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RESEARCH ARTICLE

QSAR AND DOCKING STUDIES ON PHYTOCOMPOUNDS AS LEAD MOLECULE AGAINST ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurological disease of the brain. It's is the most common form of dementia which demolishes the vital brain cells causing trouble with memory, thinking and behaviour, brutal enough to affect work. Recognized factors in Alzheimer's disease include acetylcholine deficiency, free radicals, and inflammation of the brain tissue. Many of the current drugs used to treat the disease like Donepezil have unpleasant side effects and doctors are keen to find alternatives. There is no cure for Alzheimer's disease, but drugs designed to slow disease progression are available. Herbal medicines are being used by 80% of the world population in developing countries for primary health care. Some herbs may help to improve brain function, but scientific evidence to prove that they can treat Alzheimer's disease, is limited. A list of medicinal plants curing AD were collected from literature and its phytoconstituents were tabulated. The chemical structures of the phytoconstituents (ligands) were drawn in Chemsketch and converted into mol format. The target molecule was found from literature and downloaded in PDB format. Phytoconstituents and few commercially available drugs for AD were docked against Alzheimer's disease target. The phytoconstituent present in plants were found to have better results than the commercially available drugs with a highest docking score of -6.845 for the phytoconstituent Bacoside A and B of *Bacoppa monneira*. The descriptor properties were found out using Qikprep and QSAR model was built with a SD (Standard Deviation) of 1.08 was obtained.

INTRODUCTION

A neurological disease is defined as a pathologic condition that affects and impairs normal electrical impulses throughout the brain or nervous system. General symptom that may occur during the course of the disease include malfunction of the motor system, voluntary and involuntary movement, sensory network, cognitive function, memory and abstract thinking (Mohammad *et al*., 2004). Alzheimer's disease (AD) is named after German physician Aloes Alzheimer, who first described it in 1906 (Singh *et al.*, 2012). It is the most common form of dementia in the elderly. This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. Most individuals who have advanced disease are 85 years of age and older. Females are slightly more likely than males to develop Alzheimer's disease (Hajiaghaee *et al.*, 2011).

Working of nerve cells in the body

The brain has 100 billion nerve cells (neurons). Each nerve cell connects to many others to form communication networks. In addition to nerve cells, the brain includes cells specialized to support and nourish other cells. Brain cells operate like tiny factories. They receive supplies, generate energy, construct equipment and get rid of waste. Scientists believe Alzheimer's disease prevents parts of a cell's factory from running well. But just like a real factory, backups and breakdowns in one system cause problems in other areas. As damage spreads, cells lose their ability to do their jobs and eventually, die (Alzheimer's Association, 2005).

Role of plaques and tangles

The brains of individuals with Alzheimer's have an abundance of plaques and tangles. Plaques are deposits of a protein fragment called beta amyloid that builds up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that builds up inside cells. Most experts believe that they somehow play a critical role in blocking communication among nerve cells and disrupting processes the cells need to survive .The destruction and death of nerve cells causes memory failure, personality changes, problems in carrying out daily activities and other symptoms of Alzheimer's disease (Alzheimer's Association, 2005). The beta amyloid peptide, with 39-42 amino acid residue plays a significant role in the development of AD. New studies suggest novel strategies for AD therapy. The most viable of these at the moment is targeting the disruption of neurotransmitter systems. Counteracting overproduction of amyloid-β is attractive in theory and has spurred the development of secretase inhibitors as well as active and passive immunization techniques (Hajiaghaee *et al.*, 2011).

Genes responsible for AD

Mutations in the presenilin (PSEN1 and PSEN2) and amyloid precursor protein (APP) genes cause autosomal dominant early onset AD. The apolipoprotein E (APOE) gene is the fourth gene implicated in AD. Most of the early onset AD cases are due to mutations in the PSEN1 gene, while mutations in the APP and PSEN2 genes are rare. Carriers of the variant of APOE have an increased risk of both senile and presenile AD (Anil *et al*., 2012).

