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RESEARCH

Elucidating the cytogenotoxic potential of gabapentin: in vitro and in silico analysis

Gabapentinin sitogenotoksik potansiyelinin aydınlatılması: in vitro ve siliko analizi

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Abstract

Purpose: This investigation aimed to evaluate the potential cytogenotoxic effects of gabapentin (GBP) on neuroblastoma cells (SH-SY5Y cell line) given its broad range of applications. Furthermore, the interaction between GBP and DNA polymerase beta (DNApolβ) was evaluated using in silico methods.

Materials and Methods: The 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay was used to investigate the cytotoxicity of GBP at concentrations of 1 µM, 10 µM, 100 µM and 1000 µM. The IC_{50} value of GBP was calculated, as were the genotoxic effects of GBP at concentrations of 0.14 µM, 0.28 µM, 0.56 µM and 1.12 µM, using the Comet assay. Additionally, AutoDock 4.0 was used to predict the interaction between GBP and the DNApolβ molecule in silico.

Results: GBP significantly decreased the viability of SH-SY5Y cells by 70.2 ± 3.084% and 86.8 ± 3.324% at concentrations of 1 µM and 10 µM, respectively. Concentrations of GBP (0.14 µM, 0.28 µM, 0.56 µM and 1.12 µM) were found to be statistically significant for the damaged cell index (DCI) in SH-SY5Y cells at 298.219 ± 104.66, 593.436 ± 120.16, 1216.378 ± 215.96 and 1589.733 ± 472.65, respectively. The genetic damage index (GDI) for these concentrations was found to be statistically significant at 4.150 ± 1.92, 6.568 ± 1.27, 8.216 ± 0.60 and 9.181 ± 1.16, respectively. The Gibbs free binding energy of GBP with DNApolβ was calculated as -7.35 kcal/mol.

Conclusion: The results of this study indicate that GBP, used in the treatment of epilepsy and neuropathic pain, increases both cytotoxicity and genotoxicity in SH-SY5Y neuroblastoma cells. Furthermore, in silico predictions have revealed a significant interaction between GBP and DNApolβ.

Keywords:. Neuroblastoma, gabapentin, cytotoxicity, genotoxicity, SH-SY5Y cell

Öz

Amaç: Bu araştırma, geniş uygulama alanı göz önüne alındığında, gabapentinin (GBP) nöroblastoma hücreleri (SH-SY5Y hücre hattı) üzerindeki potansiyel sitogenotoksik etkilerini değerlendirmeyi amaçlamıştır. Ayrıca, GBP ve DNA polimeraz beta (DNApolβ) arasındaki etkileşim in silico yöntemler kullanılarak değerlendirilmiştir.

Gereç ve Yöntem: 3-(4,5-dimetiltiyazol-2-il)-5-(3-karboksimetoksifenil)-2-(4-sülfofenil)-2H-tetrazolyum (MTS) deneyi, 1 µM, 10 µM, 100 µM ve 1000 µM konsantrasyonlarında GBP'nin sitotoksisitesini araştırmak için kullanılmıştır. Comet deneyi kullanılarak GBP'nin IC_{50} değeri ve 0,14 µM, 0,28 µM, 0,56 µM ve 1,12 µM konsantrasyonlarında GBP'nin genotoksik etkileri hesaplanmıştır. Ek olarak, GBP ve DNApolβ molekülü arasındaki etkileşimi in silico tahmin etmek için AutoDock 4.0 kullanılmıştır.

Bulgular: GBP, SH-SY5Y hücrelerinin canlılığını 1 µM ve 10 µM konsantrasyonlarında sırasıyla %70,2 ± 3,084 ve %86,8 ± 3,324 oranında önemli ölçüde azaltmıştır. GBP konsantrasyonları (0.14 µM, 0.28 µM, 0.56 µM ve 1.12 µM) SH-SY5Y hücrelerinde hasarlı hücre indeksi (DCI) için sırasıyla 298.219 ± 104.66, 593.436 ± 120.16, 1216.378 ± 215.96 ve 1589.733 ± 472.65 değerlerinde istatistiksel olarak anlamlı bulunmuştur. Bu konsantrasyonlar için genetik hasar indeksi (GDI) sırasıyla 4.150 ± 1.92, 6.568 ± 1.27, 8.216 ± 0.60 ve 9.181 ± 1.16 olarak istatistiksel olarak anlamlı bulunmuştur. GBP'nin DNApolβ ile Gibbs serbest bağlanma enerjisi -7,35 kcal/mol olarak hesaplanmıştır.

