Int.J.Curr.Res.Aca.Rev.2017; **Special Issue-4***: 97-105*

EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Special Issue-4 (October-2017)

Journal home page: http://www.ijcrar.com

Identification of Potent Inhibitor among Ligands of Dicranopteris Linearis, against Parkinson's Disease Using In-Silico Docking Analysis

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KEYWORDS

Parkinson disease, *Substantia nigra*, *Dicranopteris linearis*, Molecular docking

A B S T R A C T

Parkinson's disease (PD) is the chronic neurodegenerative disorder which is diagnosed with the dopaminergic neuronal loss in substantia nigra (SN). One of the pathological condition of PD is the presence of intracellular proteinaceous substances termed 'Lewy bodies' composed of aggregated alpha-synuclein which is responsible for its toxic effect on SN. The aim of the present study is to recognize strong inhibitors (ligands) from the Dicranopteris linearis which binds to α-synuclein and prevents self-association. Molecular docking was performed using the molecular modeling software "auto dock". The studies were done to evaluate the binding affinity characteristics of α-synuclein with the Dicanopterislinerasis derived compounds (1)3',4',7-Trimethylquercetin(2)Phytol (3)dioctyladipate (4) dibutyl phthalate (5)triethyl citrate**.** The study revealed that the active site of α-synuclein is best fit with 3',4',7-Trimethylquercetin among the 5 compounds docked. The other compounds showed Interactions but to a lower level. Hence 3',4',7-Trimethylquercetin with three interactions and one Hydrogen Bond may be developed as a potent drug against Parkinson's disease (PD).

Introduction

Pteridophytes (ferns and fern allies) are one of the oldest and primitive vascular plant groups. They grow in varied climatic zones of different phytogeographical regions (pratibha *et al.*, 2011). Dicranopteris linearis (L.), locally known to the Malays as ''Resam'', is a plant that belongs to the family Gleicheniaceae. It belong to the family of the ferns and is among the few branching ferns that can quickly develop up to 2m tall.The leaves of D.linearis is used for the folklore medicine (Zainul *et al.*, 2007).

Phytochemical study has revealed the presence of flavonoids, particularly flavonol 3-Oglycosides, triterpenes, saponins and steroids in the leaves of D. Linearis(Jamal Hussaini *et al.*, 2012). In D.linearis leaves shows the presence of compounds such as

(1) 3',4',7-Trimethylquercetin (2) Phytol (3) Dioctyl adipate (4) Dibutyl phthalate (5)Triethyl citrate (Kalpana *et al.,* 2016**)**. D.linearis extracts have been shown to possess antinociceptive, anti-inflammatory and antipyretic activities, and potential cytotoxic and antioxidant activity. (Suvarnalatha Devi *et al.,* 2015) (Figure 1).

Various forms of activated oxygen, generally known reactive oxygen species (ROS), have been implicated in many diseases (Zakaria *et al.,* 2007). ROS, which can be classified into free radicals (i.e. superoxide ions (O2-) and hydroxyl radicals (OHÕ)) and non-free-radicals (hydrogen peroxide (H2O2)) are produced from endogenous sources or from exogenous sources (Barry Halliwell *et al.,* 1995). In recent years, researches are concerned to find the possible therapeutic potential of antioxidants in controlling degenerative diseases associated with marked oxidative damage. D.linearis have been shown to possess antioxidant property (Zakaria *et al.,* 2007).

Parkinson's disease [PD] is the second most common neurodegenerative disorder.It is a debilitating motor related disease and is incurable. The key pathological Condition of PD are loss of nigral neurons (and loss of pigmentation in this area), and the presence of insoluble proteinaceous cytoplasmic inclusions termed Lewy bodies (LB) and Lewy neurites in the remaining cells (George *et al.,* 2009). The first gene associated with PD was SNCA which codes for a protein called α- synuclein (Kathleen *et al.,* 2008). Lewy bodies are accumulations of amyloid-like fibrils, which are comprised primarily of an oligomerized form of α-synuclein, a natively unfolded protein consisting of 140 amino acids(Maria *et al.,* 1998).

