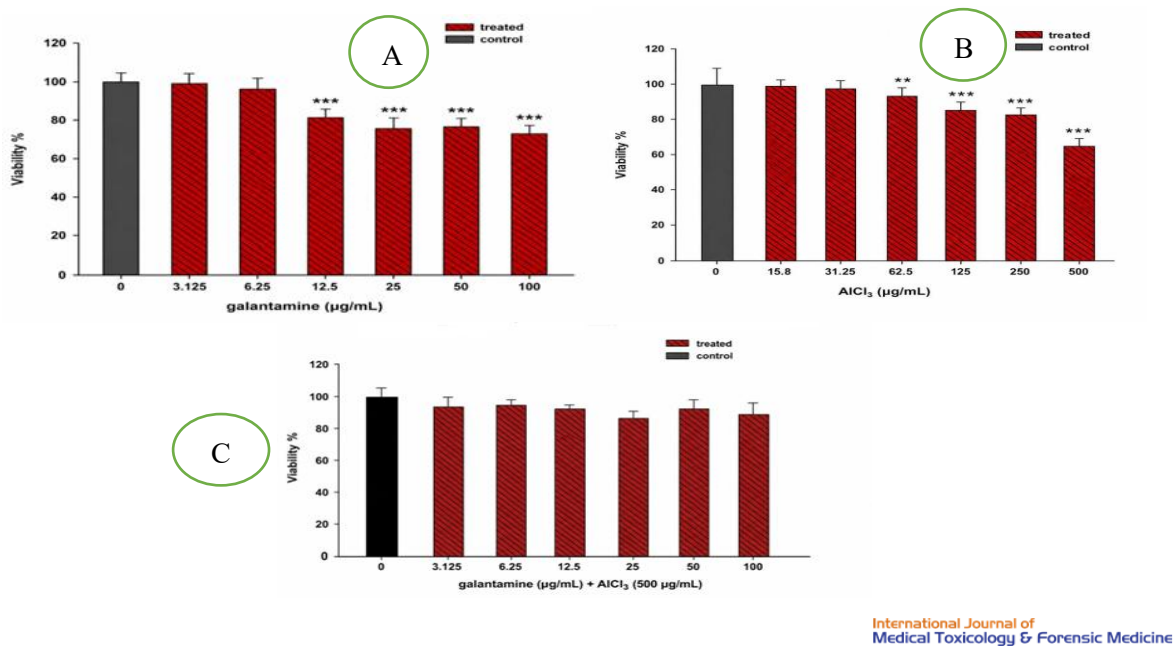

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Figure 1. Impact of galantamine and $AlCl_3$ on SH-SY5Y cell survival and neuroprotection. (A) Survival rates of SH-SY5Y cells after a 24-hour incubation with varying baseline doses of galantamine (0–100 µg/mL). (B) Cell viability percentages following 24 hours of treatment with increasing toxic concentrations of $AlCl_3$ (0–500 µg/mL). (C) Protective effects on cell viability when cells were pretreated for 24 hours with galantamine (6.25, 25, and 100 µg/mL) prior to exposure to a toxic 500 µg/mL dose of $AlCl_3$. Results are displayed as mean ± SEM (n = 3). Asterisks indicate statistical significance relative to control groups: *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. One-way ANOVA revealed overall significance for panels A and B ($p < 0.001$), but not for panel C ($p > 0.05$).