Sonuç: Bu çalışmanın sonuçları, epilepsi ve nöropatik ağrı tedavisinde kullanılan GBP'nin SH-SY5Y nöroblastoma hücrelerinde hem sitotoksisiteyi hem de genotoksisiteyi artırdığını göstermektedir. Dahası, in silico tahminler GBP'nin DNApolβ ile önemli bir etkileşim içinde olduğunu göstermiştir.

Anahtar kelimeler: Nöroblastoma, gabapentin, genotoksisite, sitotoksisite, SH-SY5Y hücre hattı

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INTRODUCTION

Cancer is one of the most prevalent diseases of our time, resulting in over 20 million fatalities worldwide[1]. Pain is one of the most common symptoms reported by cancer patients. It may arise from visceral, bony or brain tissues, and can manifest through acute or inflammatory nociceptive mechanisms, encompassing neuropathic processes and nociplastic contributions[2,3]. Pain in cancer patients is usually a complex syndrome, although it is rarely neuropathic. Neuropathic pain is caused by pressure and damage to peripheral or central neurons resulting from growing tumours[5].

Traditional analgesics are often unsuccessful in treating neuropathic pain, so other treatment techniques are necessary. In this context, antiepileptic medications have emerged as a common alternative for the treatment of neuropathic pain[6,7].

The Neuropathic Pain Special Interest Group (NeuPSIG) recommends gabapentin as a first-line treatment for neuropathic pain among antiepileptic drugs[8]. Gabapentin was initially used to treat epilepsy. Apart from epilepsy therapy, it has a wide range of uses, including the treatment of bipolar disorder, migraine prophylaxis and restless legs syndrome[9,10,11]. Gabapentin is a gamma-aminobutyric acid (GABA) analogue and is established as an effective treatment for neuropathic pain due to its ability to bind to α2δ subunits of calcium receptors in the spinal cord, thereby reducing the release of excitatory neurotransmitters[12].

However, the possible side effects and cellular effects associated with long-term, widespread use of gabapentin have also been the subject of research. Some studies have revealed that gabapentin may exhibit different biological effects in various cell lines. For instance, Baldewig et al. found that gabapentin produced cytotoxic effects in various cancer cell lines[13]. Similarly, Prakash et al. reported that gabapentin exhibited teratogenic effects in pregnant mice[14]. Conversely, Al-Musawi et al. found that gabapentin did not exhibit cytotoxic effects in different cell lines in their study[15].

It is important to investigate the cytogenotoxic effects of gabapentin in order to understand the potential side effects of its long-term use, particularly in the treatment of neuropathic pain and epilepsy. Genotoxicity refers to effects that may lead to DNA damage in cells, which can result in serious health problems such as the development of cancer in the long term.

Our study aimed to evaluate the genotoxic and cytotoxic effects of gabapentin on SH-SY5Y cells using a comet assay and an MTS assay. Additionally, *in silico* analysis using AutoDock Tools (ADT) demonstrated the binding energy level of gabapentin to DNA polymerase beta (DNA pol β). Therefore, elucidating the cytogenotoxic effects of gabapentin in the neuroblastoma cell line SH-SY5Y and its binding affinity with DNA polymerase β will be an important step in understanding the drug's safety profile. This will contribute to filling the gap in the literature.

MATERIALS AND METHODS

Cells and media

Gabapentin (CAS No. 60142-96-3) was used as the test material. The neuroblastoma cell line (SH-SY5Y) was purchased from the American Type Culture Collection (ATCC) in the USA and plated in DMEM containing 10% FBS (fetal bovine serum) and 1% penicillin streptomycin. The cells were incubated at 37 °C with a CO_2 pressure of 5%. All experiments involving the handling of live cells were conducted in a Class II Biosafety Cabinet. The incubator provided the cells with a live environment under 5% CO_2 pressure. As the cells used in this study were purchased from ATCC and studied under *in vitro* conditions, there was no need for impact committee authorisation.