Studies in human postmortem material indicate that reactive oxygen species are important in the pathogenesis of PD (Dawson *et al.,* 2003). There are also consistent findings of decrements in mitochondrial complex I (complex I). Derangements in complex I clearly lead to aggregation and accumulation of -synuclein (Sherer *et al.,* 2000). Oxidatively modified α- synuclein is more prone to aggregation than native protein (Souza *et al.,* 2000).Oxidative damage appears to play a role in the aggregation of α- synuclein in PD, as there is selective α- synuclein nitration in synuclein lesions in PD and related disorders.Even though mutations in α- synuclein are a very rare cause of hereditary PD, its apparent role as the major structural feature of the LB has placed α-synuclein at center stage in the pathophysiology of PD (Dawson *et al.,* 2003).In the cellular level, PD is categorized by the accretion of Lewy body plaques in neurons of the substantia nigra (Frisco *et al.,* 2011). In dementia with Lewy bodies, in which dementia and motor deficits are linked closely in time, accumulation of α-synuclein is seen throughout the brain, including the cortex (Kostas *et al.,* 2011).

Materials and Methods

Uniprot

UniProt is the Universal Protein resource is a free accessible database. It provides comprehensive, high quality of protein sequence and functional information. The UniProt databases provides the UniProt Knowledgebase (UniProtKB), the UniProt Reference (uniRef) and the UniProt Archive (UniParc) www.uniprot.org/) (Amos Bairoch *et al.,* 2004).The primary sequence of Alpha synuclein (PDB ID : P37840) was retrieved from UniProt (www.uniprot.org) (Figure 2)

Pubchem

PubChem is a public repository for information on chemical substances and their biological activities, PubChem consists of three inter-linked databases, Substance, Compound an BioAssay.The 2D structure compounds of 3',4',7-Trimethylquercetin, Phytol, Dioctyl adipate, Dibutyl phthalate, Triethyl citrate are obtained from PubChem.(https://pubchem.ncbi.nlm.nih.gov) (Table 1)

Chemsketch

ACD/Chemsketch is a molecular modeling program used to create and modify images of chemical structures. Chemsketch has the function of generating structures from SMILES and also produce SMILES from structures. ACD/Labs software, which will draw molecular structures, reactions and calculate chemical properties The 2D structure compounds of *D.linearis* are converted into 3D structure and saved in MDL mol format.

Open Babel

Open Babel is free software, a chemical expert system mainly used for converting chemical file formats. The "MOL" format of 3D structure compounds are converted into "PDB" format using open babel.

Autodock

AutoDock is a molecular modeling simulation software. It is free and is available under the GNU General Public License. The docking results are more accurate and reliable.The current version of AutoDock 4.2, using the Lamarckian Genetic Algorithm and binding energy, docking scoring function will provide results of docking between protein and ligands with 10 conformations (Protein-ligand docking with AutoDock).

PYMOL

PYMOL is an open source, three dimensional visualization tool to view the macromolecular structures like proteins and nucleic acids. PyMol is used to visualize and analyze the docking results. It is freely available from (www.pymol.org)

Results and Discussion

Protein structure preparation

Structure of α synuclein was retrieved from the database Protein Data Bank (http://www.rcsb.org/pdb). The proteins were prepared by deleting the water molecules. The PDB ID of α synuclein (1xq8).

Ligand structure preparation

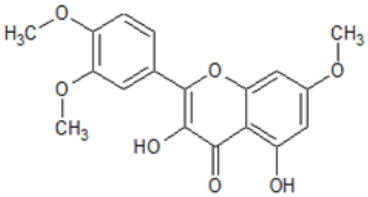
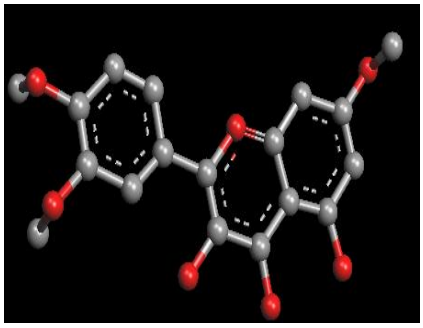
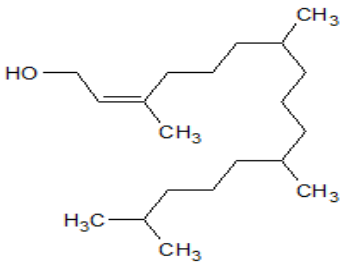
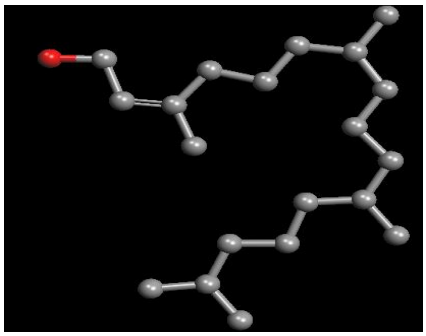
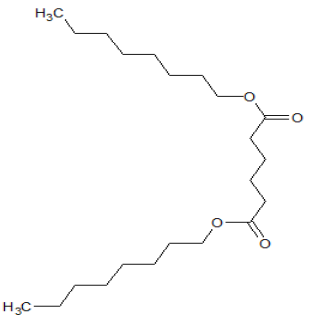
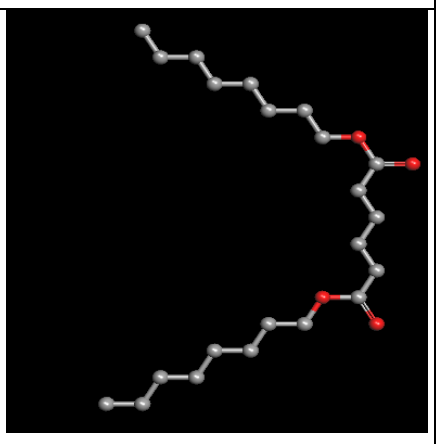
The 2D structure of compounds such as3',4',7-Trimethylquercetin, Phytol, Dioctyl adipate, Dibutyl phthalate, Triethyl citrate identified in *D. linearis* were obtained from Pubchem Database. These compounds also satisfy the Lipinski's rule of five (Table 2). The 2Dstructure of the compounds is drawn using Chemsketch and the 3D structure of the compounds computed using ACD/labs and then 3D structure of ligand was saves as "MOL" format then converted into "PDB" format from "MOL" format using Open Babel.

