DOI: https://doi.org/10.54393/fbt.v5i4.220

FUTURISTIC BIOTECHNOLOGY
https://fbtjournal.com/index.php/fbt
ISSN (E): 2959-0981, (P): 2959-0973
Vol 05 Issue 04, (Oct-Dec, 2025)

Original Article

OPEN ACCESS

Computational Drug Repurposing of a Ketamine–Methylphenidate Conjugate for Targeting GLIPR1 in Human Glioma

Muzamal Hussain[1,2], Saad Karim Abbasi[3], Faiz Ahmad Joyia[4], Moin Sajjad[5], Noor ul Eman[6], Kashaf Shafique[1], Nazia Kanwal[2] and Kashif Iqbal[1]

[1]Institute of Physiology and Pharmacology, Faculty of Veterinary Science, University of Agriculture Faisalabad, Faisalabad, Punjab, Pakistan
[2]Department of Biological Sciences, Faculty of Sciences, The Superior University, Lahore, Punjab, Pakistan
[3]Institute of Microbiology, Faculty of Veterinary Science, The University of Agriculture, Faisalabad, Punjab, Pakistan
[4]Centre of Agricultural Biochemistry and Biotechnology, The University of Agriculture, Faisalabad, Punjab, Pakistan
[5]Department of Biological Sciences, Faculty of Sciences, The Superior University, Lahore, Punjab, Pakistan
[6]Department of Biochemistry, The University of Agriculture, Faisalabad, Punjab, Pakistan

ARTICLE INFO

Keywords:
Glioma, Ketamine, Methylphenidate, Conjugate, Docking, Tumor, Brain

How to Cite:
Hussain, M., Abbasi, S. K., Joyia, F. A., Sajjad, M., Eman, N. U., Shafique, K., Kanwal, N., & Iqbal, K. (2025). Computational Drug Repurposing of a Ketamine–Methylphenidate Conjugate for Targeting GLIPR1 in Human Glioma: Computational Targeting of GLIPR1 Using a Ketamine–Methylphenidate Conjugate. Futuristic Biotechnology, 5(4), 67-72. https://doi.org/10.54393/fbt.v5i4.220

***Corresponding Author:**
Kashif Iqbal
Institute of Physiology and Pharmacology, Faculty of Veterinary Science, University of Agriculture Faisalabad, Faisalabad, Punjab, Pakistan
kashif.iqbal@uaf.edu.pk

Received Date: 24th October, 2025
Revised Date: 12th December, 2025
Acceptance Date: 27th December, 2025
Published Date: 31st December, 2025

ABSTRACT

Gliomas are the most aggressive primary brain tumors, characterized by high mortality, therapeutic resistance, and limited treatment options due to blood–brain barrier constraints. Glioma pathogenesis-related protein 1 (GLIPR1) is highly upregulated in malignant gliomas and minimally expressed in normal brain tissue, making it a promising molecular target. Drug conjugation strategies may improve CNS delivery and therapeutic efficiency against such targets. **Objectives:** This study aimed to investigate the binding potential and pharmacokinetic feasibility of a ketamine–methylphenidate conjugate against the glioma-associated protein GLIPR1 using in silico approaches. **Methods:** The three-dimensional structure of GLIPR1 (PDB ID: 3Q2U) was retrieved and prepared using Discovery Studio. Structural validation was performed through Ramachandran plot analysis, SOPMA, and PROCHECK. Active site prediction was carried out using PrankWeb, and physicochemical properties were assessed with ProtParam. The ketamine–methylphenidate conjugate (SDF format) was obtained from Nouman Ali *et al.* and evaluated for ADMET properties using pkCSM. Molecular docking was performed using CB-Dock, and ligand–protein interactions were analyzed via Discovery Studio. **Results:** Docking analysis revealed a favorable binding affinity (–6.9 kcal/mol), supported by two hydrogen bonds, five hydrophobic interactions, and one electrostatic interaction. Pharmacokinetic profiling indicated suitable absorption, moderate BBB permeability, and an acceptable safety profile, supporting CNS applicability. **Conclusions:** The findings suggest that the ketamine–methylphenidate conjugate is a promising CNS-penetrant candidate with potential relevance in glioma management, warranting further experimental validation.

