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Research Article

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

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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 Pub Chem 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 2050[1,2]. 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 problem[3,4]. 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 donepazil is the key approach to treat AD[6]. These drugs have several side effects like gastrointestinal disturbances and problem associated with bioavailability[7,8]. 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 system[9]. 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 antimicrobial[10], hepatoprotective[11], wound healing[12], anthelmintic[13] antitussive[14], antioxidant[15] and hypoglycemic[16]. 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 acids[17].

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 Pub Chem 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) software[18].

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: 1B41) 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 Å[19]. 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, ALA204, 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 phytocompounds 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 phytocompounds 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 phytocompounds with acetylcholinesterase are listed in Figure 2 (A-E).

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

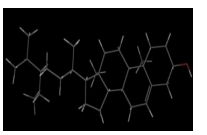
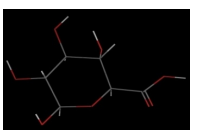
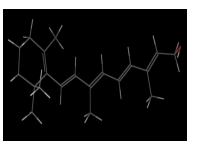
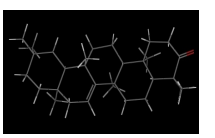
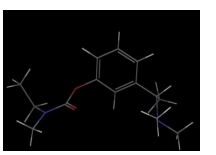
S. No.	Name of the phytocompounds	Pub Chem IDs	Structures
1.	β-Sitosterol	222284	
2.	Pectin	441476	
3.	Retinol	445354	
4.	Taraxerone	92785	
5.	Rivastigmine (Synthetic drug)	77991	

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

S. No.	Synthetic drug and Phytocompounds	Glide Score (Kcal/mol)	Interactions (D-H…O)	Bond length (Å)
Synthetic Drug				
1.	Rivastigmine	-5.6	Tyr124(O-H…N)	2.395
Phytocompounds				
1.	β-Sitosterol	-8.70	TYR124(O-H...O)	1.753
2.	Pectin	-7.82	(O-H...O)ARG296 ARG296(N-H...O) PHE295(N-H...O) (O-H...O)TYR124 (O-H...O)TYR124 (O-H...O)TYR337	1.916 1.871 2.373 2.299 2.105 2.170
3.	Retinol	-7.24	SER203(O-H...O)	1.706
4.	Taraxerone	-6.40	ARG296(N-H...O) PHE295(N-H...O)	2.111 2.462

Figure 1: 3D Structure of Human Acetylcholinesterase

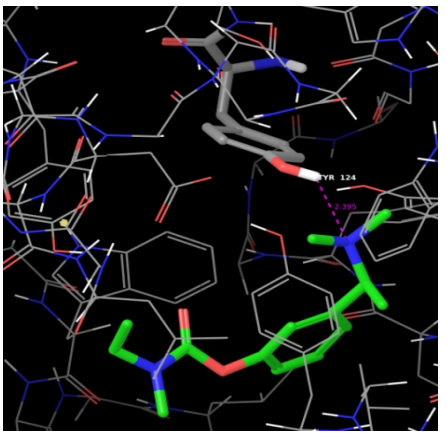


Figure 2(A): Interaction of synthetic drug (Rivastigmine) with Acetylcholinesterase