Medicinal plants in the treatment of AD

Although there is no cure for AD, it can be managed with the available drugs, to some degree. A number of scientific research have been carried out on medicinal herbs. Herbs have anti-inflammatory and anti-oxidant activities that may be used in the treatment of AD. Some of the medicinal herbs used in this treatment are *Salvia officinalis, Rosmarinus officinalis, Curcuma longa, Matricariarecutita, Melissaofficinalis, Commiphora whigitti,*

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Galnthus nivalis, Panaxginseng, Bacoppa monneira, Angelica archangelica, Collinsonia Canadensis, Bertholettia excels, Tinospora cordifolia, Urticadioica, Magnolia officinalis, Huperzia serrata, Gingko biloba, Withania somnifera. These herbs are responsible for slowing down the brain cell degeneration caused by alzheimer's.They enhance the brain's ability to function,abd therefore,provide stability when used consistently (Anil *et al*., 2012).

MATERIALS AND METHODS

PubChem is designed to provide information on biological activities of small molecules, generally those with molecular weight less than 500 daltons. PubChem's integration with NCBI's Entre z information retrieval system provides sub/structure, similarity structure, and bioactivity data. Isis/Draw was a chemical drawing structure program for Windows, published by MDL information systems. ChemSketch is a chemical structure drawing program developed by ACD/labs. It uses many standard file formats for the import and export of drawing. Schrödinger software suite is a drug design software using both ligand and structure-based methods. Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level. The Protein data bank is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. Quantitative Structure-Activity Relationship (QSAR) is one of the most important methods in chemo metrics, which give information that is useful for drug design and medicinal Chemistry.

Collection & modelling of phytoconstituents chemical structure

- Phytoconstituents of various plants curing AD was collected from literature
- Chemical structures of the phytochemicals (ligands) were drawn using Chemsketch and was converted into mol format in Argus lab
- The target molecule was found from literature and downloaded from PDB (MAGL-Monoglyceride lipase)

Docking and QSAR studies

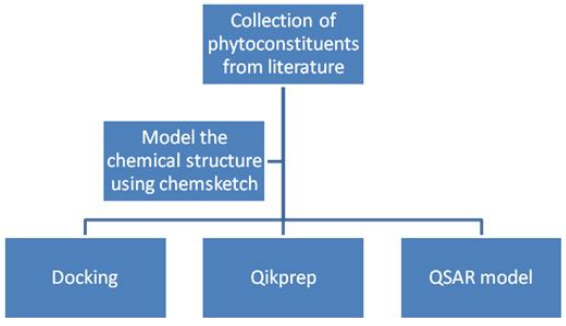
The docking of phytochemicals (ligand) aganist the target protein was done using Schrodinger Glide. This module involves the following steps:

- Ligand preparation
- Protein preparation
- Grid generation
- Docking and analysis

Qikprep and QSAR model

The ligands descriptor property could be found using Schrodinger Qikprep module and QSAR model was build using Schrodinger Strike module.

Flowchart Showing the Materials and the Methods



RESULTS AND DISCUSSION

Ligand Bacoside A interacting with target protein showing 5 hydrogen bonds is shown

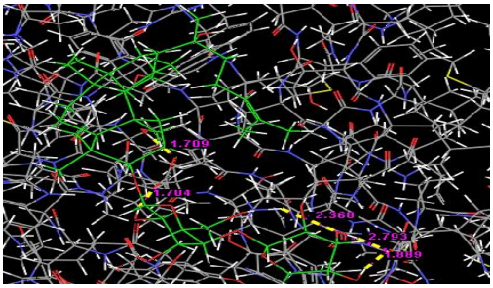


Figure 1. Ligand Bacoside A docked with target protein

Ligand Chlorogenic acid interacting with target protein showing 5 hydrogen bonds is shown