Evaluation of cytotoxic effect by MTS assay

The MTS (Promega; Fitchburg, WI, USA) assay was performed according to the manufacturer's instructions. Basically, 5,000 neuroblastoma cells were placed in the wells of a 96-well plate and were treated with four different concentrations of gabapentin (1, 10, 100 and 1,000 μM) for 24 hours. After incubation with the MTS substance for 4 hours, the absorbance of the wells was detected at 490 nm using a spectrophotometer (Spectramax; BMG Labtech., Offenburg, Germany). The percentage of surviving cells was used to measure the cytotoxic effects of gabapentin. The LogIC_{50} value was obtained using GraphPad Prism version 9.0.0, with the IC_{50} dose determined to be 0.28 μM. A positive

control was created using 35% hydrogen peroxide (H_2O_2) (100 µl).

Evaluation of genotoxic effect by Comet test

The Comet assay procedure was substantially modified from the methodology outlined by Singh et al. (17). Cells from the cell culture were added to each Eppendorf tube at a concentration of 5×10^5 cells per tube. Precise doses of the test substance (100 µl) were then added to the tubes containing the cells. The samples were then incubated at 37 °C for one hour before being centrifuged at 3,000 rpm and 4 °C for five minutes. The supernatant was then discarded and cell viability assessed to ensure it remained above 90%. Then, 100 µl of phosphate-buffered saline (PBS) was added to the remaining cell pellet.

Next, 75 µl of low-melting agar (LMA) was rapidly blended with the cells and placed onto microscope slides, which were then cladded with coverslips. The slides were stored in an airtight container in the refrigerator for 20–25 minutes. After this incubation period, the coverslips were removed and the slides placed in a dish containing a lysis solution. The slides were then placed in the refrigerator for between 1 and 16 hours, and the procedure was restarted the following day.

Following lysis, the slides were placed in a buffer solution in an electrophoresis tank and left to settle for 20–25 minutes. Electrophoresis was then performed for 20 minutes at 25 V and 300 mA, while maintaining the tank temperature at +4 °C. After electrophoresis, the slides were immersed in a dish containing neutralisation buffer and kept at 4 °C for five minutes. This process was repeated twice. Once these steps were complete, 50 µl of SyBR-Safe dye, prepared in buffer, was added to each slide and the slide was covered with a coverslip. Finally, microscopic examination was conducted.

A total of 100 cell images were analysed and documented for each group. The cells were evaluated based on the severity of nuclear damage, with scores assigned in increasing order of damage. The cells were graded according to nuclear damage index by modifying the study of Tabakcioglu et al[18].

In silico molecular docking

The AutoDock 4.0 programme was used to determine the binding affinity and modes of binding between gabapentin and DNApol b. The 3D structures of DNApol b (PDB ID: 5WNX) and gabapentin were downloaded from the Protein Data Bank and PubChem databases, respectively. Energy minimisation and preparation of the receptor and ligand in the appropriate format were performed according to the recommendations of previous investigators[19,20]. After 100 independent docking runs, the complex (receptor + ligand) file for the run with the lowest Gibbs free binding energy was created and visual analysis was performed using Discovery Studio Visualizer[21].

Statistical analysis

A statistical analysis was performed using GraphPad Prism version 9.0.0 for Windows. The normality of the data was checked using the Shapiro–Wilk test. Cell survival and genotoxicity measurements were examined using one-way analysis of variance (ANOVA), followed by a Tukey's multiple comparison test. Results are reported as mean ± SD. Differences were considered statistically significant at $p < 0.05$. The significance levels are given in the figures as follows: * $p < 0.05$, ** or $p < 0.01$.

RESULTS

Treatment of SH-SY5Y cells with doses of gabapentin at 1, 10, 100 and 1000 µM substantiated a statistically significant decrease in cell viability at 1 and 10 µM relative to the control group (Figure 1: p**<0.01). Although a decline in cell survival was observed following the administration of 100 and 1000 µM gabapentin doses, this decrease was not statistically significant (*p<0.05).

The DNA damage of VGB in human lymphocytes was measured using the DNA Damage Index and the percentage of injured cells. The Comet test results are displayed as follows: Table 1. This showed that, relative to the control, the percentage of damaged cells and the genetic damage index rose with all gabapentin doses, and this increase was statistically significant.