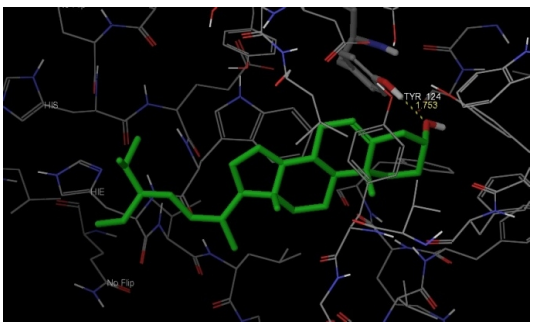


Figure 2(B): Interaction of β-Sitosterol with Acetylcholinesterase

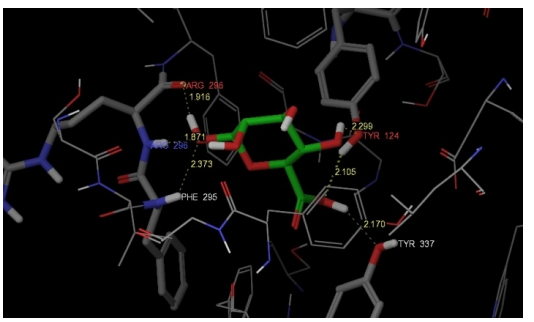


Figure 2(C): Interaction of Pectin with Acetylcholinesterase

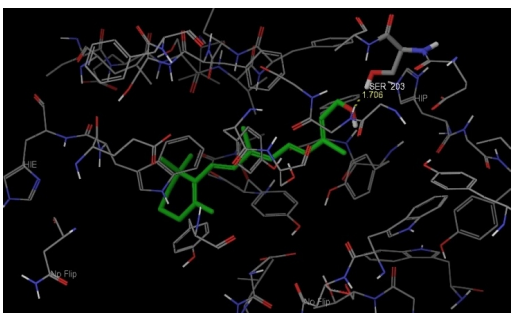


Figure 2(D): Interaction of Retinol with Acetylcholinesterase

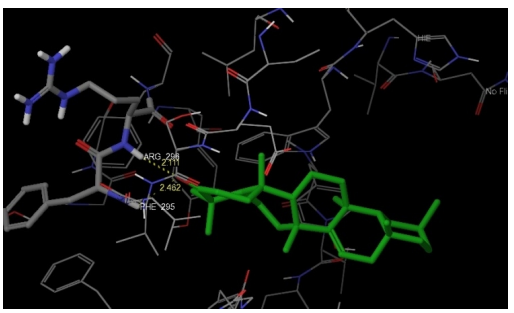


Figure 2(E): Interaction of Taraxerone with Acetylcholinesterase

DISCUSSION

Alzheimer's disease, a neurodegenerative disease, is mainly associated with loss of cholinergic neurons in brain[20,21]. acetylcholinesterase is a principal enzyme that hydrolysis acetylcholine which is involved in the development of AD[22] and has an independent action in the central nervous system[23]. They are mainly present in nervous tissue, muscles, plasma and blood cells[24]. Inhibition of this enzyme is the present senario for the AD treatment[25]. Tacrine, the first Acetylcholinesterase inhibitor approved by FDA in 1993 for the treatment of AD[26], has been deregistered due to prominent hepatotoxicity. Rivastigmine, an effective synthetic drug with low risk of side effects[27] delays the breakdown of acetylcholine and enhances cholinergic neurotransmission. In modern world medicinal plants play a major role in the development of new drugs[28] and considered to be a primary health care system. Prasannakumar *et al*[29] 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*[30]. β -Sitosterol, a phytosterol isolated from the fruit of *Coccinia grandis* showed anti hepatotoxic activities on serum transaminases and hepatic antioxidant enzymes in CCl_4 intoxicated rats[31]. The compound also possesses antibacterial and antioxidant activity[32]. 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[33]. Retinol possesses antibacterial[34], anti-inflammatory and antioxidant activity[35]. The compounds pectin and retinol have been reported to possess *in silico* anti-atherosclerotic activity[36]. Taraxerone, a pentacyclic triterpenoid compound was isolated from the ethyl acetate extract of *Sedum sarmentosum* showed high antioxidant activity[37]. The methanolic leaf extracts of *Strobilanthes crispus* L showed

acetylcholinesterase inhibitory activities which may be due to the presence taraxerone in the plant[38]. Antioxidant plays a potential role in the AD patients due to the accumulation of free radical in brain and existence of oxidative stress[39-41]. The methanolic extract of the *Coccinia grandis* fruit possess antioxidant activity[15] which may be due to the presence of β-sitosterol, pectin, retinol and taraxerone compounds in the fruit. The *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 β-sitosterol, pectin, retinol and taraxerone which are from the fruits of *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.

