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Comparative Molecular Docking Study of Phytoconstituents Identified in *Morinda Citrifolia* Linn on Acetylcholinesterase and Butyrylcholinesterase

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ABSTRACT

Alzheimer's disease (AD) or Senile Dementia of the Alzheimer Type (SDAT) is an irreversible but progressive neurodegenerative disorder caused by the loss of neurons and synapses in the cerebral cortex and certain sub-cortical regions. ChEs in vertebrates have been classified into two types, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), on the basis of distinct substrate specificities and inhibitor sensitivities which serves as enzyme targets for AD. The search can be focused on plant natural products that may offer treatment for AD than currently used drugs. As an attempt to identify such natural alternates with cholinomimetic and neuroprotective activities, a set of 22 compounds identified from Morinda citrifolia fruit juice was docked against human acetylcholinesterase (PDB ID:1B41) / butyrylcholinesterase (PDB ID: 2PM8) enzymes retrieved from protein data bank using Molegro Virtual Docker (MVD). Among the compounds analysed, five compounds, namely, (+)-3,3'-bisdemethyltanegool ,3,3'-bisdemethylpinoresinol,(-)-pinoresinol, isoamericanoic acid A, quercetin are docked with a MolDock score of -124.227, -115.403, -107.812, -106.993, -106.634 respectively for AChE and (+)-3,3'-bisdemethyltanegool, (-)-pinoresinol, americanin A, Deacetylasperuloside, 3,3'-bisdemethylpinoresinol are docked with a MolDock score -132.26, -126.487, -115.81, -114.994, -109.8 respectively for BChE and all these phytoconstituents satisfies Lipinski's rule of '5' for drug likeliness property. The compounds were identified as potent and selective inhibitors of AChE/BChE compared to currently available drug molecules, tacrine, rivastigmine and huperazine A which showed inhibitory activity for AChE (MolDock score was -69.7799, -95.5779 and -72.1161) and for BChE (MolDock score was -70.3026, -91.32 and -68.5103). These phytoconstituents from M. citrifolia may serve as potential lead compound for developing new anti- alzheimer drug.

Keywords: *Morinda citrifolia*; Docking; Acetylcholinesterase; Butyrylcholinesterase

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INTRODUCTION

Morinda citrifolia Linn Rubiaceae known commercially as Noni grows widely throughout the Pacific and is one of the most significant sources of traditional medicines among Pacific island societies. The Noni plant is used in combinations for herbal remedies. The fruit juice is in high demand in medicine for different kinds of illnesses such as arthritis, diabetes, high blood pressure, muscle AChEs and pains, gastric ulcers, menstrual difficulties, headaches, heart disease, AIDS, cancers, gastric ulcers, sprains, mental depression, senility, poor digestion, atherosclerosis, blood vessel problem, and drug addiction [1].

A number of phytoconstituents has been identified in the fruits of *Morinda citrifolia* such as Allantoin, Octanoic acid, Vanillin, n Decanoic acid, 1, 2-dihydroxy-anthraquinone, Hexoic acid, Isoscopoletin, Morindin, 1, 3-dimethoxy-anthraquinone, quercetin, scopoletin, kaempferol, Asperuloside, americanin A, citrifolinin B, Dehydromethoxygaertneroside, (-) -pinoresinol, 3,3'-bisdemethylpinoresinol, (+) -3,3'-bisdemethyltanegool, Borreriagenin, Deacetylasperuloside, isoamericanoic acid A [2-5]. Traditional synthesis of a series of new compounds utilizing combinatorial chemistry and high-throughput screening can be carried out at high cost and also are time consuming whereas on the other hand, docking various ligands to the protein of interest followed by scoring to determine the affinity of binding and to reveal the strength of interactions has become increasingly important in the contest of drug discovery. As the extracts and fruit juice of *M.citrifolia* have been shown to possess neuroprotective against alzheimer's disease in some earlier studies [6,7], it was considered worthwhile to study the interaction of phytoconstituents identified with both AChE / BChE and compared with existing drug molecules by molecular docking studies.

MATERIALS AND METHODS

Preparation of Ligand

We have collected the structures of phytoconstituents of *M.citrifolia* and currently available drug molecules from PubChem database (http://puBChEm.ncbi.nlm.nih.goc/). Our AChE/ BChE inhibitor database comprises 22 bioactive compounds from *M. citrifolia*. The inhibitors were converted to pdb format and optimized by means of ligand preparation using default settings in Molegro Virtual Docker (MVD-2010,4.2.0) [8]. The collected structures (ligands) were prepared for further studies.

