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Repurpose The Natural Compounds By Molecular Docking Of The Himalayan Region Against Glioblastoma Multiforme.

Gautam Bhardwaj[1], Suresh Kumar[2] Rajiv Kumar Tonk[3*],

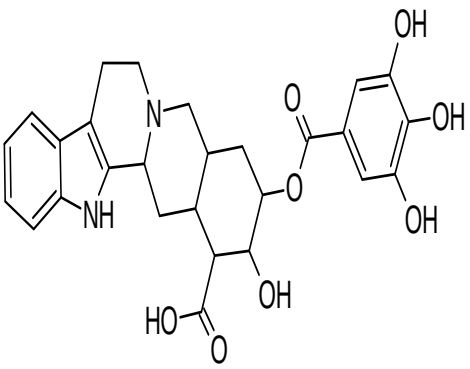
[1,3]Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar sector-3, M-B Road, New Delhi- 110017, India*
Email ID; tonkrk@dpsru.edu.in
[2]Division of medical laboratory technology, School of Allied Health Science, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar sector-3, M-B Road, New Delhi- 110017, India.
Email ID; s.kumar@dpsru.edu.in

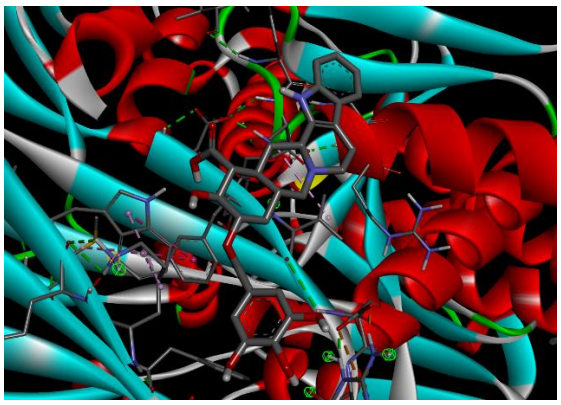
***Corresponding author:** Rajiv Kumar Tonk*
[*]Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar sector-3, M-B Road, New Delhi- 110017, India.
Email ID; s.kumar@dpsru.edu.in

***Abstract*:**

Mastishk vriddhi caused death in humans from ancient times to be also known as Glioblastoma multiforme. It is grade IV astrocytoma and appears as star-shaped glial cells in the frontal and temporal lobes of the brain. Temazolamide with radiation therapy to treat Glioblastoma currently but still not succeed completely and exhort threat as drug resistance.DYRK1A and IDH target the cell cycle and manage mitochondrial dysfunction to control oncoprotein 2-hydroxy glutarate—this study structure-based drug design method to screen natural compounds from the Himalayan region.

Keywords: Glioblastoma multiform, IDH, Mitochondrial dysfunction, DYRK1A, Reserpine, Indole alkaloid





Introduction

Cancer is of multiple types, and deaths are second in the world. Cancer is a threat due to non-identified in early stages, drug resistance and microbial infection in patients. Glioblastoma Multiform (GBM) is initially a cancer of the nervous system. It occurs in men than women at a median age of 64 and a rate of 0.03 per cent of the

population.(Ellor, Pagano-Young and Avgeropoulos, 2014; Ostrom *et al.*, 2014, 2015; Thakkar *et al.*, 2014) Researchers work to target cancer by surgical eradication that is not feasible in the nervous system. Another opportunity is metastasis in body organs, and People die due to complications of cancer. Cancer in humans develops by positively modulating different protein kinases, DYRK1A, mTOR, EGFR, AKT2, MAPK8, SMG1, MAP3K7, RPS6KA3 and PAK4 kinases.(Bijnsdorp *et al.*, 2021) Serine threonine involves DYRK1A and m-TOR, a promising target for Glioblastoma.(Laplante and Sabatini, 2012; Abekhoukh *et al.*, 2013) DYRK1A positive regulate in Glioblastoma by phosphorylation at Ser251 of transcription factor Myocyte-specific enhance factor 2D (MEF2D).(Wang, Zhao and Sun, 2021)(Wang *et al.*, 2017) DYRK1A expression associated tumor regulated proteins c-MET and EGFR in pancreatic ductal adenocarcinoma and non-small cell lung cancer.(Li *et al.*, 2019; Luna *et al.*, 2019) Isocitrate dehydrogenase(IDH) enzyme in cells that convert isocitrate to alpha-ketoglutrate, but due to mutation in IDH results overexpression of oncometabolite 2-hydroxyglutrate that competitive inhibit alpha-ketoglutrate dependent dioxygenase and tumor progression in glioma, acute myeloid leukaemia (AML), intrahepatic cholangiocarcinoma and chondrosarcoma.(Yang *et al.*, 2012) IDH has three subtypes IDH1, IDH2 and IDH3,IDH1 occurs at cytosol and peroxisomes IDH2/3 at mitochondria, and mutation occurs in IDH1/2.(Yan *et al.*, 2009; Clark, Yen and Mellinghoff, 2016; Dang, Yen and Attar, 2016; Voelxen *et al.*, 2016) mTOR/PI3K inhibition with or without temozolomide and radiation therapy.(Ma *et al.*, 2015) Glioblastoma treatment is now an opportunity for researchers. Drug discovery is a challenging, time-consuming and expensive task. In this article, the known and acceptable natural chemical compounds from the Himalayan region are repurposed to treat Glioblastoma. Drug repurposing reduces the time and expense of drug discovery—the structure-based drug design method to repurpose the natural active chemical compounds for Glioblastoma.