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REFERENCES

1. Hebert LE, Scherr PA, Bienias JL. Alzheimer disease in the US population Prevalence estimates using the 2000 census. Arch Neurol 2003; 60: 1119–12. http://dx.doi.org/10.1001/archneur.60.8.1119
2. Wimo A, Winblad B, Aguero Torres H. The magnitude of dementia occurrence in the world. Alzheimer Dis Assoc Disord 2003; 17: 63–67. http://dx.doi.org/10.1097/00002093-200304000-00002
3. Perry NSL, Bollen C, Perry EK, Ballad C. Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacology Biochemistry and Behavior 2003; 75: 651–659. http://dx.doi.org/10.1016/S0091-3057(03)00108-4
4. Citron M. Beta-secretase inhibition for the treatment of Alzheimer's disease-promise and chellenge. Trends in Pharmacological Sciences 2004; 25: 92–97. http://dx.doi.org/10.1016/j.tips.2003.12.004
5. Voet D, Voet JG. Serine proteases. In: Biochemistry, 2nded. USA: John Wiley and Sons; 1995.
6. Lahiri DK, Rogers JT, Greig NH, Sambamurti K. Rationale for the development of cholinesterase inhibitors as anti-Alzheimer agents. Curr Pharm Des 2004; 10: 3111-3119. http://dx.doi.org/10.2174/1381612043383331
7. Schulz V. Ginkgo extract or cholinesterase inhibitors in patients with dementia: what clinical trial and guidelines fail to consider. Phytomedicine 2003; 10: 74–79. http://dx.doi.org/10.1078/1433-187X-00302
8. Melzer D. New drug treatment for Alzheimer's diseases: lessons for healthcare policy. British Medical Journal 1998; 316: 762–764. http://dx.doi.org/10.1136/bmj.316.7133.762
9. Tamilselvan N, Thirumalai T, Elumalai EK, Balaji R, David E. Pharmacognosy of *Coccinia grandis*: a review. Asian Pacific Journal of Tropical Biomedicine 2011; S299-S302.
10. Shaheen SZ, Bolla K, Vasu K, Singara Charya MA. Antimicrobial activity of the fruit extract of *Coccinia indica*. African Journal of Biotechnology 2009; 8(24): 7073-7076.
11. Vadivu R, Krithika A, Biplab C, Dedeepya P, Shoeb N, Lakshmi KS. Evaluation of Hepatoprotective activity of the fruit of *Coccinia grandis* Linn. International Journal of health Research 2008; 1(3): 163-168.
12. Bambal VC, Wyawahare NS, Turaskar AO, Deshmukh TA. Evaluation of wound healing activity of herbal gel containing the fruit extract of *Coccini indica* Wright and ARN. (Cucurbitaceace). International Journal of Pharmacy and Pharmaceutical Science 2011; 3(4): 319-322.
13. Shivhare Y, Soni P, Singh P, Dangi S, Baghel SS. Evaluation of Anthelmintic Activity of *Coccinia indica* (fruits). Journal of Chemical and Pharmaceutical Research 2011; 3(1): 488-491.
14. Pattanayak SP, Sunita P. *In vivo* anti tussive activity of *Coccinia grandis* against irritant aerosol and sulfur dioxide-induced cough model in rodents. Bangladesh Journal Pharmacol 2009; 4: 84-87. http://dx.doi.org/10.3329/bjp.v4i2.1537
15. Deshpande SV, Patil MJ, Parmar KK, Daswadkar SC, Khodade RB. A study on antioxidant activity of fruit extracts of *Coccinia grandis* L.VOIGT. International Journal of Drug Research and Technology 2011; 1(1): 69-72.
16. Ramakrishnan M, Bhuvaneshwari R, Duraipandiyan V, Dhandapani R. Hypoglycaemic activity of *Coccinia indica* Wight and Arn. Fruits in Alloxan-induced diabetic rats. Indian Journal of Natural Products and Resources 2011; 2(3): 350-353.
17. Berman HM. The Protein Databank: a historical perspective. Acta Cryst 2008; 64(1): 88-95. http://dx.doi.org/10.1107/S0108767307035623
18. Richard AF, Jay LB, Robert BM, Thomas AH, Jasna JK, Daniel TM *et al*. Glide: A new approach for rapid, Accurate Docking and Scoring.1 method and Assessment of docking Accuracy J Med Chem 2004; 47(7): 1739-1749. http://dx.doi.org/10.1021/jm0306430
19. Kryger G, Harel M, Giles K, Toker L, Velan B, Lazar A *et al*. Structure of recombinant native and E203Q mutant human Acetylcholinesterase complexed with the snake-venom toxin fasciculin –II. Acta crystallogr D Biol Crystallogr 2000; 56: 1385-94. http://dx.doi.org/10.1107/S0907444900010659
20. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 1976; 2(8000): 1403. http://dx.doi.org/10.1016/S0140-6736(76)91936-X
