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Research Article

IN VITRO CYTOGENOTOXIC PROFILE AND *IN SILICO* MOLECULAR DOCKING ANALYSIS OF LEVETIRACETAM IN SH-SY5Y NEUROBLASTOMA CELL LINE

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ABSTRACT

Objective: Levetiracetam (LEV) is an antiepileptic drug (AED) commonly used to control epilepsy seizure activity. There are studies elucidating the potential risks of LEV in vitro, in vivo or in the treatment of different diseases depending on the amelioration of damage at the protein level or cytogenotoxicity. The aim of our study was to determine the in vitro cytogenotoxic effects of LEV and its molecular mechanism of action by in silico analysis.

Materials and Methods: SH-SY5Y cell line was grown under standard conditions (37°C, 5% CO_2). CCK-8 kit was used to determine the cytotoxic effect. Genotoxicity potential was elucidated by Comet assay. Molecular mechanism of action was proposed by in silico molecular docking analysis.

Results: The cytotoxic effect of LEV was observed only at the lowest dose (1 μM). While the rate of damaged cells did not change in the Comet assay, there was a statistical difference in the genetic damage index. In silico results showed that the binding affinity of LEV to BDNA was weakly strong while it was strong to DNAPolβ.

Conclusion: LEV did not show cytotoxic effect (except the lowest dose) on SH-SY5Y cell line but it was found to have genotoxic effect.

Keywords: Cytogenotoxicity; Levetiracetam; SH-SY5Y; Comet Assay; Molecular Docking

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INTRODUCTION

Epilepsy affects people of all age groups and is defined as a chronic non-contagious brain disease. The World Health Organization reports that nearly fifty million people inflicting from epilepsy. This makes epilepsy one of the most common global diseases (Access Date: 13.12.2024, https://www.who.int/news-room/fact-sheets/detail/epilepsy). Signs or transient symptoms of epilepsy are observed as a result of excessive abnormal neuronal activity in the brain. Epileptic seizures cause inflammation and reactive oxygen species (ROS) formation due to neuronal damage (1,2).

Levetiracetam (LEV) is an antiepileptic (AED) drug that is widely used to control seizure activity. LEV is a pyrrolidine derivative related to the nootropic agent piracetam. It is structurally different from all other AEDs. (3-5).

Both low-grade and high-grade gliomas have been reported to frequently cause brain tumor-associated epilepsy. Low-grade gliomas have a 60-100% chance of seizures, while glioblastomas have a 40-60% chance of seizures. In addition to treating symptoms, LEV and valporic acid are evidence-based medicines for low-grade gliomas and some brain tumors. The polytherapeutic administration of LEV and valproic acid has been reported to have favorable results in the treatment of recurrent seizures (6). In a different study, it was reported that LEV therapy may not be effective for all glioblastoma patients, but that LEV may be more suitable for treating certain molecular profiles of glioblastoma (7).

The SH-SY5Y neuroblastoma cell line has emerged as an important model derived from metastatic bone tumor and used to study immunology, neuroscience and neurotoxicity (8). The use of SH-SY5Y cells as models has recently increased considerably. For example, in addition to Parkinson's disease and Alzheimer's disease, they have been used to elucidate the pathogenesis of many viral infections such as poliovirus, herpes simplex virus (HSV), enterovirus (EV71), varicella-zoster virus (VZV) and, human cytomegalovirus (9).

Recent studies have aimed to determine potential risks such as the treatment of different diseases or cytogenotoxicity depending on the improvement of LEV in vitro, in vivo or protein level damage. LEV applied in vitro has been reported to dose-dependently reduce proliferation in tumor cells, induce cellular senescence and increase the efficacy of combined therapy when used with agents such as TMZ (10). In an in vivo study in pregnant rats, it was reported that LEV induced maternal and fetal DNA damage and long-term use during pregnancy may be harmful (11). In a study in which LEV-treated SV2a (synaptic vesicle protein 2A) was the molecular target, it was observed that LEV ameliorated mitochondrial dysfunction and changes in fission/fusion balance in Alzheimer's model disease (12).

