Phytomolecules for Therapeutic Targets of Alzheimer's Disease Pathology - A Virtual Analysis

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ABSTRACT

Introduction: Life style of humans, with changes in diet, exercise and life style practices which play an important role in enhancing the progression of age related degenerative problems like dementia. The most common cause of dementia in the world is Alzheimer's disease which ultimately decrease the cognitive function mainly learning and memory. The objective of the study was to find the multi target potential efficacy of the ligands, Glabridin and Diosmetin in altering the two main molecular targets of Alzheimer's disease (AD). The target enzymes were amyloid binding alcohol dehydrogenase (ABAD) and β-site amyloid precursor protein cleaving enzyme 1(BACE1).

Material and methods: In this study, we analyzed that multi-target potential of the two natural compounds on the two prior target enzymes of Alzheimer's disease which are mainly involved in producing neurodegeneration. Drug likeness properties, absorption, digestion metabolic and toxicity profile and molecular docking were analyzed to determine therapeutic aspect by virtual methods.

Results: Binding energy and Vander Waals force of Diosmetin were higher than Glabridin with the target ABAD and less than with BACE1 which showed that both drugs can be used in modulating the enzyme phosphorylation in Alzheimer's disease.

Conclusion: Glabridin and Diosmetin could be used as promising drug candidates as ABAD inhibitor and BACE1 inhibitor in Alzheimer's disease.

Keywords: Alzheimer's Disease, Amyloid Binding Alcohol Dehydrogenase, β-site Amyloid Precursor Protein Cleaving Enzyme 1, Glabridin, Diosmetin

INTRODUCTION

Development and progression of disease is depending upon the accumulation or phosphorylation of some enzymes in brain tissues and lead to Alzheimer's disease (AD) and these enzymes act as disease modulating proteins. Of late researchers are targeting proteins or enzymes to treat the diseases. Many enzymes have been identified and targeted to stop the progression of AD such as acetyl cholinesterase (AChE), amyloid binding alcohol dehydrogenase (ABAD) and β-site amyloid precursor protein cleaving enzyme1(BACE1) in the fields of molecular pathology. These enzymes play a crucial role in early stage of AD.[1]

Inhibition of AChE activity may helpful in maintaining Ach (Acetyl Choline) levels in AD. However, targeting to inhibit ABAD and BACE1 would be beneficial than AChE inhibitors. ABAD produces the mitochondrial damage while binding with amyloid beta proteins in AD.[2] BACE1 is a main precursor for cleaving amyloid beta proteins which may better target to stop synthesize and accumulation. Finding of active sites for drugs in targets to bind is primary step in drug discovery.[3] Molecular docking explores the active sites, binding affinity and the force of drug molecules against the targets.[4]

Combined approaches involving AChE in drug discovery are really effective to find novel drugs for treating AD. This is more effective when combined with virtual screening and animal experiments. Assessing the drug's ability to cross blood brain barrier (BBB), absorption in intestines and bioavailability are important factors for being a novel drug.[5] Inhibition of some enzymes may produce beneficial effects in neurodegenerative disorders such as AD and Parkinson's disease. Researchers have discovered many drug therapies for dementia caused by AD and other causes of Dementia.[6] Many intracellular and extracellular enzymes are responsible for pathogenesis of CNS disorders.[7] Glabridin and Diosmetin from various medicinal plants were identified from different literature reviews for treating cognitive impairment and neuro degenerative disorders. Virtual screening helps to identify pharmacological properties and binding abilities of selected phytochemicals with these targets ABAD and BACE1. In this study efficiency of phytochemicals such as Glabridin and Diosmetin were virtually screened for identifying the drug likeliness potential in treating cognitive impairment.

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MATERIAL AND METHODS

This was a prospective study done in department of Pathology in a tertiary care institution after getting approval from the Institutional research committee.

Ligands or drug molecules preparation

Chemical data or 3d structures of Glabridin and Diosmetin were downloaded from Pubchem database as .sdf format and converted into the pdb format by Openbable software and used as input format for molecular docking.

Drug likeness scoring

The selected ligand's structures were downloaded from Pubchem database either in *.mol or *.sdf file format as input file for DruLiTo software. Here ligand structures were filtered by Lipinski's rule, various filters such as Ghose filter and BBB likeness.