INTRODUCTION

Gliomas are the most prevalent primary malignant tumors of the central nervous system, accounting for an estimated 80% of all brain tumors worldwide [1]. It is estimated that over 320,000 new cancer cases of brain and central nervous system tumors appear per year, of which gliomas are the most predominant, and glioblastoma multiforme is the most prevalent of them. Gliomas are very fatal, and despite the progress in neuro-oncology, the disease has claimed more than 248,000 people annually all over the world [2]. The usual treatment is maximal surgical resection, which is followed by radiotherapy and temozolomide-based chemotherapy, but the median survival of glioblastoma is still about 12-15 months [3]. The fact that treatment is significantly constrained by tumor

DOI: https://doi.org/10.54393/fbt.v5i4.220

recurrence, therapeutic resistance, and the lack of blood-brain penetration of molecular therapeutic agents has made the development of new molecular targets and therapeutic approaches urgently necessary [4]. Glioma pathogenesis-related protein 1 (GLIPR1) is a membrane-bound protein that is highly expressed in aggressive glioma and is expressed at low levels in normal brain tissue. GLIPR1 is composed of a secretion signal peptide, a conserved cysteine-rich CAP domain, and a transmembrane region, all of which are involved in tumor proliferation and invasion [5]. Depository investigations of the flexible GLIPR1 fragment show that the central cavity is sufficiently clear with an ability to bind zinc and has distinctive surface charge distributions, which are plausible to accommodate functional ligand interactions. GLIPR1 is a selective molecular target that shows a positive correlation with glioma grade and its invasiveness. It has been shown to play a role in tumor growth and inflammatory regulation, as well as in glioblastoma-targeted therapy, making it a desirable target for structure-based drug design [6]. The most commonly used central nervous system-active agents to treat neuropsychiatric symptoms commonly associated with gliomas include ketamine and Methylphenidate, which are used to treat depression, cognitive dysfunction, fatigue, and attentional deficits. Ketamine has an antidepressant and neuroplasticity-promoting activity (NMDA) receptor antagonist, has been shown to have rapid effects and has been shown to have implications in cancer-related depression and pain management [7, 8]. A clinically used drug is the dopamine and norepinephrine reuptake inhibitor, Methylphenidate, which is used to enhance attention, executive functions, and fatigue associated with cancer in brain tumor victims [9, 10]. Both drugs are effective at penetrating the blood-brain barrier, a critical constraint in the therapy of glioma [11, 12]. Their well-established CNS safety profiles and neuromodulatory effects justify exploring the potential repurposing of these therapies beyond symptomatic treatment. Building on the established CNS-penetrant profiles of ketamine and methylphenidate, we propose a structure-guided repurposing strategy via conjugation to selectively target the glioma-associated protein GLIPR1. The rationale for this approach is threefold. First, GLIPR1 represents a structurally defined and tumor-selective "druggable" target. Its resolved crystal structure reveals a central hydrophilic cavity with distinctive surface charge distributions, suitable for accommodating small molecules [6]. Second, the individual pharmacologist of the parent drugs may synergistically address the glioma microenvironment. Ketamine, as an NMDA receptor antagonist, could potentially disrupt glutamate-driven oncogenic signaling and paracrine stimulation of glioma growth [7, 8]. Concurrently, methylphenidate, a dopamine/norepinephrine reuptake inhibitor, might modulate catecholamine levels within the tumor milieu, which have been implicated in glioma proliferation and stemness[9].