Material and Method

Software and Tools

All experimental *in silico* work was performed using an Intel i-7 with 16 GB of RAM. Open source software, including Discovery Studio, ChemDraw,(Hunter, 1997) and OpenBabel(O'Boyle *et al.*, 2011), were used to prepare protein, structure drawing, and conversion to the working format. The design of compound pharmacokinetics was determined using Swiss ADME. Docking experiments were performed using AutoDock Vina.

Pre-design pharmacokinetic Parameters to determine drug-likeness

ADME analysis(Daina, Michielin and Zoete, 2017) was performed using Lipinski's Rule of Five, as determined by IT. The Bioavailability Radar tool in Swiss ADME was used to analyze physicochemical properties and filter potent compound molecules. The Bioavailability Radar provides better results by evaluating six parameters: solubility, size, polarity, lipophilicity, flexibility, and saturation.

Protein selection, Preparation, and Docking by using Autodock Vina

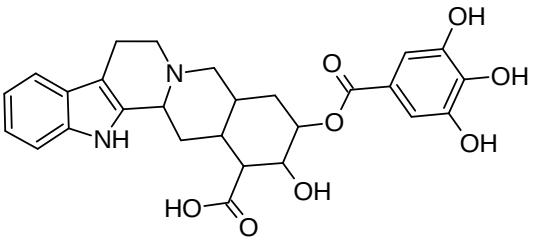
Structure-based drug design was performed using the docking method, Autodock Vina (Morris *et al.*, 2009) (Docking *et al.*, 1998), and visualization was done using Discovery Studio Visualizer. (BIOVIA, 2017) The protein selected for SBDD Dyrk1a inhibitor was obtained from the UniProt database with ID 13627 (PDB ID: 6Q8K, PDB ID: 6VEI, PDB ID: 6VFZ) (Tazarki *et al.*, 2019)(Balaji E *et al.*, 2023) The 3D crystal structure of the protein (PDB ID: 6Q8K), IDH1 (PDB ID: 6VEI) and IDH2 (PDB IDH: 6VFZ), was retrieved from the RCSB PDB website. The downloaded protein was prepared using Discovery Studio Visualizer, which involved the removal of heteroatoms and water and MGL tools to add hydrogen and assign charges. Autodock Vina, only grid parameters were defined, and docking was performed. The docking results were further analyzed using Discovery Studio Visualizer.

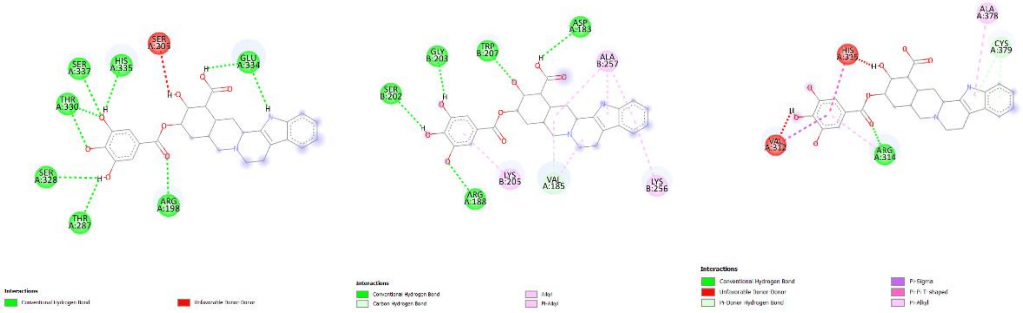
Serine threonine kinase class have DYRK1A and mTOR observed in computationally structure-based drug design approach to design anticancer agents. In cancer treatment, serine-threonine kinase targets to manage the disorder. Natural compounds to repurpose as serine threonine kinase inhibitors.