Although LEV shows a favorable pharmacokinetic profile with rapid and high absorption, low potential for pharmacological interactions, and a long-lasting pharmacodynamic effect when used in two doses per day, the mechanism of action of LEV remains unclear as a scientific gap is not clearly understood. Preclinical studies propose that it may have neuroprotective and antiepileptogenic effects with the potential to slow or halt disease progression (13). A clear understanding of the mechanism of action of this drug is critical to developing a more effective approach to treating epilepsy patients with neuro/glioblastoma. For this purpose, we planned to determine the cytogenotoxic effects of LEV in our study. We also aimed to elucidate the molecular interaction of LEV/B-DNA for DNA damage mechanism and the interaction of LEV/DNAPolβ enzyme for DNA repair mechanism by in silico analysis.

MATERIALS AND METHODS

In vitro cell culture and cell line

SHSY-5Y cells were preferred to determine the cytogenotoxic effects of LEV in epilepsy patients with neuroblastoma. The American Type Culture Collection (ATCC, Shanghai, China) provided the human neuroblastoma (SH-SY5Y) cells. 10% FBS and 1% penicillin/streptomycin with glutamine were added to the DMEM to maintain the cells. The cells were cultured in a humidified atmosphere with 5% CO2 at 37 °C.

Treatment with levetiracetam

To determine the possible cytotoxic impacts of LEV, SH-SY5Y cells were cultured at doses of 0.1, 1, 10 and 100 mM. The logIC 50 value was computed in GraphPad Prism version 9.0.0 and the IC 50 dosage was determined as 0.68 μM. To test the genotoxic effect, LEV was administered to neuroblastoma cells at doses half (0.34 μM) twice (1.34 μM).

Investigation of cytotoxic effect with CCK-8 assay

CCK-8 kit was used to determine the cytotoxic effects of LEV. To assess cell viability, 10 μl of 0.4% trypan blue was added to 100 μl of cell suspension. Experiments were

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continued when the lower limit of viability was 90%. 5 × 104 cells were added to 96 well plate and after 24 hours, 0.1 mM, 1 mM, 10 mM and 100 mM doses of LEV were applied in 3 replicates with control and solvent control groups, respectivelyAt the end of the time, 10 µl CCK-8 was added to each well and absorbance measurements were performed at 450 nm after 1 hour. IC50 doses were determined using GraphPad Prism version 9.0.0 program. The IC50 dose was determined as 0.68 µM. LEV was applied to neuroblastoma cells at half (0.34 µM) and twice (1.34 µM) the IC50 value.

Comet assay

The Comet assay protocol was performed using the protocol established by Singh et al. (14) with significant modifications. 5 × 105 cell suspensions were added to each eppendorf tube. Doses of LEV (in 100 µl) were added to the cell suspension. The tubes were incubated at 37 °C for 1 hour and centrifuged at 3000 rpm and +4 °C for 5 minutes after incubation. After centrifugation, the supernatant was discarded and cell viability was assessed (viability >90%). The cells were resuspended by adding 100 µl phosphate buffered (PBS, pH:7.4) to the pellet in the tubes.

For resuspended cells, 75 µl of low melting point agar (LMA) was quickly mixed with 100 µl of cells and spread onto slides, which were then covered with coverslips. The slides were kept in a closed box in the refrigerator for 20-25 minutes to allow the gel to set. The coverslips were then removed and the slides were placed in lysis solution. Slides were kept in lysis solution at +4oC for 1-16 hours. After lysis, the slides were kept in electrophoresis buffer for 20-25 min and electrophoresed at 25 V and 300 mA for 20 min (tank temperature +4 °C). The slides were then kept in neutralization buffer at +4 °C for 5 min; this procedure was repeated twice. For staining, 50 µl of SyBR-safe dye prepared in buffer was added to each slide and then covered with coverslips. Finally, cell damage was assessed by fluorescence microscopy.

To determine genotoxic damage, 100 cell images of control, positive control and doses were analyzed (each group). Cells were evaluated according to the severity of DNA damage.

Grade 0 = No damage, Grade 1 = Slightly damaged, Grade 2 = Moderately damaged, Grade 3 = Highly damaged, Grade 4 = Extremely damaged.