ADMET Prediction:

All ligand's canonical smiles were used as input file format for admetSAR predictions. It is an online tool for comprehensive analysis of phytochemicals. Pharmacokinetic profile and pharmacodynamic activities of ligand molecules were determined. The different routes of entry like Blood brain barrier (BBB), Human Intestinal absorption (HIA), CaCo2 permeability, P-glycoprotein efflux (p-gp) substrate/ inhibitor were tested.

Proteins or enzymes preparation

The target enzymes were retrieved from Protein Data Bank and downloaded as pdb format for molecular docking studies.

1. Amyloid binding alcohol dehydrogenase - (PDB ID: 1SO8),
2. β-site amyloid precursor protein cleaving enzyme1 - (PDB ID: 2QP8)

Molecular docking

Each target enzymes were docked with Glabridin and Diosmetin by autodock v 4 software that deals with all kinds of molecular docking from protein and ligand setup. The pdb formats of these two medicinal plant components were used as ligands and pdb formats of ABAD and BACE1 were used as targets for docking. Their docked poses and binding affinity provided a graphical environment for pharmacological interactions and post docking analysis. Best docked poses saved as preferred display and post screening analysis retrieved as Microsoft excel format.

RESULTS

AdmetSAR prediction values:

Pharmacological properties of Glabridin and Diosmetin were analyzed by AdmetSAR prediction. AdmetSAR prediction values of BBB permeability, human intestinal absorption

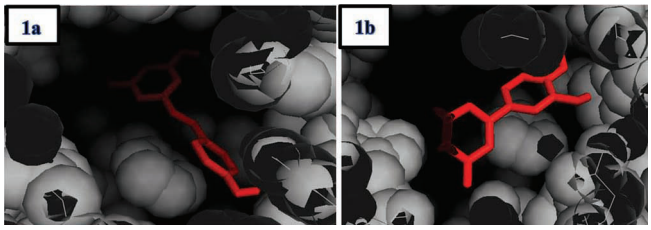

Figure-1: Best docking pose of Glabridin with Amyloid binding alcohol dehydrogenase (ABAD) 1a and β-site amyloid precursor protein cleaving enzyme 1 (BACE1) 1b

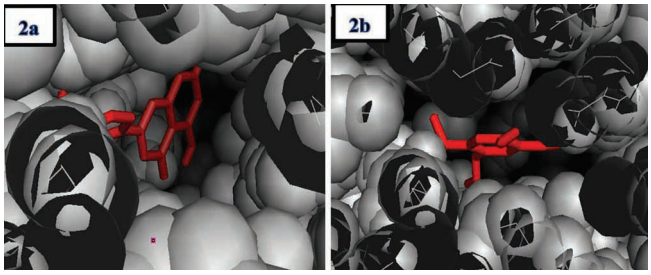

Figure-2: Best docking pose of Diosmetin with Amyloid binding alcohol dehydrogenase (ABAD) 2a and β-site amyloid precursor protein cleaving enzyme 1 (BACE1) 2b

S. No	Ligands	BBB permeability	HIA	CYP450 inhibition/ Substrate	ADME Toxicity	Carcinogenicity	LD50 in rats
1	Diosmetin	0.64	0.98	Substrate/ Non inhibitor	Non toxic	Non carcinogenic	2.72
2	Glabridin	0.58	0.99	substrate/ Non inhibitor	Non toxic	Non carcinogenic	2.94
BBB-blood brain barrier, HIA-human intestinal absorption and CYP450-cytochrome P450, Correlation regression Values of phyto-chemicals for prediction of pharmacological properties by admetSAR tool							

Table-1: The admetSAR prediction values of Glabridin and Diosmetin

S. No	Ligands	Molecular Weight	xLog p	H Bond Acceptor	H Bond Donor	TPSA
1	Glabridin	228.08	1.194	3	3	60.9
2	Diosmetin	300.06	-0.723	6	3	96.22
TPSA- Topological polar surface area.						

Table-2: The values of drug-likeness properties of Glabridin and Diosmetin

S.No	Ligands	Total Binding energy (kcal/mol)		Vander Waals force		H bond	
		ABAD	BACE1	ABAD	BACE1	ABAD	BACE1
1.	Glabridin	-132.3	-136.0	-120.3	-126.8	-11.9	-9.1
2.	Diosmetin	-136.6	-117.1	-115.2	-98.5	-21.4	-18.6

Table-3: The post docking analysis of Glabridin and Diosmetin with Amyloid binding alcohol dehydrogenase (ABAD) and β-site amyloid precursor protein cleaving enzyme 1 (BACE1)

(HIA), CYP450 inhibition/Substrate, ADME Toxicity, carcinogenicity and LD50 in rats were given in Table 1.