Glioma is one of the most aggressive and poorly prognostic brain tumors without a high number of targeted therapeutic options to be used, despite the development of conventional treatment modalities. In spite of the fact that GLIPR1 has been identified as a pathogenic contributor to glioma, its feasibility as a drug-targetable protein has not been thoroughly investigated, and there has not been any previous research comparing a ketamine-methylphenidate conjugate with this protein. Hence, the study aimed to numerically examine the binding affinity, molecular stability, and pharmacokinetic viability of a ketamine methylphenidate conjugate targeting GLIPR1 by in silico methods.

METHODS

The RCSB Protein Data Bank (https://www.rcsb.org/) was used to obtain the three-dimensional crystal structure of human glioma pathogenesis-related protein 1 (GLIPR1), with accession number 3Q2U [6]. BIOVIA Discovery Studio was used to prepare the protein structure, in which all heteroatoms, co-crystallized ligands, and water molecules were removed to optimize the receptor [13]. The refined protein was structurally validated using PROCHECK (https://saves.mbi.ucla.edu/) Ramachandran plot analysis, which confirmed its stereochemical reliability, whereas the secondary structure composition was analyzed with Structure Prediction using SOPMA (https://npsa.lyon.inserm.fr/cgi-bin/npsa_automat.pl?page=/NPSA/npsa_sopma.html) and the PSIPRED tool (https://bioinf.cs.ucl.ac.uk/psipred/) [14, 15] The active binding site was predicted using the PrankWeb server (https://prankweb.cz/), which identifies cavities accessible to the ligand using machine-learning algorithms [16]. The three-dimensional Structure Data File (SDF) of this pre-designed conjugate was obtained directly from the authors' work. To ensure the ligand was in a suitable conformation for docking, geometry optimization was performed. The initial SDF structure was imported into Avogadro software (version 1.2.0), where energy minimization was conducted using the MMFF94 force field. The optimization process involved 500 steps of the steepest descent algorithm followed by 500 steps of the conjugate gradient algorithm until a convergence gradient of 0.01 kcal/mol.Å was reached. This step ensures the ligand is in a low-energy, stable conformation representative of its probable state in solution before protein binding. The optimized structure was then saved for subsequent docking analyses. Molecular docking was performed using the CB-Dock server, which utilizes AutoDock Vina as its

DOI: https://doi.org/10.54393/fbt.v5i4.220

docking engine [17]. The workflow was as follows: the prepared GLIPR1 receptor structure (PDB: 3Q2U) in PDBQT format and the geometry-optimized ligand (ketamine-methylphenidate conjugate) in SDF format were uploaded to the server. The binding site coordinates were defined based on the center of the predicted active site cavity from PrankWeb, with the grid box dimensions set to X=35.905 Å, Y=1.474 Å, and Z=4.654 Å to encompass the entire binding pocket. The docking search parameters included an exhaustiveness of 8 (default) and the generation of 9 binding poses. The docking algorithm was set to its default run mode. The conformation with the most favorable (lowest) binding affinity (kcal/mol) was selected for further analysis. To assess the reliability of the docking protocol, a validation step was performed by re-docking the co-crystallized ligand (if available) or by comparing the predicted binding pose with known binding modes from literature. Protein-ligand interaction analysis, including the identification of hydrogen bonds, hydrophobic contacts, and electrostatic interactions, was performed on the top-ranked pose using Discovery Studio Visualizer [18].

RESULTS

The structural analysis of the target protein has been depicted in figure 1. Figure 1A shows the 3D design of the receptor with red color representing α-helices, blue color representing β-sheets, and grey color representing random coils, which illustrates the secondary structure in general. Figure 1B represents the active site of the receptor that is predicted, implying the key amino acid residues that are used in the binding of the ligand. Figure 1C is the three-dimensional structure validation of the Ramachandran plot. The analysis showed that 91.1% of residues are found in the most preferred regions, 7.7% in the additionally allowed regions, and none in the disallowed regions, indicating the protein model's high stereochemical stability and reliability. The secondary structure composition predicted using SOPMA (Figure 1D) shows that there are 63 α-helical residues (30.73%), 15 extended strand residues (7.32%), and 127 random coil residues (61.95%), showing that the composition of the receptor structure consists primarily of flexible regions.

