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VIRTUAL SCREENING OF PHYTOCHEMICALS WITH ANTI- ALZHEIMER GLYCOGEN SYNTHASE KINASE – 3 BETA ACTIVITY

Neurology

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ABSTRACT

Glycogen synthase kinase- 3 (GSK-3) belongs to group of serine/threonine protein kinases. GSK-3 exists in human body as two isoforms alpha and beta . GSK-3 overactivity is implicated in various neurological diseases like Alzheimers disease, multiple sclerosis etc . The primed-substrate binding domain and kinase domain are the two key functional domains of GSK-3. In this study we have docked 1200 phytochemical structures downloaded from MAPS database to 1Q41 PDB structure of GSK-3Beta using Schroedinger Glide and Autodock Vina at the active site occupied by Indirubin-3-monoxime a synthetic GSK-3-Beta inhibitor which is co-crystallized to GSK-3Beta in 1Q41. The docking scores were compared to that of Indirubin-3-monoxime. Various Phytochemical compounds were found to have good docking scores in both docking programmes and may have GSK-3Beta inhibitory potential . Coumestrol, 6-Desmethylantofine, Canthin -6-one glucoside, and Tubulosine interact with the ASP200 which forms key part of active site, and there by may act as competitive inhibitors.

KEYWORDS

Glycogen synthase Kinase-3, Phytochemicals, Alzheimer disease

INTRODUCTION:

Glycogen synthase kinase 3 (GSK-3) is an enzyme belonging to the group of serine/threonine protein kinases[1] GSK-3 is found in human body in two isoforms GSK-3 Alfa and GSK-3 Beta[2]. GSK-3 consists of two functional domains. The primed substrate binding domain attracts and binds to target proteins and brings them near to Kinase domain. The Kinase domain which consists of key amino acids 85, 97, 181, 200 does the phosphorylation of substrates[3,4,5]. Uncontrolled activity of GSK-3 has been found in diseases like Alzheimers, Multiple Sclerosis, Diabetes Mellitus, Bipolar disorder [6,7,8,9,10,11]. In Alzheimers disease GSK-3 hyperactivity facilitates phosphorylation of Tau, formation of amyloid plaques and apoptosis of neurons[12,13,14,15,16].GSK-3 inhibitors have been found to be effective in animal models for diseases like Huntington chorea, stroke, Spinocerebellar ataxia [17,18,19].

Currently, molecular docking approach has been used in modern drug screening of lead molecules and to understand drug-receptor interactions. This paper reports screening of various phytochemicals against GSK-3-Beta enzyme extracted from Protein Data Bank (PDB), by utilizing the Glide software of Schrödinger [20,21,22] and Autodock Vina Software Software[24].

METHODOLOGY:

DOCKING WITH GLIDE SOFTWARE

1200 phytochemical compounds structures were downloaded from MAPS website[25]. The structures of compounds were downloaded as sdf files in Maestro suite and prepared using LigPrep module. OPLS 2005 was used for energy optimisation. These matched compounds were further docked to the GSK-3 beta structure using Glide software.The structure of GSK-3Beta (PDB ID 1Q41) was obtained from the PDB (http//www.rcsb.org)[26]. The structure contains ligand Indirubin-3- monoxime co-crystallized to GSK-3-Beta was optimised for docking using protein preparation wizard of Schrödinger Module. Hydrogen atoms were added to the protein at appropriate amino acids. The receptor grid was generated using Receptor Grid Generation Panel. The receptor site was made of residues LYS 85,, VAL135, ILE62, GLU137, THR138, ARG141, ASP200, VAL70, ALA83, ASP133, VAL110, LEU132, TYR134. The prepared ligands were docked using Standard precision mode in Glide.The docking scores were compared with docking scores of compound Indirubin3 -monoxime which is a GSK3-Beta inhibitor co-crystallized to GSK-3-Beta.