Molecular Docking Studies

Molecular Docking is an effective and competent tool for *in silico* screening software by using "Auto Dock". Molecular docking is a computational tool to optimize the best-fit orientation with protein binding

site and ligand.It is used to determine the interaction between the ligands and the protein, based on the docking score. AutoDock Tool assigned hydrogens bonds, Kollman charges, parameters and fragmental volumes to the protein was prepared save as "PDBQT "format. AutoGrid was used for the preparation of the grid map using a grid box size is (126*126*126)along with properties in the configuration file was computed saved as ".gpf" file format.This was followed by docking calculation which involves search parameter and Lamarckian Genetic Algorithm (LGA) to search for the best conformations. Then the file was saved as ".dpf" file format.The docking used to retained the interaction between protein and ligand information For each interaction of protein and compound its shows maximum 10 conformations were obtained.

Table.1 2D and 3D structure of ligands

Compounds	2D structure	3D structure
3',4',7-Trimethylquercetin; Quercetin		
Phytol		
Dioctyl adipate		

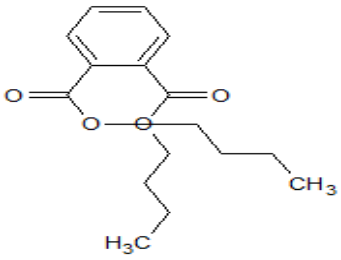
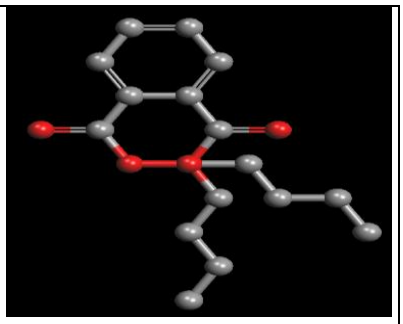
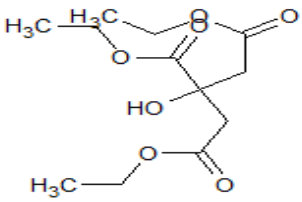
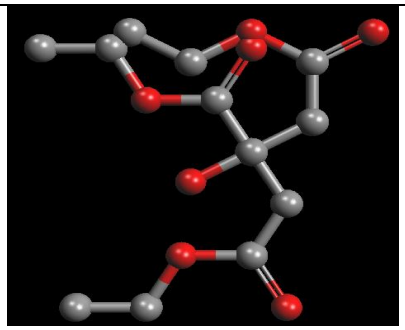
Dibutyl phthalate		
Triethyl citrate		

Table.2 Lipinski's rule of the ligands

Compounds	Chemical Formula	Molecular weight	Hydrogen bond acceptors	Hydrogen bond donors
3',4',7-Trimethylquercetin; Quercetin	$C_{18}H_{16}O_7$	344.319 g/mol	7	2
Phytol	$C_{20}H_{40}O$	296.539 g/mol	1	1
Dioctyl adipate	$C_{22}H_{42}O_4$	370.574 g/mol	4	0
Dibutyl phthalate	$C_{16}H_{22}O_4$	278.348 g/mol	4	0
Triethyl citrate	$C_{12}H_{20}O_7$	276.285 g/mol	7	1

Table.3 Interaction between atoms of the ligands from *D. linearis* and the amino acid residues of protein along with the hydrogen bond distance and docking score