21. Whitehouse PJ, Price DL, Coyle JT, Delong MR. Alzheimer disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. American Neurological Association 1981; 10(2): 122-126. http://dx.doi.org/10.1002/ana.410100203
22. Moyo M, Ndhlala AR, Finnie JF, Staden JV. Phenolic composition, antioxidant and acetylcholinesterase inhibitory activities of *Sclerocarya birrea* and *Harpephyllum caffrum* (Anacardiaceae) extracts. Food Chemistry 2010; 123: 69–76. http://dx.doi.org/10.1016/j.foodchem.2010.03.130
23. Klegeris A, Korkina LG, Greenfield SA. A possible interaction between acetylcholinesterase and dopamine molecules during auto oxidation of the amine. Free Radical Biology and Medicine 1995; 18(2): 223-230. http://dx.doi.org/10.1016/0891-5849(94)00115-Z
24. Brimijoin S. Molecular forms of acetylcholinesterase in brain, nerve and muscle: nature, localization and dynamics. Prog Neurobiol 1983; 21: 291-322. http://dx.doi.org/10.1016/0301-0082(83)90015-1
25. Yang Z, Zhang X, Duan D, Song Z, Yang M, Li S. Modified Tlc bio autographic method for screening acetylcholinesterase inhibitors from plant extracts. Journal of Separation Science 2009; 32(18): 3257-3259. http://dx.doi.org/10.1002/jssc.200900266
26. Tumiatti V, Minarini A, Bolognesi ML, Milelli A, Rosini M, Melchiorre C. Tacrine derivatives and Alzheimer's disease. Curr Med Chem 2010; 17(17): 1825-38. http://dx.doi.org/10.2174/092986710791111206
27. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 2000; (2): CD001191.
28. Edeoga HO, Okwu DE, Mbaebie BO. Phytochemical Constituents of Some Nigerian Medicinal Plants. Afr J Biotechnol 2005; 4: 685-688. http://dx.doi.org/10.5897/AJB2005.000-3127
29. Prasannakumar G, Sudeesh S, Vijayalakshmi NR. Hypoglycemic effect of *Coccinia indica*: Mechanism of action. Planta Med 1993; 59: 330-2. http://dx.doi.org/10.1055/s-2006-959693
30. Kundu S, Ray AB. Chemical examination of *Coccinia indica* fruit. J Indian Chem Soc 1987; 64(12): 776-777.
31. Shivaji PG, Chandrashekar RMV. Anti hepatotoxic Activities of Ci Compound: ß Sitosterol Isolated from Fruits and Leaves of *Coccinia indica*. Ind J Pharm Edu Res 2012; 46(1): 4-8.
32. Gupta R, Sharma AK, Dobhal MP, Sharma MC, Gupta RS. Antidiabetic and antioxidant potential of b-sitosterol in streptozotocin-induced experimental hyperglycemia. Journal of Diabetes 2011; 3: 29–37. http://dx.doi.org/10.1111/j.1753-0407.2010.00107.x
33. Shi C, Wu F, Zhu X, Xu J. Incorporation of β-sitosterol into the membrane increases resistance to oxidative stress and lipid peroxidation via estrogen receptor-mediated PI3K/GSK3β signaling. Biochim Biophysic Acta 2013; 1830: 2538-44. http://dx.doi.org/10.1016/j.bbagen.2012.12.012
34. Pechere MGL, Siegenthaler G, Pechere JC, Saurat JH. The Antibacterial Activity of Topical Retinoids: The Case of Retinaldehyde. Dermatology 2002; 205(2): 153-8. http://dx.doi.org/10.1159/000063903
35. Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of vitamin A and carotenoids and their relevance for heart disease. Free Rad Biol Med 1999; 26: 746–761. http://dx.doi.org/10.1016/S0891-5849(98)00266-4
36. Shalini G, Ravikumar P, Jeyam M. Screening the phytocompounds of *Coccinia indica* for atherosclerosis through docking studies. Archives of Pharmacy and Biological Sciences 2014; 2(1): 10-15.
37. Mo EK, Han BH, Kim SM, Yang SA, Kang SK, Oh CJ *et al*. Identification of D-Friedoolean-13-en-3-one (Taraxerone) as an Antioxidant Compound from Sedom (*Sedum sarmentosum*). Food Sci. Biotechnol 2012; 21(2): 485-489. http://dx.doi.org/10.1007/s10068-012-0061-x

38. Koay YC, Wong KC, Osman H, Ibrahim MS, Eldeen, Asmawi MZ. Chemical Constituents and Biological Activities of *Strobilanthes crispus* L. Rec Nat Prod 2013; 7(1): 59-64.
39. Grundman M. Vitamin E and Alzheimer disease: the basis for additional clinical trials. Am J Clin Nutr 2000; 71: 630S–36S.
40. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr 2000; 71: 621S–29S.
41. Behl C. Alzheimer's disease and oxidative stress: implications for novel therapeutic approaches. Prog Neurobiol 1999; 57: 301–23. http://dx.doi.org/10.1016/S0301-0082(98)00055-0

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