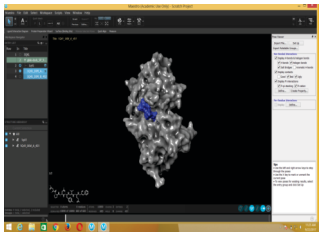
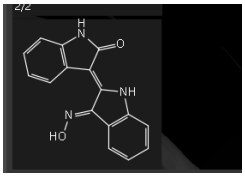


Fig.1 Gsk3-beta Structure With Binding Site- Pdb 1q41 Molecular Surface



Indirubin- 3- Monoxime

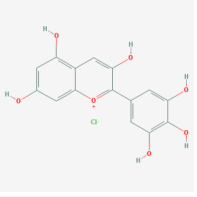
DOCKING WITH AUTODOCK VINA

The pdb structures of ligands which showed good Glide docking scores and the protein structure 1Q41 were converted to pdbqt format using MGL (Molecular Graphics Laboratory) tools of downloaded from www.scripps.edu. Grid box was centered at x 38.110,y 10.598, z 37.215 at the binding pocket of Indirubin3 –monoxime with grid points with 48 56x60 dimensions. The configuration text file was

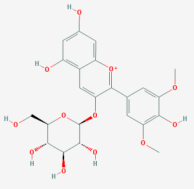
created and the ligands were docked to the protein as described in protocol for Autodock Vina . The docking scores were compared with docking scores of compound Indirubin3 -monoxime which is a GSK3-Beta inhibitor co-crystallized to GSK-3-Beta.

RESULTS AND DISCUSSION

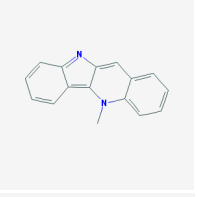
S.No	Phytochemical	Glide Docking score	DOCKING ENERGY	Mol Weight g/mol	Polar Area Å2	H - Bond Donor	H – Bond Acceptor	Vina Docking score	Amino acids H-Bonds
	Indirubin3 –monoxime	-10.763		277.283	77.5	3	3	-10.2	Val135, Asp133
1.	Delphinidin	-10.142817	-52.816974	338.696	122	6	7	-10.8	Asp133, Tyr134, Pro136, Val135
2.	Malvidin-3-glucoside	-10.035111	-72.212931	493.441	180	7	11	-9.5	Pro136, Thr138, Gln185, Asn64
3.	Cryptolepine	-9.958465	-39.528375	232.286	17.8	0	1	-10.7	Val135
4.	Tubulosine	-9.835080	-62.225948	475.633	69.8	3	5	-12.5	Gln185, Asp610, Asp200 Asn186
5.	Pelargonidin	-9.448445	-45.713067	271.248	81.9	4	4	-9.8	Val135 Asp133 Pro 136
6.	Ellipticine	-9.222334	-48.558943	305.33	90.2	3	6	-9.2	val135
7.	Canthin-6-one 9-glucoside	-9.076015	-99.940319	398.371	134	4	8	-11.9	Gly68, Val135, Asp200, Gln185
8.	Neocryptolepine	-9.072007	-76.795828	232.286	17.8	0	1	-10.8	Val135
9.	Rubiadin	-8.878453	-59.384142	254.241	74.6	2	4	-10.5	Val135, Pro136,
10.	Sulfuretin	-8.424282	-51.073548	270.24	87	3	5	-9.1	Val135
11.	6-Desmethylantofine	-8.304562	-85.865763	349.43	41.9	1	4	-12.2	Asp200, Val135, Asp133
12.	Coumestrol	-8.204099	-62.459297	268.224	79.9	2	5	-10.8	Val135, Asp200
13.	Dalparvone	-8.162714	-68.279804	500.071 g	308	10	18	-11.6	Pro136, Ile62
14.	Tectoridin	-8.097163	-84.761278	462.407 g	175	6	11	-12.1	Val135, Ile62, Glu97



