AN IN SILICO EVALUATION OF COCCINIA GRANDIS FRUITS AGAINST ALZHEIMER'S DISEASE

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DO: 10.7897/2277-4572.034166
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Received on: 05/05/14 Revised on: 02/07/14 Accepted on: 05/08/14

ABSTRACT

The aim of the present study is to find the effectiveness of reported phytocompounds from Coccinia grandis fruits against Alzheimer's disease. Acetylcholinesterase is an important target in the treatment of Alzheimer's disease and it was taken as a receptor for this study. The reported phytocompounds were taken as ligand molecules and the 3D structure of human acetylcholinesterase was retrieved from PDB database. The 3D structure of synthetic drug and reported phytocompounds were obtained from PubChem database. Docking studies were performed using Glide (a Schrodinger module). From the results, it was observed that the phytocompounds β-Sitosterol (-8.70 Kcal/mol), Pectin (-7.82 Kcal/mol), Retinol (-7.24 Kcal/mol) and Taraxerone (-6.40 Kcal/mol) had better glide score than the synthetic drug rivastigmine (-5.6 Kcal/mol). Hence, it is suggested that intake of Coccinia grandis fruits can be used to reduce the severity and progress of Alzheimer's disease.

Keywords: Coccinia grandis, Alzheimer's disease, acetylcholinesterase, β-sitosterol, pectin, retinol, taraxerone

INTRODUCTION

Alzheimer's disease (AD) is the common form of dementia and there were about 25 million persons affected with AD worldwide out of which 4.5 million belongs to United States. It is expected to increase about 114 million by the year 2050¹.². Malfunction of several biochemical pathways in elderly people lead to Alzheimer's disease. Cholinergic hypothesis has been the most successful approach to deal with this problem³.⁴. Acetylcholine (ACh), an organic substance involved in the transfer of signals in brain, is hydrolyzed into choline and acetyl group which is catalyzed by acetylcholinesterase enzyme (AChE)⁵. The synthesized ACh gets accumulated in the vesicles and released into the synaptic cleft thereby regulates neurotransmission. Increasing the level of ACh in brain with acetylcholinesterase inhibitors like rivastigmine, galantamine, tacrine and donepezil is the key approach to treat AD⁶. These drugs have several side effects like gastrointestinal disturbances and problem associated with bioavailability⁷.⁸. Hence there is an urge for finding better inhibitor for acetylcholinesterase from natural source to treat AD without any adverse effects. Coccinia grandis is commonly known as Ivy gourd which belongs to Cucurbitaceae family used in Indian traditional medicinal system⁹. The fruit has been used to treat leprosy, fever, asthma, bronchitis and jaundice dysentery, vomiting, mouth ulcers, diabetics, gastrointestinal disturbances and bronchitis. They possess various pharmacological activities such as antimicrobial¹⁰, hepatoprotective¹¹, wound healing¹², anthelmintic¹³, antitussive¹⁴, antioxidant¹⁵ and hypoglycemic¹⁶. The present study employs an in silico docking approach to understand the mechanism of natural compounds reported from Coccinia grandis fruit using GLIDE against AD. The docked phytocompounds were compared with the synthetic drug rivastigmine to find the efficacy of the phytocompounds.

MATERIALS AND METHODS

Retrieval of protein structure

The 3D structure of the selected Human acetylcholinesterase was retrieved from the Protein Data Bank (PDB), is a repository for the 3D structural data of large biological molecules, such as proteins and nucleic acids¹⁷.

Binding site prediction

The site binding of the receptor acetylcholinesterase was identified using CASTp server. It is a pictorial database which shows the molecule that make up of the structure (i.e. protein chains, ligands and metal ions) and schematic diagrams of their interactions. The PDB ID of the target protein was given as input.

Preparation of ligand structures

The reported phytocompounds of Coccinia grandis fruit used for docking analysis were selected from literature. The structures of the phytocompounds and synthetic drug were retrieved from PubChem database in the sdf file format.

Docking analysis

Docking analysis was carried out for the target protein acetylcholinesterase with the selected phytocompounds and the synthetic drug using GLIDE (a Schrodinger module) software¹⁸.

RESULTS

Complex structure of human acetylcholinesterase and binding site prediction

The 3D structure of human acetylcholinesterase was retrieved from the Protein Data Bank (PDB ID: 1B4I) and viewed using PyMOL (Figure 1). The sequence length of the protein is 539 amino acids and the resolution of the structure is 2.76 Å¹⁹. PRO 31, MET33, GLN 71, TYR 72, ASP 74, GLY 82, THR 83, TRP 86, ASN 87, PRO 88, GLY 120, GLY 121, TYR 124, SER 125, GLY 126, LEU 130, TYR 133, GLU 202, SER 203, ALA 204, TRP 236, TRP 286, VAL 294, PHE 295, ARG 296, PHE 297, TYR 337, PHE 338, TYR 341,
TRP 439, HIS 447, GLY 448 and TYR 449 are the binding site residues of acetylcholinesterase retrieved from the CASTp server.

**Structure of the ligand molecules**

The structures of the phyto compounds and synthetic drug were obtained from Pub Chem and listed in Table 1. The 3D structures of the compounds were docked with the target protein human acetylcholinesterase using GLIDE.

**Docking analysis**

In the present study, 4 major compounds reported in *Coccinia grandis* fruit were docked with the 3D structure of acetylcholinesterase using GLIDE. The docked phyto compounds are compared with the synthetic drug Rivastigmine. The compounds with better results than the drug were identified based on Glide Score (G-Score) and tabulated (Table 2). Glide Score is predicted based on the hydrophobic interactions, hydrophobically packed H-bonds, lipophilic, low molecular weight and electrostatic interactions. The interactions of the synthetic drug and phyto compounds with acetylcholinesterase are listed in Figure 2 (A-E).