Preparation of Receptor

The X-ray crystal co-ordinates of AChE (PDB ID: 1B41) and BChE (PDB ID: 2PM8) were retrieved from protein data bank. Since ChEs have their crystal structure in a state that represent the pharmacological target for the development of new drugs to cure AD, these two PDBs were selected for modeling studies. It is well known that PDB files often have poor or missing assignments of explicit hydrogens, and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization and charges were assigned using the MVD. The potential binding sites of both ChE receptors were calculated using the built-in cavity detection algorithm implemented in MVD. The search space of the simulation exploited in the docking studies was studied as a subset region of 25.0 Angstroms around the active side cleft. The water molecules are also taken in to consideration and the replaceable water molecules were given a score of 0.50.

Molecular Docking

MVDs docking search algorithms and scoring functions:

Ligand docking studies were performed by MVD, which has recently been introduced and gained attention among medicinal chemists. MVD is a fast and flexible docking program that gives the most likely conformation of ligand binding to a macromolecule. MolDock software is based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm [9]. It has an interactive optimization technique inspired by Darwinian Evolution Theory (Evolutionary Algorithms - EA), in which a population of individuals is exposed to competitive selection that weeds out poor solutions. Recombination and mutation are used to generate new solutions. The scoring function of MolDock is based on the Piecewise Linear Potential (PLP), which is a simplified potential whose parameters are fit to protein-ligand structures and a binding data scoring function [10,11] that is further extended in GEMDOCK (Generic Evolutionary Method for molecular DOCK) [12] with a new hydrogen bonding term and charge schemes.

Parameters for Docking Search Algorithms

MolDock optimizer:

In MVD, selected parameters were used for the guided differential evolution algorithm: number of runs =5 by checking constrain poses to cavity option), population size=50, maximum interactions =2000, crossover rate=0.9, and scaling factor=0.5. A variance-based termination scheme was selected rather than root mean square deviation (RMSD). To ensure the most suitable binding mode in the binding cavity, Pose clustering was employed, which lead to multiple binding modes.

Parameters for Scoring Functions

MolDock score:

They ignore-distant-atoms option was used to ignore atoms far away from the binding site. Additionally, hydrogen bond directionality was said to check whether hydrogen bonding between potential donors and acceptors can occur. The binding site on the protein was defined as extending in X, Y and Z directions around the selected cavity with a radius of 25 Angstroms.

Hardware

Dell studio 15 Dual core processor windows 7 mold. Windows edition: Windows 7 ultimate copyright©2009 Microsoft corporation, System processor Intel (R) Core(TM)2 Duo CPU T6400 Hz 2.00 GHz, Installed Memory (RAM) 3.00 GB, system type 32-bit operating system.

RESULTS AND DISCUSSIONS

To find the potential inhibitors of anti-alzheimer's drug target enzymes AChE/BChE, all the bioactive compounds from *M.citrifolia* and currently used drug molecules (ligands) collected were docked into the active site. The docking results of this ligand are given in Tables 1 and 2 for AChE and BChE respectively. The ranking of ligand is based on the MolDock score. The active site of AChE and BChE is subdivided into several subsites; the esteratic subsite, also called the catalytic triad (CT, Ser200, His440, Glu327), oxyanion hole (OH, Gly118, Gly119, Ala201), anionic subsite (AS, Trp84, Tyr121, Glu199, Gly449, Ile444), acyl binding pocket (ABP, Trp233, Phe288, Phe290, Phe292, Phe330, Phe331) and peripheral anionic subsite (PAS, Asp72, Tyr121, Ser122, Trp279, Phe331, Tyr334) are buried at the bottom of a 20 Å deep aromatic cleft .

Table 1: Top 1 pose for each ligand based on MolDock score and applying Lipinski's rule of 5 on AChE (PDB ID: 1B41)