Number of grade 0 cells (G0) × 0
Grade 1 cell number (G1) × 1
Grade 2 cell number (G2) × 2
Grade 3 cell number (G3) × 3
Grade 4 cell number (G4) × 4

N = Total number of cells examined (100)
Total Damage Score (Genetic Damage Index = GDI)
Genetic Damage Index (GDI)= (0×G0 + 1×G1 + 2×G2 + 3×G3 + 4×G4)/N
Damaged Cell Percentage (DCP)= (G2 + G3 + G4)/N

In silico molecular docking analysis

The 3D structure of the levetiracetam molecule was downloaded from the PucChem (https://pubchem.ncbi.nlm.nih.gov/) database in .sdf format. The structure of the molecule was then saved in .pdb format using BIOVIA Discovery Studio Visualizer. BDNA (PDB ID: 1BNA) and DNA-added Human Polymerase Beta enzyme complex (PDB ID: 1BPZ, DNAPolβ) molecules were selected as receptors and downloaded from the Protein Data Bank (https://www.rcsb.org/) database in .pdb format.

To perform molecular docking analyses, AutoDock 4.0 (Sanner1999) was used to predict possible binding sites on the crystal structure of LEV at the BDNA and DNAPolβ receptors. AutoDockTools (ADT), receptor and ligand molecules were used to prepare parameters before docking analysis. Polar hydrogen atoms were retained while non-polar hydrogens were incorporated. Gasteiger charges were calculated by ADT as previously described by Ricci and Netz (2009) (15) and Nasab et al. (2017) (16). All rotatable bonds of the ligands were allowed to rotate and then the prepared receptor and ligand structures were saved in PDBQT format. A grid box size of 60 x 60 x 60 Å points with a grid spacing of 0.375 Å was set. Dockings was performed at coordinates X:14.78, Y:20.976, Z:8.807 for B-DNA and X:12.985, Y:7.256, Z:12.063 for DNAPolβ. Dokings were generated from 25 GA (Genetic Alghorithm) executions, 5x105 energy evaluation numbers and a maximum of 27,000 generation runs using a starting population of at most 150 individuals. Selected values of 0.02 and 0.8 were applied to the population as mutation and transition rates, respectively. After 100 independent docking runs between LEV and receptors, all possible binding modes were clustered and ranked for the selected pose of ligands based on the binding free energy kcal/mol of the conformation with the best docking pose with the lowest binding free energy. The best docking pose obtained between ligand and receptor using AutoDock 4.0 was analyzed using BIOVIA Discovery Studio Visualizer 2016 (17).

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Statistical analysis

Statistical analysis was performed with GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com). The normal distribution of the data was confirmed by Shapiro-Wilk normality test. Cell viability and genotoxicity values were evaluated by one-way analysis of variance (ANOVA) and compared by Tukey's multiple comparison test. Results were obtained as mean ± SD. $p < 0.05$ was considered statistically significant. Importance status are shown in the figures as follows:

*= $p < 0.05$, **= $p < 0.01$, ***= $p < 0.001$ and ****= $p < 0.0001$.

RESULTS

Cytotoxic effect of levetiracetam in SH-SY5Y neuroblastoma cells

In SH-SY5Y cell line, 1, 10, 100 and 1000 µM doses of LEV were compared with control group and solvent control. A partial decrease in cell viability was observed at higher doses of LEV (10, 100 and 1000 µM) compared to the control groups, but no statistical significance was observed. Only when the lowest dose (1 µM) was compared with the control, the difference was statistically significant (Figure 1; $p<0.01$).

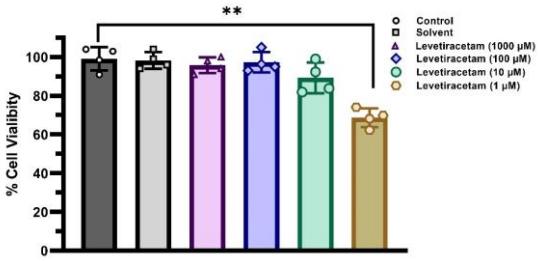

Figure 1. Effect of levetiracetam on cell viability in SH-SY5Y cell line. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$

Genotoxic effect of levetiracetam in SH-SY5Y neuroblastoma cells (Comet Assay)

According to the results of Comet assay, genetic damage index and damaged cell ratio were determined. Damaged cells were classified according to Figure 3.

In SH-SY5Y cell line, 0.34, 0.68 and 1.34 µM doses of LEV were compared with control group and positive control. None of the doses of LEV increased cellular damage (Figure 2B.). The positive control significantly increased cellular damage as expected.