Ligand	Alpha synuclein protein		Ligand Atom	Distance (Å)	No of hydrogen bonds	Docking score (kcal/mol)
	Residue	Atom				
3',4',7-Trimethylquercetin; Quercetin	VAL40 LYS45	H HZ-3	O O	2.1 2.5	1	-4.16
Phytol	LYS 450	HZ-3	O	2.3	-	-2.26
Dioctyl adipate	VAL 95 LYS 96	O HZ-3	O O	2.5 2.7	1	1.35
Dibutyl phthalate						-0.94
Triethyl citrate	VAL 40	H	O	2.1	1	-1.66

Fig.1 *Dicranopteris linearis L.*

Fig.2 Crystal structure of Alpha synuclein

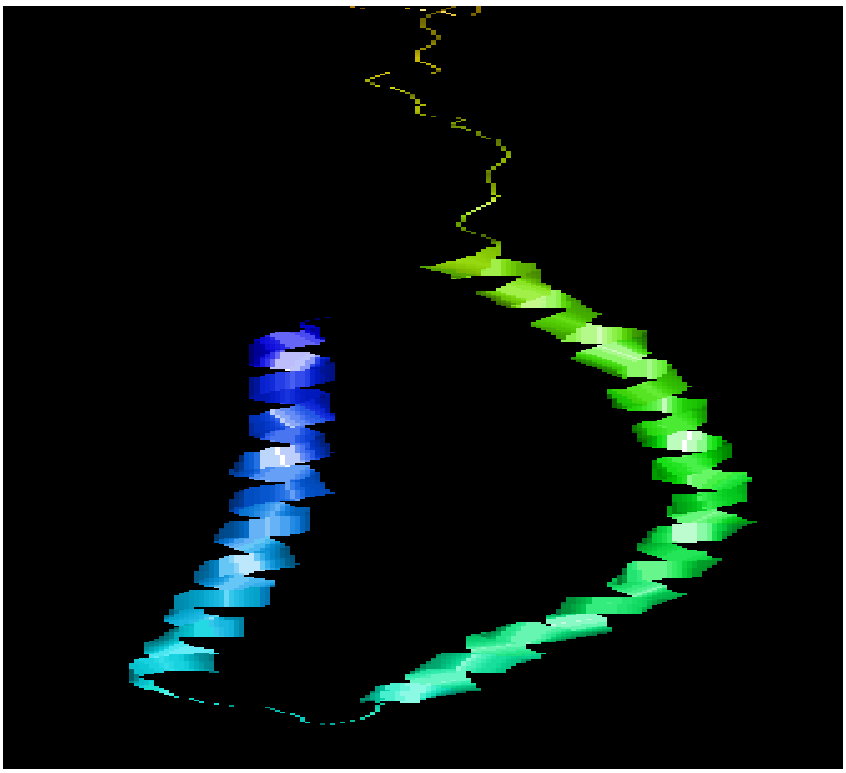
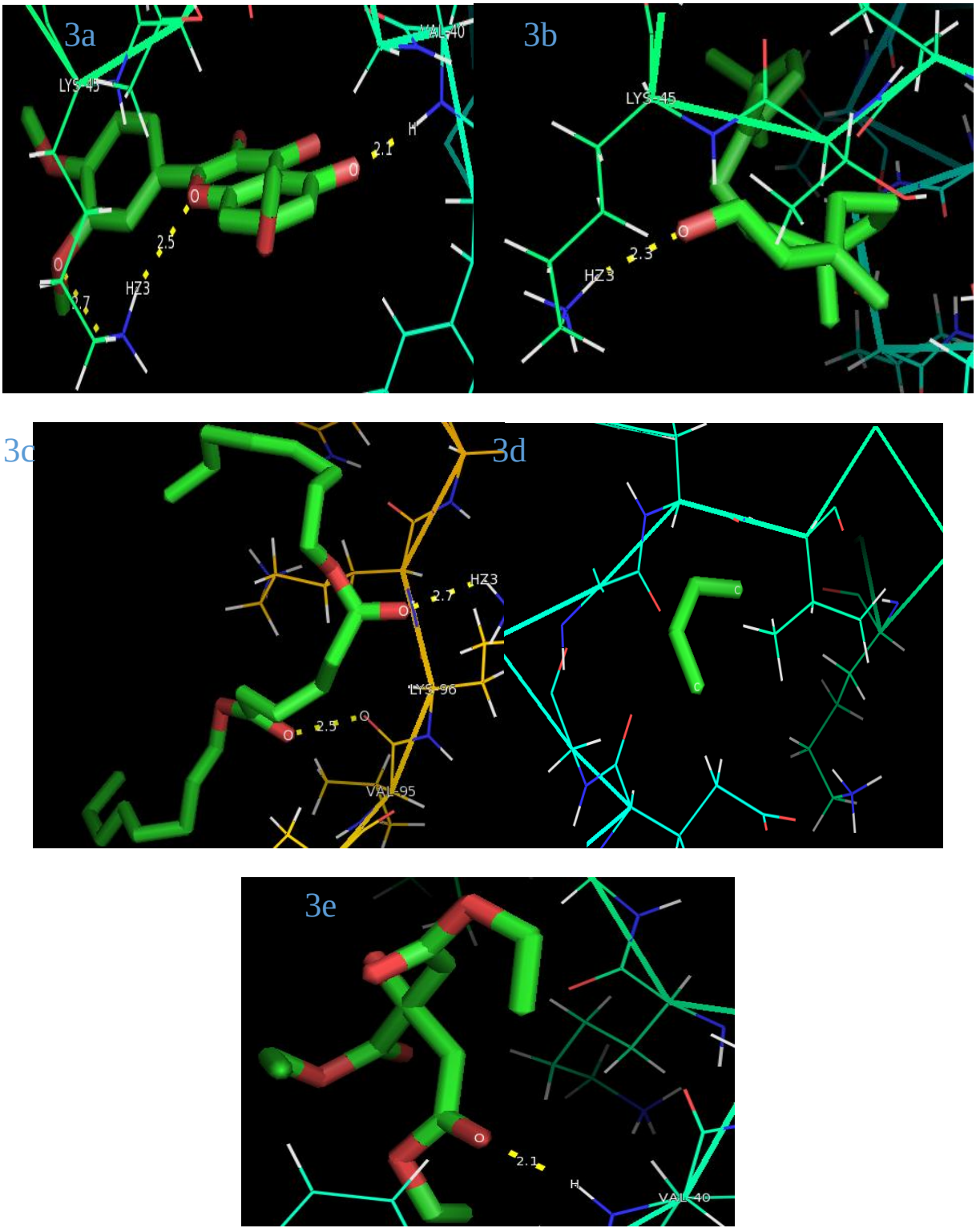