PubChem ID	Ligand	MolDock Score	Re rank Score	H Bond	Molecular Weight [g/mol]	Molecular Formula	Log P	H-Bond Donor	H-Bond Acceptor
[00]11203960	Dehydromethoxygaertneroside	-179.614	-109.844	-8.71295	240.21092	$C_{14}H_8O_4$	-0.1	5	14
[00]151621	Morindin	-168.25	-99.7315	-9.67862	332.30474	$C_{17}H_{16}O_7$	-0.6	8	14
[01]5351518	Asperuloside	-135.728	-98.4434	-5.61205	286.2363	$C_{15}H_{10}O_6$	-2.4	4	11
[00]44593378	Deacetylasperuloside	-130.287	-97.5299	-8.58053	144.21144	$C_8H_{16}O_2$	-3	5	10
[00]10873461	citrifolinin B	-124.937	-85.3398	-7.6983	172.2646	$C_{10}H_{20}O_2$	-3.2	5	12
[00]44423052	(+)-3,3'-bisdemethyltanegool	-124.227	-94.7819	-10.4588	192.16812	$C_{10}H_8O_4$	0.6	6	7
[00]24992964	3,3'-bisdemethylpinoresinol	-115.403	-93.4557	-5.44479	268.26408	$C_{16}H_{12}O_4$	1.6	4	6
[00]12309637	(-)-pinoresinol	-107.812	-83.2098	-2.5	192.16812	$C_{10}H_8O_4$	2.3	2	6
[00]46226513	isoamericanoic acid A	-106.993	-84.3006	-8.97877	116.15828	$C_6H_{12}O_2$	1.7	3	7
[00]5280343	quercetin	-106.634	-81.4073	-8.8934	328.31604	$C_{18}H_{16}O_6$	1.5	5	7
[00]5459018	americanin A	-105.994	-74.0129	-7.85951	214.21516	$C_{10}H_{14}O_5$	1.7	3	6
[00]5280863	kaempferol	-97.2375	-77.3282	-6.32952	158.11544	$C_4H_6N_4O_3$	1.9	4	6
[00]Rivastigmine	Rivastigmine	-95.5779	-75.4124	-1.78946	250.34	$C_{14}H_{22}N_2O_2$	2.24	0	4
[01]44583980	Borreriagenin	-88.1042	-71.2213	-5	152.14732	$C_8H_8O_3$	-1.5	3	5
[00]204	Allantoin	-84.2071	-66.7818	-6.03864	576.50282	$C_{27}H_{28}O_{14}$	-2.2	4	3
[02]2969	n- Decanoic acid	-76.3079	-63.1102	-2.98015	414.36068	$C_{18}H_{22}O_{11}$	4.1	1	2
[02]6293	1, 2-dihydroxy-anthraquinone	-75.6724	-63.5793	-0.14404	418.34938	$C_{17}H_{22}O_{12}$	3.2	2	4
[00]Huperazine A	Huperazine A	-72.1161	-58.8041	-2.14292	242.32	$C_{15}H_{18}N_2O$	1.54	0	3
[01]69894	Isoscopoletin	-71.1847	-60.2539	-1.41837	330.33192	$C_{18}H_{18}O_6$	1.5	1	4
[00]361511	1, 3-dimethoxy-anthraquinone	-70.5029	-65.5463	-2.52925	302.2357	$C_{15}H_{10}O_7$	2.8	0	4
[00]5280460	scopoletin	-69.9682	-59.3564	-0.745131	358.38508	$C_{20}H_{22}O_6$	1.5	1	4
[00]Tacrine	Tacrine	-69.7799	-64.0732	0	234.7246	$C_{13}H_{15}ClN_2$	2.71	2	0
[00]1183	Vanillin	-68.04	-56.2506	-4.89722	372.324	$C_{16}H_{20}O_{10}$	1.2	1	3
[00]379	Octanoic acid	-66.7875	-55.739	-3.4205	564.49212	$C_{26}H_{28}O_{14}$	3	1	2
[00]8892	Hexoic acid	-60.5111	-48.9568	0	348.3472	$C_{18}H_{20}O_7$	1.9	1	2

It was found out by ligand energy inspector that the phytoconstituents as well as the drug molecules were able to bind to the any one of the sub sites of AchE and BchE. We analysed 22 physically relevant properties of bioactive compounds from *Morinda citrifolia*, among which were molecular weight, H-bond donors, H-bond acceptors and Log P (octanol/water), according to Lipinski's rule-of-five (Tables 1 and 2) by EPI suite software [13]. Lipinski's rule of 5 is a thumb to evaluate drug likeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a orally active drug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including its ADME. However, the rule does

not predict if a compound is pharmacologically active. In this study, all the showed allowed values for the properties analysed and exhibited drug-like characteristics based on Lipinski's rule-of-five. Four compounds of *Morinda citrifolia* namely Dehydromethoxygaertneroside, citrifolinin B, Asperuloside and Morindin deviate Lipinski's rule-of-five even though they had the maximum Moldock score [14,15]. Molecular docking studies revealed that the potential of plant phytoconstituents of *Morinda citrifolia* to inhibit cholinesterase was attributable to cumulative effects of strong H_2-bonds, cationin-π, π-π interactions and hydrophobic interactions. A comparison of the docking results of selected phytoconstituents with standard drugs/molecules (Rivastigmine, Tacrine, Huperazine A) was found to have better affinity.