To determine the genetic damage index, 0.34, 0.68 and 1.34 µM doses of LEV were compared with the control group and positive control. Compared to the control, 0.34 and 0.68 µM doses did not increase genetic damage, but the highest dose (1.34 µM) significantly increased the genetic damage index (Figure 2A; $p<0.05$).

In silico molecular docking analysis

In our molecular docking analysis, we investigated whether LEV causes damage by directly binding to DNA or by inhibition of molecules involved in DNA repair mechanism. Molecular docking between LEV and B-DNA (PDB ID: 1BNA) revealed that LEV binds to B-DNA with a Gibss free binding energy of -5.21 kcal/mol (Figure 4). LEV had the best docking pose in the minor groove of BDNA. Similarly, molecular docking analysis with LEV and DNA-added Human Polymerase Beta enzyme complex (PDB ID: 1BPZ, DNAPolβ) showed that LEV binds to DNAPolβ with a Gibss free binding energy of -6.10 kcal/mol. This Gibss free binding energy was considered significant as it was stronger than the limit binding energy (-6.0 kcal/mol) (Figure 5) (18).

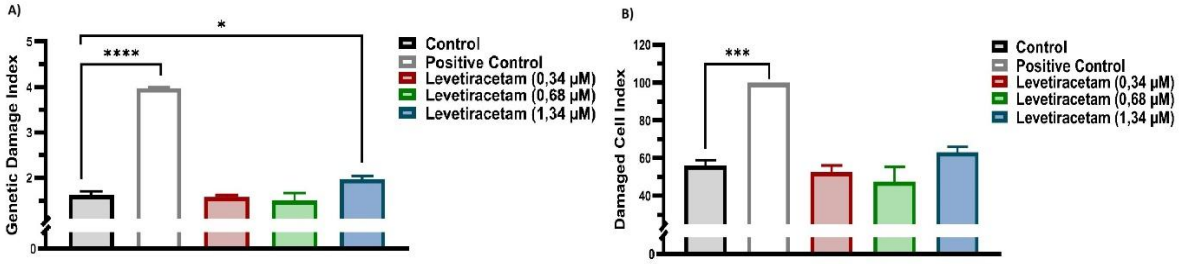

Figure 2. Mean ± SD values of Genetic Damage Index and Damaged Cell Index of Levetiracetam

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$

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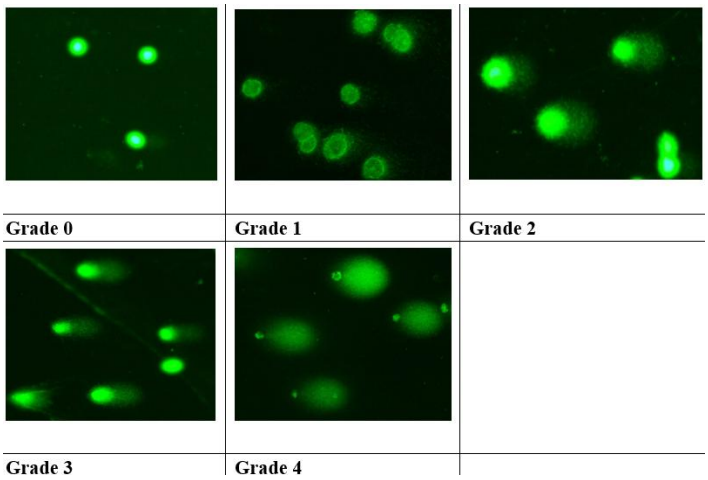