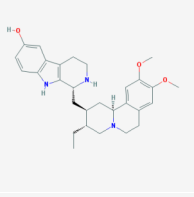
- Delphidin



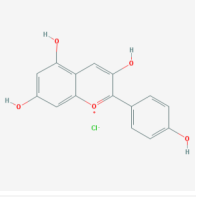
- Malvidin-3-glucoside



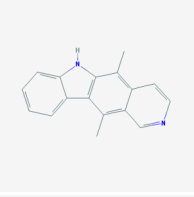
- Cryptolepine



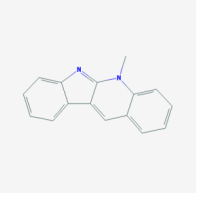
- Tubulosine



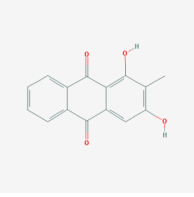
Pelargonidin



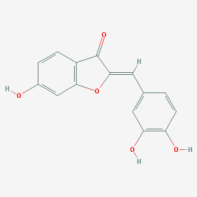
- Ellipticine



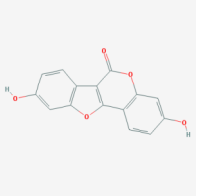
Neocryptolepine



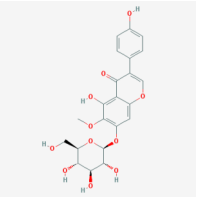
- Rubiadin



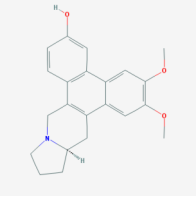
- Sulfuretin



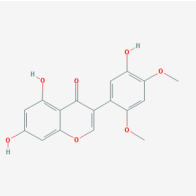
-Coumestrol



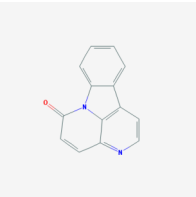
-Tectoridin



- 6-Desmethylantofine



- Dalparvone



- Canthin-6-one

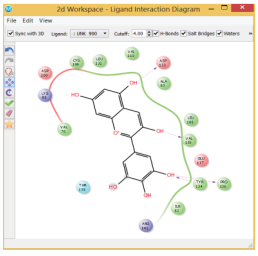


Fig- 2 Delphinidin ligand interaction

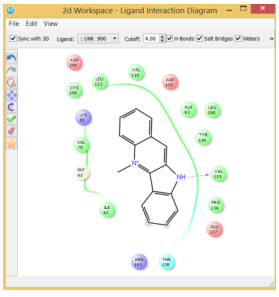


Fig-3 Cryptolepine Ligand Interaction

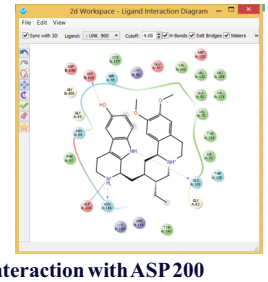


Fig-4 Tubulosine interaction with ASP 200

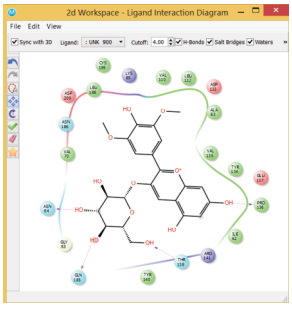


Fig-5 Malvidin glucoside interaction with THR138

Indirubin -3 -monoxime the had the best Glide docking score of -10.763. Delphinidin , Malvidin-3-glucoside, Cryptolepine and Tubulosine had slightly lower but comparable glide docking scores of -10.142, -10.035, -9.958, -9.835 respectively. But when docked by autodock vina Indirubin -3-monoxime had a docking score of -10.2. whereas Delphinidin, coumestrol, Dalparvone, Tectoridin, 6-Desmethylantofine, Rubiadin, Neocryptolepine, Canthin-6-one-9-glucoside, tubulosine and Cryptolepine had better docking scores compared to Indirubin-3-monoxime. As shown in the table.1. Most of these Phytochemicals form bonds with VAL135 and ASP200 similar to Indirubin-3- monoxime. Thr138 is found to serve a functional role in inhibitor binding and GSK3 inhibition26. In our study Malvidin-3-glucoside was found to have interaction with Thr138. Coumestrol, 6-Desmethylantofine, Canthin -6-one glucoside, and Tubulosine interact with the ASP200 of kinase domain and there by may act as competitive inhibitors.

CONCLUSION

Glycogen synthase kinase 3 beta has been investigated for its potential binding affinity with various phytochemicals. It has been concluded, various phytochemicals have potential to bind the GSK-3-Beta at Binding site occupied by Indirubin-3-monoxime a synthetic GSK-3-Beta inhibitor with similar binding affinities. Analysis reveals that various phytochemical ligands can occupy the dock position, where phosphorylated glycogen synthase binds substrate and carrys out its kinase function.

CONFLICT OF INTEREST

The Authors have no conflict of interest

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