Table 2: Top 1 pose for each ligand based on MolDock score and applying Lipinski's rule of 5 on BChE (PDB ID: 2PM8)

PubChem ID	Ligand	MolDock Score	Rerank Score	H Bond	Molecular Weight [g/mol]	Molecular Formula	Log P	H-Bond Donor	H-Bond Acceptor
[00]11203960	Dehydromethoxygaertneroside	-174.148	-119.88	-15.174	576.5028	$C_{27}H_{28}O_{14}$	-0.1	5	14
[01]10873461	citrifolinin B	-149.789	-93.815	-11.862	418.3494	$C_{17}H_{22}O_{12}$	-3.2	5	12
[00]5351518	Asperuloside	-133.606	-94.191	-8.8419	414.3607	$C_{18}H_{22}O_{11}$	-2.4	4	11
[01]151621	Morindin	-132.945	-2.962	-9.3129	564.4921	$C_{26}H_{28}O_{14}$	-0.6	8	14
[01]44423052	(+)-3,3'-bisdemethyltanegool	-132.26	-63.25	-12.22	348.3472	$C_{18}H_{20}O_7$	0.6	6	7
[00]12309637	(-)-pinoresinol	-126.487	-80.768	-5.041	358.3851	$C_{20}H_{22}O_6$	2.3	2	6
[01]5459018	americanin A	-115.81	-86.757	-5.7273	328.316	$C_{18}H_{16}O_6$	1.7	3	6
[00]44593378	Deacetylasperuloside	-114.994	-81.53	-11.407	372.324	$C_{16}H_{20}O_{10}$	-3	5	10
[00]24992964	3,3'-bisdemethylpinoresinol	-109.8	-81.027	-13.693	330.3319	$C_{18}H_{18}O_6$	1.6	4	6
[00]46226513	isoamericanoic acid A	-109.506	-70.113	-5.8832	332.3047	$C_{17}H_{16}O_7$	1.7	3	7
[02]5280343	quercetin	-99.4821	-29.322	-11.494	302.2357	$C_{15}H_{10}O_7$	1.5	5	7
[00]5280863	kaempferol	-95.065	-65.59	-6.5836	286.2363	$C_{15}H_{10}O_6$	1.9	4	6
[01]Rivastigmine	Rivastigmine	-91.32	-69.169	0	250.34	$C_{14}H_{22}N_2O_2$	2.24	0	4
[00]379	Octanoic acid	-90.1963	-68.96	-4.5881	144.2114	$C_8H_{16}O_2$	3	1	2
[01]6293	1, 2-dihydroxy-anthraquinone	-82.4872	-68.386	-6.0851	240.2109	$C_{14}H_8O_4$	3.2	2	4
[00]204	Allantoin	-82.2958	-64.367	-4.8905	158.1154	$C_4H_6N_4O_3$	-2.2	4	3
[02]44583980	Borreriagenin	-81.8557	-64.565	-5	214.2152	$C_{10}H_{14}O_5$	-1.5	3	5
[00]361511	1, 3-dimethoxy-anthraquinone	-80.0551	-67.195	-0.6364	268.2641	$C_{16}H_{12}O_4$	2.8	0	4
[00]69894	Isoscopoletin	-78.277	-61.498	-4.465	192.1681	$C_{10}H_8O_4$	1.5	1	4
[00]5280460	scopoletin	-78.135	-59.039	-2.4202	192.1681	$C_{10}H_8O_4$	1.5	1	4
[00]2969	n-Decanoic acid	-75.7889	-60.708	-2.5	172.2646	$C_{10}H_{20}O_2$	4.1	1	2
[00]1183	Vanillin	-71.7359	19.2429	-5.5047	152.1473	$C_8H_8O_3$	1.2	1	3
[00]Tacrine	Tacrine	-70.3026	-55.794	-1.4667	234.7246	$C_{13}H_{15}ClN_2$	2.71	2	0
[00]8892	Hexoic acid	-69.2025	-56.953	-4.574	116.1583	$C_6H_{12}O_2$	1.9	1	2
[01]Huperazine A	Huperazine A	-68.5103	-57.857	-0.4497	242.32	$C_{15}H_{18}N_2O$	1.54	0	3

CONCLUSION

This study has revealed the fact that herbal medicinal plants identified in Indian systems of Medicine are more efficacious compared to allopathic system of medicine but it draws back due to the difficulty in standardization and lack of literature. These modern techniques and analysis will be helpful in evaluating and documenting these herbal compounds identified in the Indian system of medicine as potent compounds for treatment for various ailments.

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