Results and Discussion

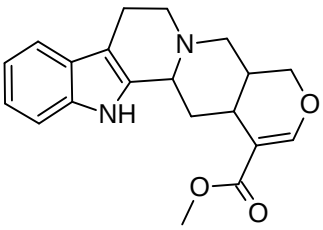
Glioblastoma multiforme is an ancient cancer known as mastihka vriddhi, mentioned in Ayurveda. This work focuses on chemical constituents found in natural products of plant origin. The Himalayan region is known for its medicinal importance to be considered in the study, and forty-four chemical moieties were validated by the docking method. The docking results in Table 1

The binding affinity of DYRK1A PDB ID:6Q8K of complex -6 Kcal/mol and natural active chemicals range from -4 to -8 Kcal/mol. Isocitrate dehydrogenase (IDH1) binding affinity of PDB ID:6VEI complex -9.9 and in natural active chemical has -4.2 to -8.3 and (IDH2) binding affinity of PDB ID: 6VFZ complex -8 Kcal/mol and in natural active chemical have -4.9 to -9





Reserpine, an indole alkaloid in nature, occur in the rauwolfia serpentine family apocynacea and responds against Glioblastoma by docking of DYRK1A -8 kcal/mol and IDH -8.3 Kcal. mol and -9Kcal/mol proteins. In a previous study, reserpine exhibited in-vitro activity against prostate cancer and mechanism of action due to apoptosis and cell cycle arrest.(Ramamoorthy *et al.*, 2018)
Ajmalicine, a natural alkaloid occurring in Vinca rosea, was reported to control proliferation in the Jurkat cells effectively.(Ahmad, Rahim and Mat, 2010)