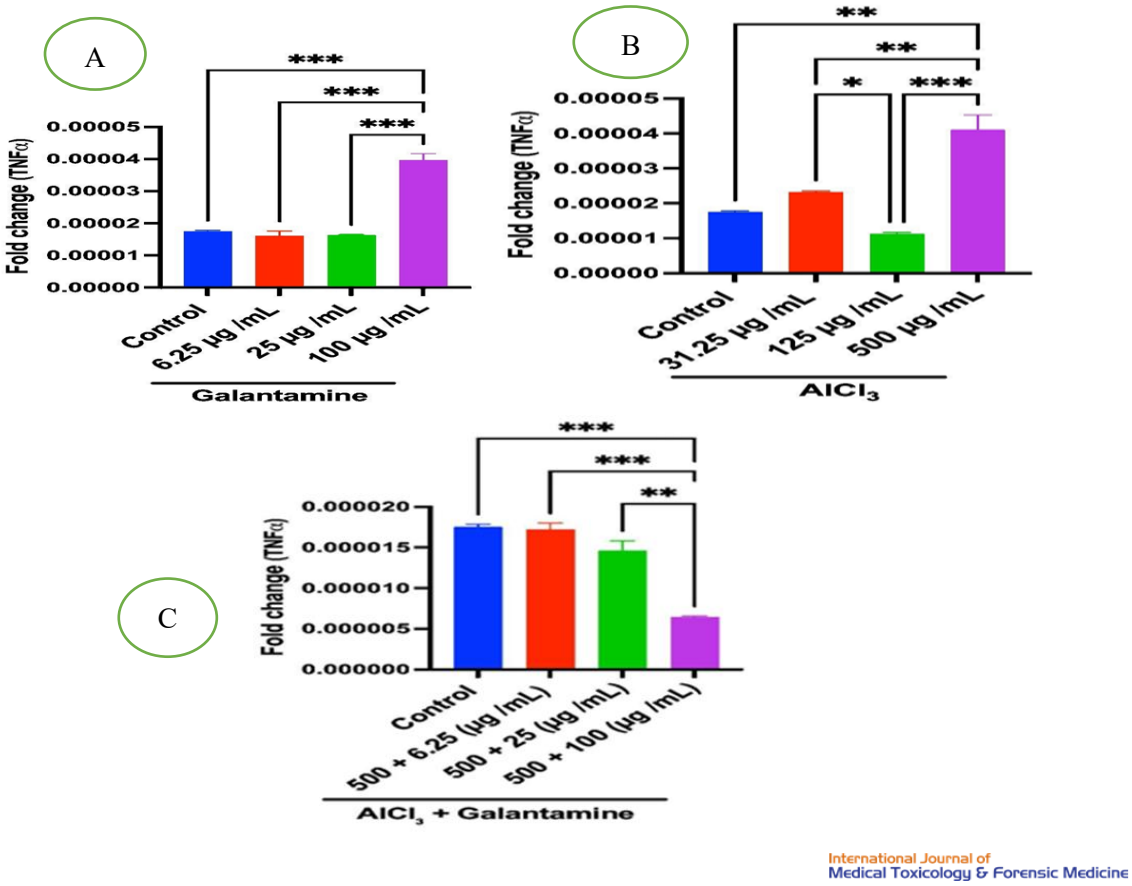

Figure 2. Relative TNF mRNA expression levels in SH-SY5Y cells. (A) Fold change in mRNA expression after treatment with specific concentrations of $AlCl_3$ (0, 31.25, 125, 500 µg/mL), highlighting overall ANOVA significance ($p = 0.0006$). (B) Fold change in mRNA expression following treatment with galantamine alone (0, 6.25, 25, 100 µg/mL), highlighting overall ANOVA significance ($p = 0.0001$). (C) Fold change in mRNA expression following co-treatment combination of $AlCl_3$ (500 µg/mL) mixed with various concentrations of galantamine (6.25, 25, 100 µg/mL), Data are presented as the mean of duplicates ($n = 2$). highlighting overall ANOVA significance ($p = 0.0003$).

Discussion

The current investigation elucidated the concentration-dependent modulatory effects of galantamine on SH-SY5Y neuroblastoma cell viability and TNF gene expression in the context of aluminum chloride ($AlCl_3$)-induced neurotoxicity. The results demonstrated that low to moderate concentrations of galantamine preserved cellular viability and downregulated TNF expression, corroborating its established neuroprotective and anti-inflammatory properties [14]. These observations align with emerging literature indicating that cholinesterase inhibitors like galantamine mitigate oxidative stress and inflammatory cascades in neuronal models [15, 16]. Conversely, exposure to the highest concentration of galantamine (100 µg/mL) resulted in a significant 25% reduction in cell viability coupled with an upregulation of TNF gene expression. This biphasic response suggests that while physiological or low pharmacological doses confer cytoprotection, supra pharmacological concentrations may induce cellular stress, diminishing the therapeutic index. Such a phenomenon is characteristic of hormesis, wherein a biological agent exhibits beneficial effects at low doses but becomes deleterious at higher exposures, a concept increasingly recognized in neuropharmacology [17, 18].