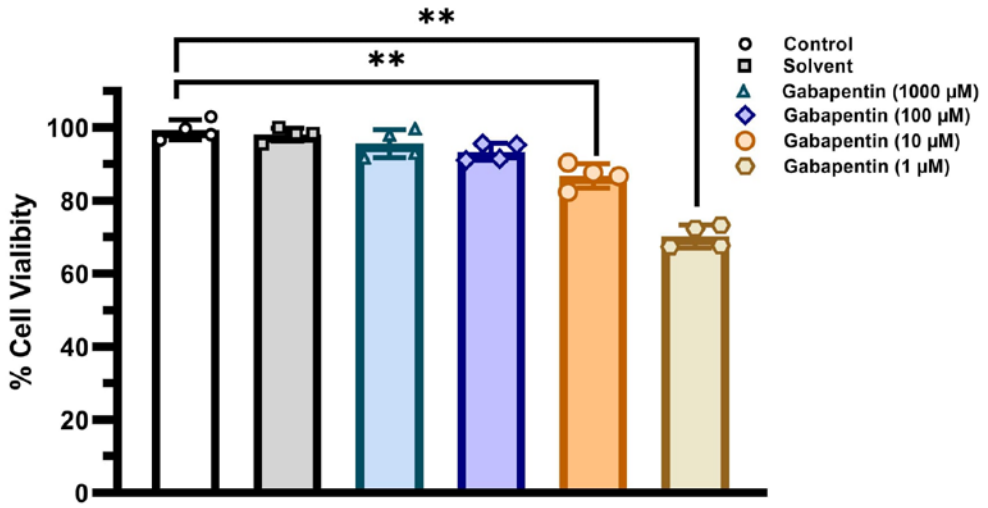
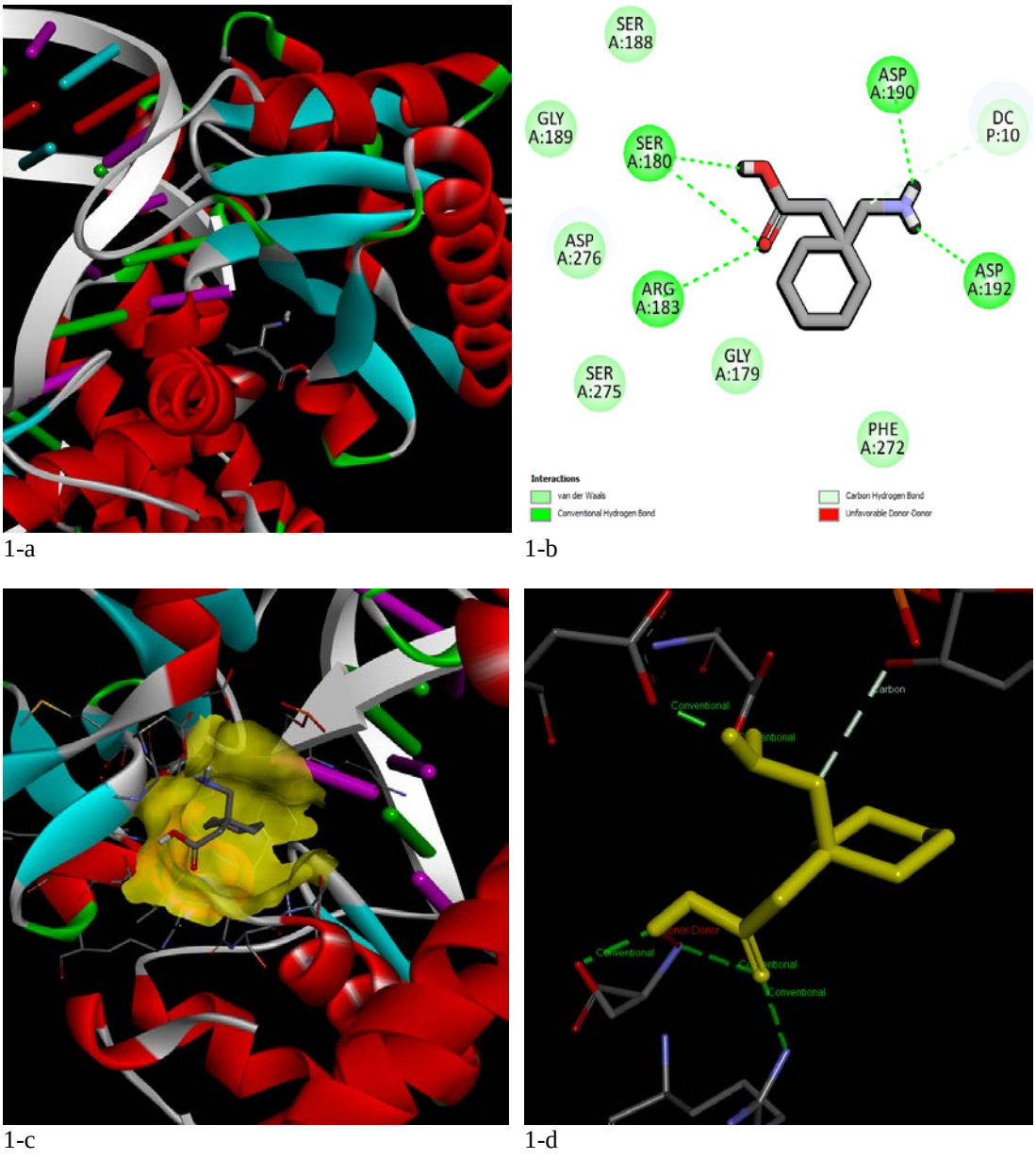