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**Table 1: Reported compounds of Coccinia grandis fruits and Synthetic drug**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of the phytocompounds</th>
<th>Pub Chem IDs</th>
<th>Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>β-Sitosterol</td>
<td>222284</td>
<td><img src="image1" alt="Image" /></td>
</tr>
<tr>
<td>2.</td>
<td>Pectin</td>
<td>441476</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>3.</td>
<td>Retinol</td>
<td>445354</td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>4.</td>
<td>Taraxerone</td>
<td>92785</td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>5.</td>
<td>Rivastigmine (Synthetic drug)</td>
<td>77991</td>
<td><img src="image5" alt="Image" /></td>
</tr>
</tbody>
</table>

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**Table 2: Glide score, Interactions and Hydrogen bond lengths of the docked complexes of synthetic drug and phyto compounds with acetylcholinesterase**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Synthetic drug and Phyto compounds</th>
<th>Glide Score (Kcal/mol)</th>
<th>Interactions (D-H...O)</th>
<th>Bond length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synthetic Drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Rivastigmine</td>
<td>-5.6</td>
<td>Tyr124(O-H...N)</td>
<td>2.395</td>
</tr>
<tr>
<td></td>
<td>Phyto compounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>β-Sitosterol</td>
<td>-8.70</td>
<td>TYR124(O-H...O)</td>
<td>1.753</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(O-H...O)ARG296</td>
<td>1.916</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARG296(N-H...O)</td>
<td>1.871</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHE295(N-H...O)</td>
<td>2.373</td>
</tr>
<tr>
<td>2.</td>
<td>Pectin</td>
<td>-7.82</td>
<td>(O-H...O)TYR124</td>
<td>2.299</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(O-H...O)TYR124</td>
<td>2.105</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(O-H...O)TYR337</td>
<td>2.170</td>
</tr>
<tr>
<td>3.</td>
<td>Retinol</td>
<td>-7.24</td>
<td>SER203(O-H...O)</td>
<td>1.706</td>
</tr>
<tr>
<td>4.</td>
<td>Taraxerone</td>
<td>-6.40</td>
<td>ARG296(N-H...O)</td>
<td>2.111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHE295(N-H...O)</td>
<td>2.462</td>
</tr>
</tbody>
</table>
DISCUSSION
Alzheimer's disease, a neurodegenerative disease, is mainly associated with the loss of cholinergic neurons in brain. Acetylcholinesterase is a principal enzyme that hydrolyzes acetylcholine which is involved in the development of AD and has an independent action in the central nervous system. They are mainly present in nervous tissue, muscles, plasma, and blood cells. Inhibition of this enzyme is the present scenario for the AD treatment. Tacrine, the first Acetylcholinesterase inhibitor approved by FDA in 1993 for the treatment of AD, has been deregistered due to prominent hepatotoxicity. Rivastigmine, an effective synthetic drug with low risk of side effects delays the breakdown of acetylcholine and enhances cholinergic neurotransmission. In modern world medicinal plants play a major role in the development of new drugs and considered to be a primary health care system. Prasannakumar et al reported the hypoglycemic action of the pectin isolated from the fruits of Coccinia indica. β-sitosterol, taraxerone and retinol are the major compounds isolated from the fruit of Coccinia grandis. β -Sitosterol, a phytosterol isolated from the fruit of Coccinia grandis showed anti hepatotoxic activities on serum transaminases and hepatic antioxidant enzymes in CCl4 intoxicated rats. The compound also possesses antibacterial and antioxidant activity. Due to the incorporation of β-sitosterol into cell membrane, glucose oxidase-induced oxidative stress and lipid peroxidation was prohibited and this compound is useful to treat neurodegenerative disorders like Alzheimer disease. Retinol possesses antibacterial, anti-inflammatory and antioxidant activity. The compounds pectin and retinol have been reported to possess in silico anti-atherosclerotic activity. Taraxerone, a pentacyclic triterpenoid compound was isolated from the ethyl acetate extract of Sedum sarmentosum showed high antioxidant activity. The methanolic leaf extracts of Strobilanthes crispus L showed
acetylcholinesterase inhibitory activities which may be due to the presence taxaroneer in the plant.\textsuperscript{38,39} Antioxidant plays a potential role in the AD patients due to the accumulation of free radical in brain and existence of oxidative stress\textsuperscript{40-41}. The methanolic extract of the \textit{Coccinia grandis} fruit possess antioxidant activity\textsuperscript{2} which may be due to the presence of \(\beta\)-sitosterol, pectin, retinol and taxaroneer compounds in the fruit. The \textit{in silico} evaluation of these compounds showed better acetylcholinesterase inhibition activity, a key enzyme for the treatment of AD. Further, it is concluded that the compounds \(\beta\)-sitosterol, pectin, retinol and taxaroneer which are from the fruits of \textit{Coccinia grandis} can be used as lead molecule in the treatment of AD for avoiding side effects. As the fruit is commonly available and edible, this can be a nutraceutical to reduce the severity and progress of Alzheimer's disease.

ACKNOWLEDGEMENT
The authors are very grateful to the University Grants Commission (UGC), New Delhi, India for providing the docking software facility of this work under the scheme of Major Research Project (F.No.36-51/2008 SR).

REFERENCES

Source of support: University Grants Commission (UGC), New Delhi, India, Conflict of interest: None Declared