The robust reduction in SH-SY5Y cell viability following exposure to 500 µg/mL $AlCl_3$ substantiates its potent neurotoxic profile and validates its utility as a reliable in vitro model for studying neurodegenerative processes [6]. Notably, this toxic insult was accompanied by a marked elevation in TNF gene expression, implicating tumor necrosis factor-alpha (TNF-α)-mediated inflammatory pathways as critical drivers of $AlCl_3$-induced neuronal injury [19]. Interestingly, treatment with a lower concentration of $AlCl_3$ (125 µg/mL) paradoxically reduced TNF expression below baseline levels. This differential expression pattern indicates that cellular homeostatic and inflammatory responses to environmental toxins like aluminum are highly dynamic and intrinsically dependent on the magnitude of the toxicological stimulus [20]. Recent studies similarly highlight that neuroinflammation is not a monolithic process but rather a highly regulated cascade responsive to the severity of the neurotoxic challenge [21].

In the experimental paradigm involving combination treatment, pretreatment with galantamine successfully, albeit partially, abrogated $AlCl_3$-induced cytotoxicity, restoring cell viability to approximately 95% of control values. Concomitantly, galantamine pretreatment modulated TNF gene expression in the presence of $AlCl_3$. Specifically, pretreatment with 100 µg/mL galantamine significantly suppressed the $AlCl_3$-induced overexpression of the TNF gene. This finding is particularly salient, as it underscores that the biological and pharmacological effects of galantamine are highly contextual, contingent upon the prevailing cellular environment and the specific nature of the neurotoxic stress [22]. The parallel between the suppression of TNF expression and the restoration of cellular viability strongly suggests a mechanistic link between the attenuation of inflammatory signaling and neuroprotection. This aligns with recent pharmacological paradigms emphasizing that targeting neuroinflammation, Specifically, TNF-α pathways offer a promising approach for alleviating neurodegenerative diseases [23, 24].

Despite the promising implications of these findings, several methodological limitations warrant consideration. First, the reliance on a single immortalized cell line (SH-SY5Y), while standard for initial in vitro toxicological assessments, inherently restricts the generalizability of the results to complex in vivo neuronal networks and glia-neuron interactions [13]. Second, the evaluation of inflammatory markers was confined to the transcriptional level (TNF mRNA expression). It is important to note that mRNA levels do not consistently align with the expression of functional proteins, as various post-transcriptional and post-translational modifications can influence this relationship, the absence of protein-level validation represents a significant constraint. Consequently, future research endeavors should incorporate complementary protein quantification techniques, such as Western blotting or ELISA, and transition to more complex biological models, including primary neuronal cultures and in vivo animal models, to comprehensively validate and expand upon these preliminary findings [25].

Conclusion

This study provides compelling in vitro evidence that galantamine effectively mitigates aluminum chloride-induced neurotoxicity in human SH-SY5Y neuroblastoma cells, primarily by preserving cellular viability and modulating the expression of the TNF gene. The observed biphasic dose-response of galantamine underscores the critical importance of dose optimization in neuropharmacological interventions. Furthermore, the attenuation of $AlCl_3$-induced TNF upregulation by galantamine highlights its potential as a dual-action therapeutic agent possessing both neuroprotective and anti-inflammatory properties. These results add to the increasing amount of data demonstrating the efficacy of cholinesterase inhibitors in the treatment of neurodegenerative diseases marked by neuroinflammation. However, comprehensive in vivo studies and protein-level molecular analyses are imperative to fully elucidate the underlying mechanisms and translate these in vitro observations into clinical applications.

Ethical Approval

The Central Biological Ethics Committee of the College of Medicine, Babylon, approved the experimental procedures (no. 4-50/6/11/2025).

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Conflicts of Interest

The authors report there are no competing interests to declare.

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