Figure 1. Effect of gabapentin (1, 10, 100 and 1000 µM) on cell viability in SH-SY5Y neuroblastoma cells. (*P < 0.05 or **P < 0.01 respectively) vs control (one-way ANOVA, post-test Tukey).

Table 1. Determination of DNA damage of gabapentin in SY-SH5Y cell line with comet assay. *P < 0.05 or **P < 0.01 respectively (one-way ANOVA, post-test Tukey) vs control.

Test substance	Time (h)	Dose (µM)	Hasarlı Hücre Yüzdesi	Genetik Hasar İndeksi
C (-)[a]	-	-	0,109±0,07	0,729±0,01
C (+)[a]	1	100 µl	2864,630±602,57	11,20±3,49
Gabapentin	1	0,14 µM	298,219±104,66*	4,150±1,92*
		0,28 µM	593,436±120,16*	6,568±1,27**
		0,56 µM	1216,378±215,96**	8,216±00,6**
		1,12 µM	1589,733±472,65**	9,181±1,16**

In silico molecular docking analysis of gabapentin with ten different amino acid residues and one DNA base showed van der Waals bonds, classical hydrogen bonds, carbon-hydrogen bonds, and an unfavourable donor-donor interaction (Figure 2b). Additionally, the Gibbs free binding energy of gabapentin with DNA polymerase β was determined to be -7.35 kcal/mol.



1-a 1-b

1-c 1-d

Figure 2. Docking data show the interaction between Gabapentin and DNA pol β (Pdb Code: 5wnx). 1a: Best 3D Docking pose, 1b: 2D aa interaction and chemical bond types, 1c: 3D electric field interaction, 1d: Ligand interaction pose

DISCUSSION

Gabapentin was licensed as an antiepileptic medicine in the 1990s and has since been used to treat neuropathic and cancer-related pain, bipolar disorder, migraines, restless legs syndrome, and certain mental health conditions. Due to its wide range of uses, the number of patients exposed to gabapentin has increased considerably[22,23]. In view of this, it is crucial to evaluate the potential risks associated with gabapentin. In the present study, the Comet assay and MTS test were utilised to investigate the potential

cytogenotoxic effects of gabapentin. Furthermore, a molecular docking study was conducted to demonstrate gabapentin's interaction with DNA polymerase β. The comet assay is a widely used method for testing the stability of genetic material and the damage caused by environmental toxins or medications to the genetic structure[24,25]. When the genotoxic effects of gabapentin on the SH-SY5Y cell line were evaluated, the comet assay findings, genetic damage index, and percentage of injured cells were statistically significant at concentrations of 0.28 μM, 0.56 μM, and 1.12 μM, which were comparable to the control. These data confirm that gabapentin can cause DNA damage at certain doses, demonstrating a genotoxic effect. An increase in tail length indicates that DNA breaks occur in cells. These results suggest that gabapentin may impair the progression of the replication mechanism during DNA synthesis by disrupting intracellular processes. This can lead to replication stress, resulting in stalled replication forks, which can then collapse or crack. When DNA integrity is adversely affected, cells may be unable to maintain their normal function, triggering cellular stress responses[26,27]. Kardoost et al. reported that gabapentin induced DNA damage in human embryonic stem cells[28]. Similarly, Yüksel et al. reported a genotoxic effect of gabapentin in their study using the Wing somatic mutation and recombination test (SMART)[29]. These results are consistent with our own findings.

Moreover, Prakash et al[14]. reported that gabapentin exhibited a teratogenic effect in a study conducted on pregnant mice. While gabapentin does not pose a risk to the mother or foetus after exposure during pregnancy, another study reported that it increases the risk of preterm birth, pre-eclampsia, and hospitalisation in the neonatal unit, particularly in late pregnancy[30]. Teratogenicity is defined as the occurrence of abnormal conditions and defects in the foetus due to chemical and environmental factors[31]. The most significant factor is the disruption of fetal DNA structure[32]. In this context, teratogenicity studies with gabapentin suggest that it is probably caused by DNA damage.