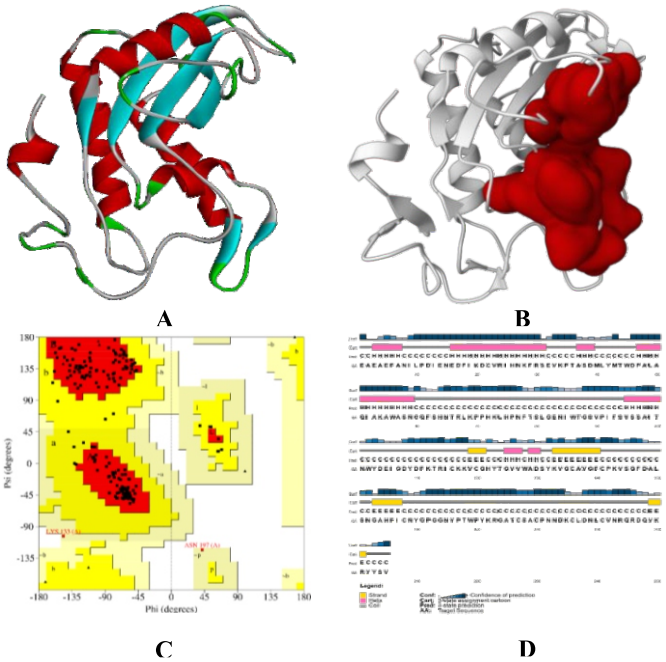

Figure 1: (A): 3D structure of GLIPR1. **(B):** Active site of the receptor highlighted in red. **(C):** Ramachandran plot validating the receptor structure. **(D):** 2D structure of receptor.

The pharmacodynamic and pharmacokinetic assessment of the ketamine-methylphenidate conjugate has indicated a positive profile for its use in central nervous system applications. The conjugate exhibits properties that favor proper gastrointestinal absorption and cellular permeability, indicating it is appropriate for oral administration. The ability to engage efflux transporters, including P-glycoprotein, indicates regulated transport across the biological membrane, and the predicted blood-brain barrier and central nervous system permeability indicate moderate, not optimal, penetration, which may facilitate the agent in brain tissue. Distribution properties indicate adequate tissue penetration, with an equal unbound fraction, resulting in sufficient bioavailability at the target site. The fact that major hepatic enzyme systems are involved but generally not broadly inhibited, as indicated by metabolic profiling, helps prevent severe drug-drug interactions. Excretion parameters indicate equal renal clearance. The toxicological forecasts are low mutagenic liability and controllable cardiac and skin risks, but hepatic involvement should be monitored.

Table 1: ADMET Properties of the Ketamine-Methylphenidate Drug Conjugate

Properties	Model Name	Unit	Predicted Outcome
Absorption	Aqueous solubility	log mol/L	-4.775
	$CaCO_2$ permeability	log Papp in 10-6 cm/s	0.855
	Human intestinal absorption	% Absorbed	92.509%
	Skin Permeability	log Kp	-2.917