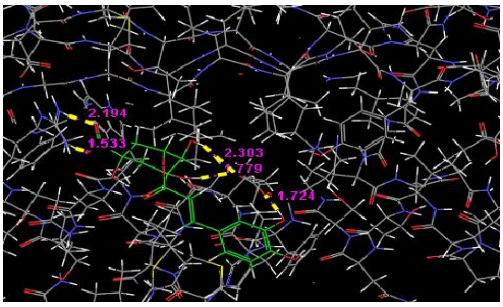


Figure 2. Ligand Chlorogenic acid docked with target protein

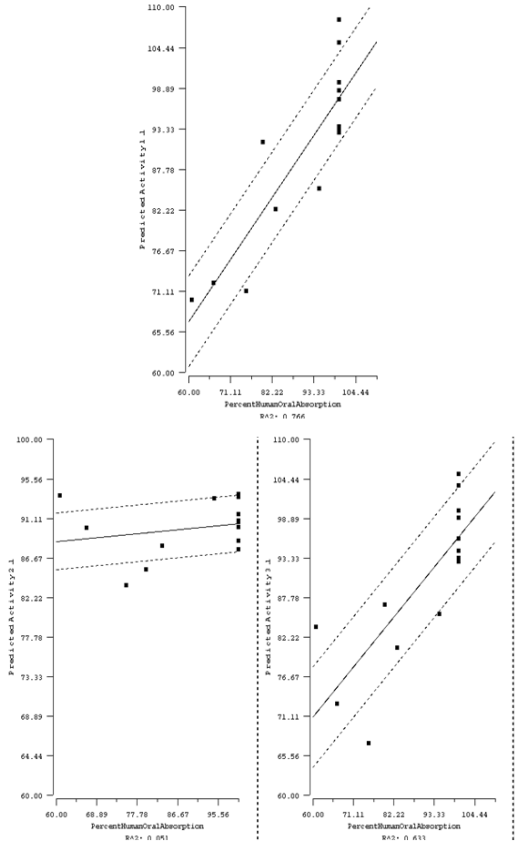


Figure 3. QSAR plot showing MLR (Multiple linear regression) in the left corner, PCA (Principal component analysis) in the centre and PLS (Partial least square) in the right corner

Table 1. List of medicinal plants used in the treatment of alzheimer's disease

S.No	Plant name	Vernacular name	Phytoconstituent
1.	*Centella asiatica*	Vallarai	Asiaticoside,Pectic acid
2.	*Salvia officinalis*	Sage	Thujone,Mycrene,Genkawine
3.	*Rosmarinus officinalis*	Rosemary	Thymol,Pinene,Linalool,Limonene
4.	*Curcuma longa*	Turmeric	Curcumin,Caryophyllene,Tumerone
5.	*Matricaria recutita*	Chamomile	Alfa-bisabolol,Caffeic acid,Farnese
6.	*Melissa officinalis*	Balm mint	Citral,Geraniol,Citranellal
7.	*Galanthus nivalis*	Common snow drop	Galanthamine,Tazettine,Ungeremine,Hamayne
8.	*Panax ginseng*	Ginseng	Ginsenosides
9.	*Angelica archangelica*	Wild celery	Ligustilide,Careen,Cymene,Limonene,Sabinene
10.	*Collinsonia canadensis*	Horse balm	Germacrene,Elemicin,Nagitanine
11.	*Urtica dioica*	Nettle roots	Formic acid,Histamine,Magnalol
12.	*Huperzia serrata*	Toothedclubmoss	Huperzine
13.	*Withania somnifera*	Ashwagantha	Withaferine A,Withanolide D
14.	*Glycyrrhizin glabra*	Liquorice	Glycyrrhetinic acid,Glycyrrhizin,Glabdrin,Licoisoflavanone
15.	*Gingko biloba*	Maidenhair	GingkoloidesA,Gingkoloides B,Gingoloides C
16.	*Bacoppa moneira*	Brahmi	Bacoside A,Bacoside B
17.	*Acorus calamus*	Sweet flag	Acaromone,Asarone,Cis&Trans Asarone
18.	*Magnolia officinalis*	Magnola bark	Magnolol