Figure 3. Classification of cells according to DNA damage Five-Class

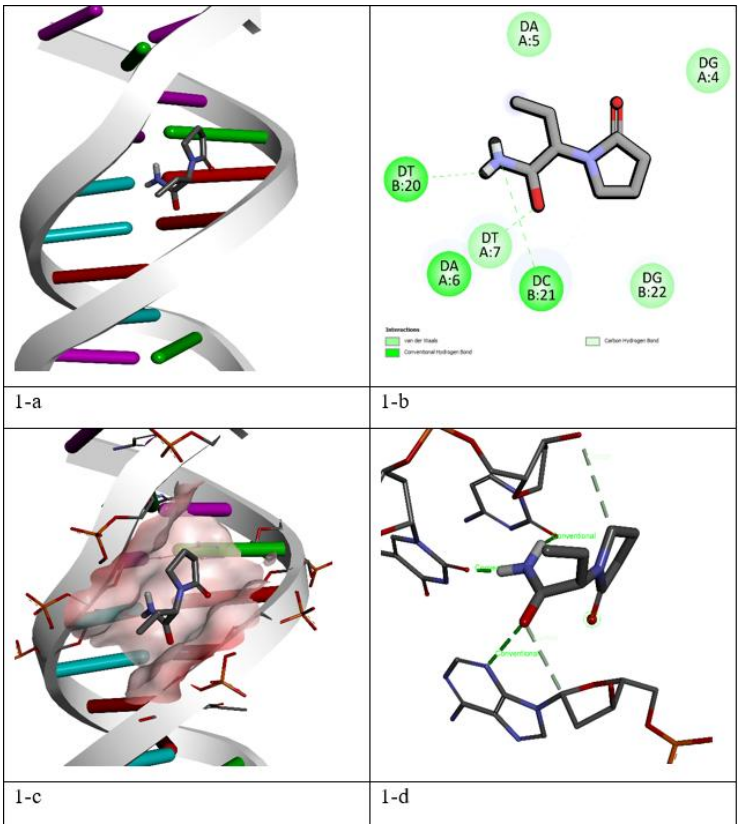

Figure 4. Illustration of the Docking interaction between levetiracetam and BDNA. 1a: Best 3D Docking pose, 1b: 2D DNA base interaction and chemical bond types, 1c: 3D electric field interaction, 1d: Ligand interaction pose

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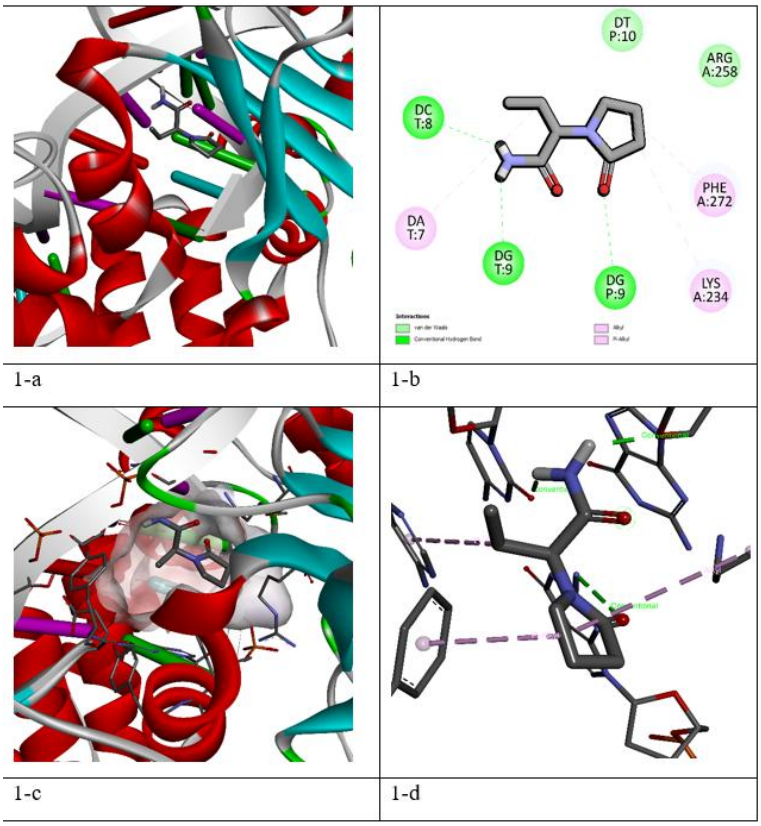

Figure 5. Illustration of the Docking interaction between levetiracetam and DNAPolβ. 1a: Best 3D Docking pose, 1b: 2D DNA base interaction and chemical bond types, 1c: 3D electric field interaction, 1d: Ligand interaction pose

DISCUSSION

The results of this study show that LEV, which is used as an antiepileptic drug, does not induce cytotoxicity in SH-SY5Y neuroblastoma cells (except for the lowest dose of 1 μM). Cytotoxicity/proliferation values of LEV were determined with the widely used CCK-8 kit (19). According to Comet assay data, LEV showed a genotoxic effect by causing DNA damage in SH-SY5Y cells (only the highest dose, 1.34 μM). The genotoxic effect observed in neuroblastoma cells after incubation with LEV provides important information about the use of LEV as a therapeutic agent.