DOI: https://doi.org/10.54393/fbt.v5i4.220

Distribution	P-Glycoprotein Substrate	–	Yes
	P-Glycoprotein I Inhibitor	–	Yes
	P-Glycoprotein II Inhibitor	–	Yes
Metabolism	VDss (Human)	Numerical (log L/kg)	1.035
	Fraction Unbound (Fu)	–	0.141
	Blood–brain barrier penetration	Numerical (log BB)	-0.245
	CNS Permeability	Numerical (log PS)	-2.014
Excretion	CYP2D6 Substrate	–	No
	CYP3A4 Substrate	–	Yes
	CYP1A2 Inhibitor	–	No
	CYP2C19 Inhibitor	–	No
	CYP2C9 Inhibitor	–	No
	CYP2D6 Inhibitor	–	No
	CYP3A4 Inhibitor	–	yes
	Total Systemic Clearance	log ml/min/kg	0.865
	OCT2 substrate (renal)	–	Yes
Toxicity	AMES mutagenicity	–	No
	Maximum Tolerated Dose	log mg/kg/day	-0.672
	hERG inhibition (I/II)	–	Type II positive
	Acute oral toxicity (Ld50, rat)	mol/kg	2.717
	Chronic Toxicity (LOAEL,Rat)	log mg/kg_bw/day	0.458
	Hepatotoxicity	–	Predicted Positive
	Skin Sensitization	–	No
	T. Pyriformis Toxicity	log ug/L	0.395
	Minnow Toxicity	log mM	1.406

The molecular docking analysis showed a strong interaction between the receptor and the ketamine-methylphenidate conjugate, with a docking score of -6.9 kcal/mol. The complex was shown to contain two hydrogen bonds, five hydrophobic interactions, and one electrostatic interaction, indicating stable binding. The detailed docking interactions and their type are given in table 2.

Table 2: Table Showing the Docking Interaction and its types Between Receptor and Ligand

Sr. No.	Name	Distance (Å)	Categories	Types
1	B: UNN0:H – A: GLY179:O	2.40185	Hydrogen Bond	Conventional Hydrogen Bond
2	B: UNN0 – A: LEU83	5.43801	Hydrophobic	Pi-Alkyl
3	B: UNN0 – A: LYS84	4.83278	Hydrophobic	Pi-Alkyl
4	A: HIS79:NE2 – B: UNN0	4.4605	Electrostatic	Pi-Cation
5	A: HIS79 – B: UNN0	4.11677	Hydrophobic	Pi-Pi Stacked
6	A: HIS79 – B: UNN0	4.95693	Hydrophobic	Pi-Alkyl
7	A: TYR181 – B: UNN0	5.4467	Hydrophobic	Pi-Alkyl
8	A: ASN180:HD22 – B: UNN0:O	2.51751	Hydrogen Bond	Conventional Hydrogen Bond

Figure 2 represents docking outcome results, with figure 2A representing the protein in blue, the ligand in yellow, figure 2B representing the 2D interaction mapping, and figure 2C representing the 3D interaction view.

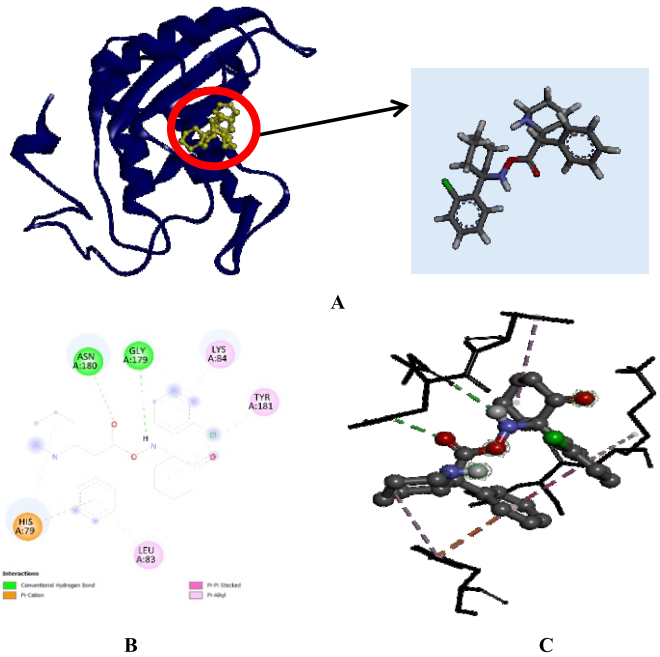

Figure 3: (A): Protein is highlighted in blue color and ligand in yellow, showing the position of the ligand within the receptor. **(B):** 2D visualization of the interactions. **(C):** 3D visualization of interactions.