Fig.3 (a)Docking result shown between α synuclein and 3',4',7-Trimethylquercetin; (b)Docking result shown between α synuclein and Phytol; (c)Docking result shown between α synuclein and Dioctyl adipate; (d)Docking result shown between α synuclein and, Dibutyl phthalate (e) Docking result shown between α synuclein and Triethyl citrate



The docking results was obtained and analyzed by using vizulation tool "PYMOL"

Before it has been visualized in Pymol, the format of the file can be changed into pdb from pdbqt which is obtained from AutoDock using Open Babel converted tool, The interaction and distance between the protein and ligand were analyzed.The docking results between α synuclein and 3',4',7-Trimethylquercetin shows binding energy -4.16 kcal/mol, between VAL40 H nd O atom and LYS45 OE and O atom. The docking study between α synuclein and Phytol shows binding energy -2.26 kcal/mol, between LYS 45 HZ-3 and O atom of and The docking study between α synuclein and Dioctyl adipate shows binding energy 1.35 kcal/mol, between VAL 95 O and LYS 96 HZ-3 and O atom.The docking study between α synuclein and Dibutyl phthalate shows binding energy -0.94 kcal/mol. The docking study between α synuclein and Triethyl citrate shows binding energy -1.16 kcal/mol, between VAL40 H and O atom. The docking score of all the compounds are least and these shows the above compounds are potent α synuclein inhibitor. Among the four compounds, 3',4',7-Trimethylquercetin is a much potent inhibitor of α synuclein protein because it comes under Lipinski's rule of five and its docking score and interactions are also good.(Figure 3).

In this study, Molecular docking were performed between α synuclein and five compounds from *D. linearis*. These compounds have good docking energy and shows satisfactory yields and 3',4',7-Trimethylquercetin is a good inhibitor than all other compounds. Hence the compounds 3',4',7-Trimethylquercetin, Phytol, Dioctyl adipate, Dibutyl phthalate, Triethyl citrate is identified from *D. linearis* are good inhibitors of the α synuclein protein. Thus the study ideal, that these compounds possess good anti-oxidant activity

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How to cite this article:

Deepa S., M. Mahalakshmi and Jayanthi D. 2017. Identification of Potent Inhibitor among Ligands of Dicranopteris Linearis, against Parkinson's Disease Using In-Silico Docking Analysis. *Int.J.Curr.Res.Aca.Rev.* Special Issue-4: 97-105.