Recent studies have shown that next generation antiepileptic drugs (ngAEDs) have neuroprotective effects on the nervous system. However, the cytogenotoxic effect of LEV, an ngAED, in SH-SY5Y cells remains unclear (20). In another study in which LEV was hypothesized to be neuroprotective ngAED, primary culture of hippocampal neurons of 7-day-old rats was performed. After the primary culture cells were exposed to β-amyloid (Aβ), which causes apoptosis of neurons, the neuroprotective effect of LEV was examined. At the end of the study, it was reported that LEV significantly reduced the harmful effect of Aβ. This suggests that in addition to its neuroprotective effect, LEV also reduces the harmful effect of Aβ by inhibiting it (21). In another study investigating the neuroprotective effect of LEV against glutamate damage, OLN-93 oligodendrocytes were used. The researchers reported that LEV protected OLN-93 oligodendrocytes against the cytotoxicity of glutamate and that this effect was mediated by inhibition of oxidative stress and cellular apoptosis (22). In a study in which a neuronal damage model was established in SH-SY5Y cells, it was reported that LEV decreased serabral edema and neurological function loss, suppressed ERK1/2 and caspase-7 expression, and dose-dependently reduced the harmful effects of hemoglobin and hemine, which cause neuronal death and release hematoma (23).

LEV was reported to reduce cell proliferation in A172 glioblastoma cells in a dose-dependent manner and to induce β-galactosidase activity, which is an aging phenotype. The study reported that LEV has a tumor suppressive effect and induces cellular senescence. It was

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also observed that LEV enhanced these effects when administered in combination with a chemotherapeutic agent such as TMZ (temozolomide) (10). In a study investigating the neuroprotective effects of LEV on hippocampal neurons against neuronal viability and hypertemia-induced damage, it was reported that LEV did not show neuroprotective effects in the in vitro hyperthermia model and triggered aponecrosis in hippocampal neurons at high doses (24). In our study, it was found that the lowest dose of LEV caused 1 µM cytotoxicity but did not show a toxic effect at higher doses. This is consistent with the phenomenon of reverse hormesis. Hormesis represents a dose-dependent pulse and traditionally implies that higher doses can be more toxic/effective. Reverse hormesis, on the other hand, is the way in which lower doses are more effective as a result of complex metabolic activities in living systems (25,26).

In the docking analysis with DNA and LEV, LEV was found to disassemble and bind hoechst 33258 molecule from DNA and exhibited a competitive tendency. It was also observed that LEV binds to the small groove in accordance with our docking results (27). According to our docking results, it was determined that the interaction between LEV and DNA was weak because it binds with an estimated Gibss free binding energy of -5.21 kcal/mol and is higher than the free binding threshold energy (-6.00 kcal/mol) (18). The estimated Gibss free binding energy between LEV and DNApolβ was found to be -6.10 kcal/mol and it interacted with DNA and amioacids in the active center of the enzyme and also exhibited a strong binding affinity since it was lower than the free threshold binding energy. Docking analysis results support our experimental data and suggest that genotoxic damage is caused by DNApolβ enzyme inhibition

When our experimental results were evaluated together with the literature data, it was observed that LEV did not show cytotoxic effect in SH-SY5Y cells but exhibited a genetotoxic profile. This was thought to be due to the disruption of the DNA repair mechanism as a result of DNApolβ enzyme inhibition.

CONCLUSION

In conclusion, LEV did not show cytotoxic effect (except the lowest dose) on SH-SY5Y cell line but it was found to have genotoxic effect. Considering the literature data, it is thought that the potential of LEV should be investigated with further tests.

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Authorship contributions
The authors contributed equally to this study.

Data availibity statement
The authors state that experimental data can be found in the article. Also, raw data are available from the authors upon reasonable request.

Declaration of competing interest
The authors declare that there is no conflict of interest related to the study.

Ethics
Because the study was conducted with in vitro cell cultures, no ethics committee approval document was required.

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