DISCUSSION

The gliomas still stand as one of the most aggressive and difficult to treat cancers of the central nervous system, mainly because they are infiltrative, molecularly heterogeneous, and do not respond to the traditional therapies. A computational study of the interaction between a ketamine-methylphenidate conjugate and the glioma-associated protein GLIPR1 used a structure-based approach [5]. GLIPR1 structural analysis revealed an organized structure with a high proportion of residues in preferred regions of the Ramachandran plot, suggesting a consistent, stable protein structure suitable for downstream analyses. The feasibility of structure-guided drug design in glioma research lies in the active site, which is predicted to feature a characteristic cavity and flexible loop regions that support ligand accommodation and interaction. Pharmacokinetic and ADMET profiling indicated that the ketamine-methylphenidate conjugate has good absorption, distribution, and penetration into the central nervous system. Of great importance is the conjugate's ability to cross the blood-brain barrier, as BBB impermeability is a major constraint for most glioma therapeutics. Predictions of metabolic activities showed that interactions among enzymes were manageable, and toxicity tests indicated a generally acceptable safety profile, with parameters that could be identified and would need monitoring during experimental validation in future research. Combined with the above, the results suggest that the conjugate has the potential to be a CNS-active compound that can penetrate glioma-related targets in

DOI: https://doi.org/10.54393/fbt.v5i4.220

brain tissue. Molecular docking results provide preliminary support for the conjugate's ability to interact with GLIPR1. A docking score of -6.9 kcal/mol suggests a moderate binding affinity, which should be interpreted with caution as it is a predictive measure. This score is comparable to those observed for other investigational ligands in early-stage docking studies. The interaction is stabilized by two hydrogen bonds, five hydrophobic contacts, and one electrostatic interaction, indicating a plausible binding mode. However, the functional inhibition of GLIPR1 by this conjugate remains to be demonstrated experimentally. Furthermore, to robustly claim "conjugate superiority," future work should include comparative docking of ketamine and methylphenidate individually against GLIPR1, as well as comparison to known reference compounds or inhibitors if available in the literature, to contextualize the -6.9 kcal/mol score. Comparing it to the research study by Asrar *et al.* which analyzed the same conjugate of ketamine-methylphenidate in the major depressive disorder and ADHD setting, there are significant differences and similarities. The conjugate in their work was shown to bind more strongly to TPH2 -8.5 kcal/mol than when each of its parent compounds was used alone, and it had stable dynamics when simulated by molecular dynamics and MMGBSA. The two studies provide a consistent finding: conjugation appears superior to ketamine or methylphenidate administration in improving pharmacological efficacy, particularly in terms of BBB permeability, binding stability, and toxicity. Although the study by Asrar *et al.* concentrated on serotonergic dysregulation in neuropsychiatric disorders, the current study expands the therapeutic use of the conjugate into the neuro-oncology field by targeting GLIPR1, a glioma-specific protein [19]. Together, these results indicate the multimodality of the ketamine-methylphenidate conjugate as a multipurpose, CNS-penetrant therapeutic agent. The similar evidence provided by both works indicates that this conjugate could be a promising method of treating various brain-related disorders, including psychiatric disorders and aggressive brain tumors, with different molecular mechanisms, although complementary. These computational findings will require further *in vitro* and in vivo validation to support these findings and determine the translational value of the conjugate in glioma therapy. The ligand was the pre-designed ketamine-methylphenidate conjugate reported by Asrar *et al.* [19]. Its geometry was optimized for docking using Avogadro software and the MMFF94 force field, employing steepest descent and conjugate gradient algorithms until a convergence gradient of 0.01 kcal/mol.Å was reached. This energy-minimized structure was used for subsequent analyses [20].