MTS is based on a soluble tetrazolium reagent in culture media[33]. In the presence of living, metabolically active cells, the phenazine methosulfate in the MTS reagent can be biodegraded by NADPH-dependent dehydrogenase enzymes[34]. Pearce et al. found that vapours from the e-cigarettes studied (Juul, Logic Power and Mistic) reduced the metabolic capacity of normal human bronchial epithelial (NHBE) cells by between 27% and 43%, and caused DNA damage[35]. Our findings support the results of MTS and show DNA damage. A statistical difference in cell viability was observed when 1 and 10 μM concentrations of gabapentin were applied. This suggests that mitochondrial function is impaired, cell metabolism is suppressed, or apoptosis signalling inhibits mitochondrial function[36,374]. Baldewig et al. reported that gabapentin exhibited a cytotoxic effect in the PC12 cell line following treatment with 100 μM[13]. Similarly, Cardile et al. examined its effects on cell viability in primary cultures of rat cortical astrocytes and reported that it exhibited a cytotoxic effect at a concentration of 50 μg/ml[38]. These data support our findings. In their study, Al-Musawi et al. reported that a concentration of 5.54 mM of gabapentin exhibited a cytotoxic effect on the HACAT cell line after two hours of treatment. In contrast, a concentration of 150 μM of gabapentin did not exhibit a cytotoxic effect after 30 minutes or 24 hours. Similarly, a concentration of 150 μM of gabapentin did not exhibit a cytotoxic effect after four hours of exposure to OKF6-TERT1 cells, but did so after 24 hours. These results differ from those of our study. This may be because the cell types, concentrations and exposure times were different, as seen in the findings of Al-Musawi et al.

Docking analysis of gabapentin and DNA polymerase β revealed that gabapentin formed strong chemical bonds with the amino acid residues ASP192, ASP190, GLY189, SER180, SER188 and ARG183, as well as with the DNA base cytosine located in the active centre of the DNA polymerase β enzyme. Examining the interaction of gabapentin with the DNA pol β enzyme more closely revealed that eight of the eleven molecules were located in the active centre of the enzyme (the other three amino acids were ASP190, SER180 and ARG183). The Gibbs free binding energy of gabapentin to the DNA polymerase enzyme was determined to be -7.35 kcal/mol. Since this binding energy indicates a much stronger binding affinity than the threshold limit of -6 kcal/mol, our result was considered significant[39]. DNA polymerase β (Polβ) is widely recognised as the primary DNA polymerase involved in base excision repair, a process that plays a vital role in repairing damaged DNA bases caused by alkylation or oxidation. Single nucleotide substitutions can induce conformational changes in the active centre of Polβ, which can negatively impact its error-repair activity. Evaluating our docking analysis results alongside

experimental data suggests that the cytotoxic and genotoxic effects observed in the MTS and Comet assays are due to strong binding and inhibition of the DNA polymerase β enzyme by gabapentin. Additionally, no docking study involving the DNA pol β (PDB ID: 5WNX) molecule was found in the literature. In this respect, our study will contribute new and unique data to the literature.

This study demonstrated that gabapentin has cytotoxic and genotoxic effects on the SH-SY5Y neuroblastoma cell line, exhibiting a strong binding affinity to DNA polymerase β. These results imply that prolonged gabapentin exposure could damage genetic material. Future studies should therefore explore whether gabapentin's inhibitory effect on DNA repair mechanisms is associated with pathophysiological events, such as neurodegenerative processes or tumour progression. Furthermore, comparative *in vitro* and *in vivo* studies involving different cell types are essential for clarifying the clinical implications of these results. A detailed elucidation of the molecular pathways that mediate gabapentin's genotoxic effects would contribute to a more comprehensive reassessment of its safety profile. Therefore, cellular signalling mechanisms such as apoptosis, oxidative stress and the DNA damage response should be thoroughly investigated in future research.

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Ethical Approval: Neuroblastoma cell line (SH-SY5Y) was used in our study. The SH-SY5Y cell line used in this study was purchased from the American Type Culture Collection (ATCC). Ethics committee approval is not required for this study performed under in vitro conditions.
Peer-review: Externally peer-reviewed.
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