Table 2. Docking score, binding energy and hydrogen bonds of phytoconstituents

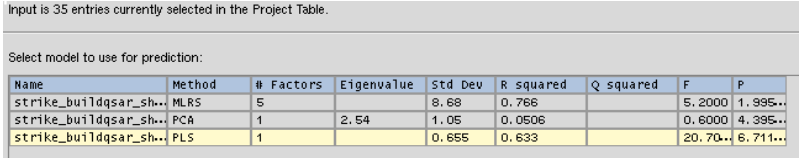
S.No	Phytoconstituents	Docking score	Binding energy	No.of hydrogen bonds
1.	Bacoside A	-6.84	-48.86	5
2.	Bacoside B	-6.84	-44.84	5
3.	Glycyrrhizin	-6.26	-40.69	5
4.	Chlorogenic acid	-5.58	-51.69	5
5.	Huperzine	-4.48	-21.02	2
6.	Lycorine	-5.60	-22.25	3
7.	Histamine	-5.44	-16.50	3
8.	Formic acid	-2.88	-8.27	2
9.	Glycyrhetinic acid	-2.92	-52.88	3
10.	Hamayne	-2.89	-25.65	4
11.	Triterpene	-2.96	-51.55	3
12.	Caffeic acid	-2.60	-18.57	3
13.	Panaxdiol	-2.44	-27.99	2

Table 3. Docking score and Docking energy of drugs curing Alzheimer

S.No	Drug	Docking score	Docking energy	Hydrogen bonds
1.	Nicardipine	-3.88	-38.05	3
2.	Galanthamine	-3.38	-35.42	3
3.	Hydralazine	-3.31	-21.98	2
4.	Propranolol	-2.69	-26.67	2
5.	Amiloride	-2.41	-21.42	3
6.	Diovan	-2.33	-33.04	3
7.	Losaratan	-2.08	-28.22	2
8.	Memantine	-1.87	-16.84	1
9.	Tacrine	-1.70	-21.49	2
10.	Rivastigmine	-1.56	-20.79	2

Table 4. Descriptor properties of the phytoconstituents

S.No	Molecule	Donor HB	Accpt HB	QPlogPo/w	Percent Human Oral Absorption	Mol. Wt.
1.	4-O-methylhonokiol	2	2.75	2.332	100	260.20
2	Acoramone	1	3	1.448	100	208.13
3.	Caffeic acid	0	5	-1.608	66.722	176.13
4.	citral	0	2	-0.056	94.774	136.13
5.	curcumin	0	10	-1.224	75.383	348.97
6.	desmethoxycurcumin	2	6.25	0.841	79.794	320.97
7.	elemicin	0	2.25	1.992	100	192.12
8.	farnesene	0	0	3.093	100	180.31
9.	formicacid	1	2	-0.619	60.914	44.13
10.	geraniol	1	1.7	2.13	100	136.10
11.	isoliquirtigenin	0.5	5.5	-0.108	83.266	244.16
12.	linalool	1	0.75	2.709	100	136.10
13.	magnolol	4	4	1.122	100	248.19
14.	myrcene	0	0	0.675	100	120.11


Input is 35 entries currently selected in the Project Table.

Select model to use for prediction:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
strike_buildqsar_sh...	MLRS	5		8.68	0.766		5.2000	1.995...
strike_buildqsar_sh...	PCA	1	2.54	1.05	0.0506		0.6000	4.395...
strike_buildqsar_sh...	PLS	1		0.655	0.633		20.70...	6.711...

Figure 4. QSAR Prediction table

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Mohammad Ali Faghihi., Salim Mottagui-Tabar., and Claes Wahlestedt.,. *(2004),"*Genetics of neurological disorders".*Future drugs Ltd.*1473-7159.

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