Weaknesses also include reliance solely on in silico methodology, the absence of experimental results, and a truncated protein structure that may not reflect physiological conditions. Furthermore, the predicted ADMET liabilities (hERG inhibition, hepatotoxicity) must be experimentally assessed using patch-clamp assays and hepatic cell viability models, respectively, to de-risk the conjugate's safety profile." *In vitro* and *in vivo* validation of the ketamine-methylphenidate conjugate should be conducted to assess its anti-glioma activity and molecular mechanism. These findings will be further supported using molecular dynamics simulations and binding free energy analyses.

CONCLUSION

In conclusion, this *in silico* investigation provides preliminary evidence suggesting that the ketamine-methylphenidate conjugate may represent a hypothetical CNS-penetrant candidate for targeting GLIPR1 in glioma. The computational analyses indicate promising but unvalidated structural compatibility, moderate BBB permeability, and a docking score suggestive of binding potential. Given the purely predictive nature of this study, these findings should be interpreted cautiously and serve as a hypothesis-generating foundation. They warrant further experimental validation, including in vitro binding assays, molecular dynamics simulations, and functional studies to substantiate the proposed mechanism and therapeutic relevance before any translational consideration.

Authors' Contribution

Conceptualization: MH
Methodology: SKA, MS
Formal analysis: SKA, FAJ, NK, KI
Writing and Drafting: SKA, FAJ, MS, NUE, KS, KI
Review and Editing: MH, SKA, FAJ, MS, NUE, KS, NK, KI

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C *et al.* CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015–2019. Neuro-Oncology. 2022 Oct; 24(5): 1-95. doi: 10.1093/neuonc/noac202.

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I *et al.* Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality

DOI: https://doi.org/10.54393/fbt.v5i4.220

Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2024 May; 74(3): 229-263. doi: 10.3322/caac.21834.

[3] Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn MJ *et al.* Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine. 2005 Mar; 352(10): 987-996. doi: 10.1056/NEJMoa043330.

[4] Jezierzański M, Nafalska N, Stopyra M, Furgoł T, Miciak M, Kabut J *et al.* Temozolomide in the Treatment of Glioblastoma Multiforme—A Literature Review and Clinical Outcomes. Current Oncology. 2024 Jul; 31(7): 3994-4002. doi: 10.3390/curronco l31070296.

[5] Li F, Zhang W, Wang M, Jia P. GLIPR1 Regulates the TIMP1-CD63-ITGB1-AKT Signaling Pathway in Glioma Cells and Induces Malignant Transformation of Astroglioma. Translational Cancer Research. 2022 Jul; 11(7): 2205. doi: 10.21037/tcr-21-2413.

[6] Asojo OA, Koski RA, Bonafé N. Structural Studies of Human Glioma Pathogenesis-Related Protein 1. Biological Crystallography. 2011 Oct; 67(10): 847-855. doi: 10.1107/S0907444911028198.

[7] Antos Z, Żukow X, Bursztynowicz L, Jakubów P. Beyond NMDA Receptors: A Narrative Review of Ketamine's Rapid and Multifaceted Mechanisms in Depression Treatment. International Journal of Molecular Sciences. 2024 Dec; 25(24): 13658. doi: 10.3390/ijms252413658.

[8] Fan W, Yang H, Sun Y, Zhang J, Li G, Zheng Y *et al.* Ketamine Rapidly Relieves Acute Suicidal Ideation in Cancer Patients: A Randomized Controlled Clinical Trial. Oncotarget. 2016 Dec; 8(2): 23.56. doi: 10.18632/oncotarget.13743

[9] Hagan AJ, Hill RM, Kingston A, Bailey S, Verity SJ. The Utility of Long-Term Methylphenidate in Preserving Intellectual Development in Survivors of Childhood Brain Tumour. Journal of Neuro-Oncology. 2025 Nov; 175(2): 801-812. doi: 10.1007/s11060-025-05177-9.