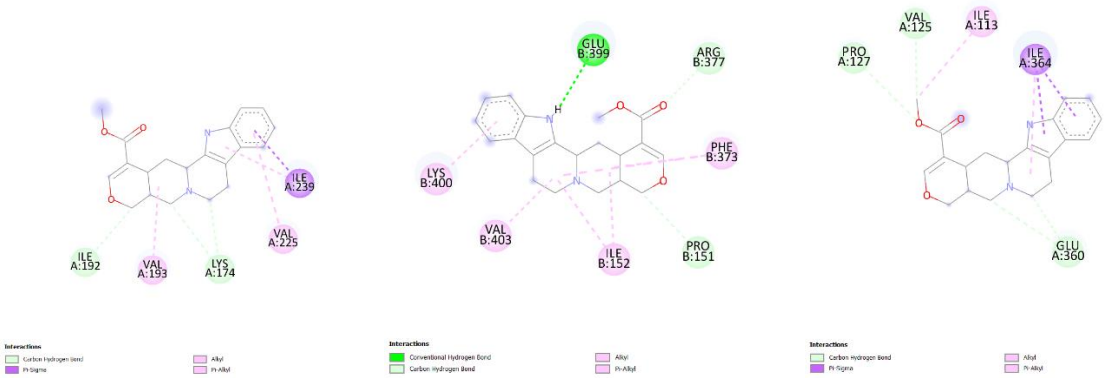


Table 1 Pharmacokinetic and binding affinity data of natural compounds

S.No	Molecule	6Q8K6/6vep9.9/6vfz8_(- Kcal/Mol	MW	Silicon-IT Log P	GI absorption	BBB permeant	Lipinski	Bioavailability
1	P-Cymene	4.9/5.7/6.4	134.22	3.29	Low	Yes	1	0.55
2	Linalool	4/5.1/4.8	152.28	3.33	Low	Yes	0	0.55
3	D-Limonene	4.7/5.6/5.6	138.25	2.98	Low	Yes	1	0.55
4	4,5-Dihydroxy 7-methoxy flavone	7.1/7.6/8	286.28	2.57	High	Yes	0	0.55
5	Phloroglucinol	4.6/5.4/4.9	126.11	0.43	High	Yes	0	0.55
6	Mandellic acid	5.2/6.8/7.4	152.15	0.76	High	No	0	0.85
7	Catechol	5.2/5.2/6.1	110.11	0.94	High	Yes	0	0.55
8	Chlorogenic acid	6.6/7.2/7.8	354.31	-0.61	Low	No	1	0.11
9	epicatechin	6.6/7.5/7.4	290.27	0.98	High	No	0	0.55
10	Astragalin	7.5/7.4/8	450.39	-1	Low	No	2	0.17
11	Curcumin	6.3/6.4/7	370.4	4.22	High	No	0	0.55
12	Ellagic acid	7.1/7.2/8.6	302.19	1.67	High	No	0	0.55
13	Carvacrol	5.2/5.2/6.1	150.22	2.79	High	Yes	0	0.55
14	ethyl 3-[2-methyl-5-(propane-2-yl)phenoxy]propanoate	0/0/0	250.33	3.96	High	Yes	0	0.55
15	1-methyl-4-(propan-2-yl)-2-[(prop-2-en-1-yl)oxy]benzene	0/0/0	190.28	4.04	High	Yes	0	0.55
16	Allicin	4.1/4.2/4.9	175.25	0.69	High	No	0	0.55
17	Berberine	7.1/7.7/7.1	338.38	3.46	High	Yes	0	0.55
18	Cinnamaldehyde	4.7/5.1/5.2	134.18	2.66	High	Yes	0	0.55
19	Reserpine	8/8.3/9	510.54	-0.12	Low	No	2	0.17
20	Ajmalicine	7.9/8.2/8.2	406.34	-1.21	Low	No	1	0.55
21	Mangeferin	8/7.8/7.8	406.34	-1.21	Low	No	1	0.55
22	Wedelolactone	7.3/7.2/7.9	316.26	1.31	High	No	0	0.55
23	Resveratrol	6.3/6.9/6.3	228.24	2.57	High	Yes	0	0.55
24	Quercetin	7.2/7/8.1	288.25	1.56	High	No	0	0.55
25	Kaempferol	6.7/7.7/8.2	286.24	2.03	High	No	0	0.55
26	Piperine	6.5/--/7.6	285.34	3.41	High	Yes	0	0.55
27	Thymoquinone	5.1/5.5/6.2	164.2	2.31	High	Yes	0	0.55
28	catechin	6.2/7.4/7.4	290.27	0.98	High	No	0	0.55
29	Methyl gallate	5.2/6.3/6	184.15	0.28	High	No	0	0.55
30	Myricetin1	7/7.5/8.1	272.25	2.05	High	No	0	0.55
31	Myrecetin2	7/8.1/8.2	304.25	0.66	High	No	0	0.55
32	Luteolin	7.5/7.4/7.7	304.25	0.66	High	No	0	0.55
33	shinaciolB	7.7/8/9.5	408.44	3.85	High	No	0	0.55
34	Apigenin	7.5/7.9/8.8	408.44	3.85	High	No	0	0.55
35	Ephemeranthoquinone	6.5/6.7/7.2	256.25	2.7	High	Yes	0	0.85
36	Gigantol	6.4/7/7.2	274.31	3.31	High	Yes	0	0.55
37	densiflorolB	6.4/7/7.2	256.3	2.81	High	Yes	0	0.55
38	Moscatilin	5.6/6.8/7.4	304.34	3.37	High	Yes	0	0.55
39	Ferulic acid	5.5/5.6/6.2	194.18	1.26	High	Yes	0	0.85
40	Salutaridine	6.8/7/8.2	327.37	2.35	High	Yes	0	0.55
41	Gastrodigenin	4.7/5.6/5.4	124.14	1.22	High	Yes	0	0.55
42	chrysotoxine	5.7/6.5/6.8	318.36	3.91	High	Yes	0	0.55
43	Wortmannin	7.7/8.1/9	428.43	3.64	High	No	0	0.55
44	KCF2 mtor	5.4/6.5/5.9	572.4	2.82	Low	No	1	0.55

Conclusion

Glioblastoma multiforme, a grade IV tumor in ancient science known as mastitis vriddhi, has caused death in humans and is an opportunity for researchers. In synthetic moiety, pharmacokinetic parameters are a challenge. Thus, the majority of drugs fail to reach the market. Various natural chemical constituents and their pharmacological value are studied from literature, simultaneously studying the pathways responsible for Glioblastoma. The natural compounds have screened against the pathway target protein. DYRK1A and IDH targets are to be identified for managing Glioblastoma multiforme. The structure-based drug design method is used to screen the natural compounds. Indole nucleus carrying alkaloid reserpine and ajmalcine are better for Glioblastoma.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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