Lipinski score from DruLiTo analysis

Lipinski's properties of the phytochemicals were analyzed using DruLiTo software. The result of the Molecular Weight, xLog p, H Bond Acceptor, H Bond Donor and topological polar surface area (TPSA) were shown in Table 2.

Docking results of the four ligands

The results showing the binding energies of selected ligands with the target enzymes were shown in Table 3. Figure 1 showed the best docking pose of Glabridin with ABAD and BACE1. Figure 2 showed the best docking pose of Diosmetin with ABAD and BACE1. Binding energy and Vander Waals force of Diosmetin were higher than Glabridin with the target ABAD and less than with BACE1 which showed that both drugs can be used in modulating the enzyme phosphorylation in AD.

DISCUSSION

The main strategy in drug delivery in neurological degenerative disorders is the ability of the drug to cross the BBB, so that it can inhibit or act on the target in brain. Transport system across the BBB mainly by absorption, endocytosis and transmembrane diffusion. The transmembrane diffusion of the drug depends upon the physiochemical properties of the drug.[5] Lipophilicity was the first of the descriptors to be identified as important for CNS penetration reasoned that highly lipophilic molecules will be partitioned into the lipid interior of membranes and will be retained there. However, ClogP correlates nicely with Log BBB with increasing lipophilicity thereby increasing brain penetration.[8] Optimal activity is observed at LogP=2. Lipophilicity increased probability of binding to hydrophobic protein targets. A drug approaching the BBB is confronted with a thick layer that is capable of non-covalent interactions with the drug.[9] The maximum penetration of the drug through blood brain barrier depends upon the highest probability value in admetSAR profile and the penetration of the drug Glabridin is predicted to be higher of about 0.9151.

Analyzing the substrate/inhibitor profile of the P-glycoprotein (P.gp) is an energy dependent efflux pump present in BBB and is responsible for efflux system. A good compound or drug is absorbed and distributed through intestinal system for its metabolic effects. Greater the human intestinal absorption in admetSAR profile, better the drug absorption from the intestine when administered orally. The admetSAR profile showed positive and no side effect on absorption as the HIA score of all ligands were higher and but the score of Glabridin is highest of 1.0. The cytochrome P450 (CYPs) enzymes are very important in metabolism and bio activation of the drug as the CYPs enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYBA4 are mainly responsible for majority of hydrolysis of drugs. Most of the drugs are withdrawn from the clinical trials because of hepatotoxicity and liver injury.[10] Glabridin and Diosmetin had good absorption score, no hepatotoxicity, non- carcinogenic, with LD50 of 1.9737 for α Diosmetin (2.7192) and Glabridin (2.9435). The LD 50 values suggest that the compounds have no oral toxicity (Table-2). The xLog p value, H bond acceptor, donor and TPSA values of the compounds obey the Lipinski's rule.

TPSA value (Topological polar surface area) indicates polar atoms in the surface of a compound. If the compound has Lower the TPSA value, better penetration through the BBB.[11] TPSA helps to identify the optimization of a drug's ability to permeate cells. Molecules with a polar surface area of greater than 140 angstroms squared tend to be poor at permeating neuronal cell membranes and to penetrate the BBB, a TPSA less than 90 angstroms squared is usually needed.[12] The compound Glabridin has low TPSA value (27.45) when compared to Diosmetin.

The AUTODOCK result of the ligands with the target ABAD showed that among the selected two ligands, the Glabridin had better docking or binding capacity with the target ABAD as the binding energy of Glabridin is -136.0kcal/ mol, which is the lowest when compared to Diosmentin. The docking result of target BACE1 shows that the Diosmetin and Glabridin become promising as therapeutic drugs as the binding energy of Diosmetin and Glabridin with the targets are -136.6kcal/ mol and -132.3 kcal/ mol respectively. Over all the docking results suggest that Glabridin and Diosmetin could bind with targets effectively and modulate the disease causing enzymes.

CONCLUSION

This study reveals the drug likeness and docking effects of Glabridin and Diosmetin that can be modulated as the molecules in AD pathology. Glabridin and Diosmetin could be used as promising drug candidates as ABAD inhibitor and BACE1 inhibitor in AD and further in- vitro and in-vivo studies are suggested to know the molecular mechanisms.

Limitations of the study

This study is an in-silico study. The results had to be compiled with animal experiments for identifying the novel drugs using Glabridin and Diosmetin for treating cognitive impairment in AD.

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