[10] Li H, Che K, Zhi Z, Xu W, Huang J, Wang X *et al.* Efficacy and safety of methylphenidate and ginseng in cancer-related fatigue: a network meta-analysis of randomized controlled trials. Translational Cancer Research. 2023 Apr; 12(4): 732. doi: 10.21037/tcr-22-2303.

[11] Stevens T, Sangkuhl K, Brown JT, Altman RB, Klein TE. PharmGKB Summary: Methylphenidate Pathway, Pharmacokinetics/Pharmacodynamics. Pharmacogenetics And Genomics. 2019 Aug; 29(6): 136-154. doi: 10.1097/FPC.0000000000000376.

[12] Kamp J, Jonkman K, van Velzen M, Aarts L, Niesters M, Dahan A *et al.* Pharmacokinetics of Ketamine and Its Major Metabolites Norketamine, Hydroxynorketamine, and Dehydronorketamine: A Model-Based Analysis. British Journal of Anaesthesia. 2020 Nov; 125(5): 750-761. doi: 10.1016/j.bja.2020.06.067.

[13] Hussain M, Kanwal N, Jahangir A, Ali N, Hanif N, Ullah O. Computational Modeling of Cyclotides as Antimicrobial Agents Against Neisseria Gonorrhoeae Porb Porin Protein: Integration of Docking, Immune, and Molecular Dynamics Simulations. Frontiers in Chemistry. 2024 Nov; 12: 1493165. doi: 10.3389/fchem.2024.1493165.

[14] Ullah O, Hanif N, Mufti AQ, Amjad F, Manzoor M, Jameel E *et al.* Insilico Insights into Resveratrol as a Potential Inhibitor of Mycobacterium Tuberculosis Enoyl-ACP Reductase (InhA) Protein: Insilico Insights into Mycobacterium Tuberculosis Enoyl-ACP Reductase. Futuristic Biotechnology. 2024 Sep: 27-33. doi: 10.54393/fbt.v4i03.134.

[15] Naveed M, Hussain M, Aziz T, Hanif N, Kanwal N, Arshad A *et al.* Computational Biology-Assisted Exploration of Phytochemicals Derived Natural Inhibitors to Block BZLF1 Gene Activation of Epstein–Bar Virus in Host. Scientific Reports. 2024 Dec; 14(1): 31664. doi: 10.1038/s41598-024-81037-2.

[16] Jendele L, Krivak R, Skoda P, Novotny M, Hoksza D. PrankWeb: A Web Server for Ligand Binding Site Prediction and Visualization. Nucleic Acids Research. 2019 Jul; 47(1): 345-349. doi: 10.1093/nar/gkz424.

[17] Wu Z, Cui Y, Mao W, Li Y, Lan H. Bufalin Promotes Apoptosis and Autophagy Through the JAK-STAT Signaling Pathway in Myeloid Leukemia. Pakistan Veterinary Journal. 2024 Oct; 44(4): 1-11.

[18] Baroroh U, Biotek M, Muscifa ZS, Destiarani W, Rohmatullah FG, Yusuf M. Molecular Interaction Analysis and Visualization of Protein-Ligand Docking Using Biovia Discovery Studio Visualizer. Indonesian Journal of Computational Biology. 2023 Jul; 2(1): 22-30. doi: 10.24198/ijcb.v2i1.46322.

[19] Asrar B, Ali N, Ali I, Naveed M. In Silico Investigation of Ketamine and Methylphenidate Drug-Drug Conjugate for MDD and ADHD Treatment Using MD Simulations and MMGBSA. Scientific Reports. 2025 Jul; 15(1): 24565. doi: 10.1038/s41598-024-82302-0.

[20] Mvondo JG, Matondo A, Mawete DT, Bambi SM, Mbala BM, Lohohola PO. In Silico ADME/T Properties of Quinine Derivatives Using Swissadme and Pkcsm Webservers. International Journal of Tropical Disease and Health. 2021; 42(11): 1-2. doi: 10.9734/ijtdh/2021/v42i1130492.