



Received on 24 August, 2017; received in revised form, 28 December, 2017; accepted, 06 January, 2018; published 01 June, 2018

COMPARATIVE MOLECULAR DOCKING STUDIES AND STRUCTURAL PREDICTION OF PLANT COMPOUNDS ON LRRK2

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Keywords:

L-DOPA, LRRK2,
Theaflavin, Baicalein, Sesamol,
Tenuigenin, Gastrodin, Phloroglucinol

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ABSTRACT: Neurodegenerative disease is the condition of brain cells that lose of its ability to generate the neurotransmitters and this leads to the accumulation of proteins in the brain. These condition causes memory loss and problems in the cognitive functions. Neurological diseases are characterized by four major types such as Alzheimer's disease, Parkinson's disease, Huntington disease, Amyotrophic lateral sclerosis. Parkinson's disease is a second neurological disorder, characterized by a selective loss of dopaminergic neurons in the substantianigra, causing a subsequent reduction of dopamine levels in the striatum. Loss of dopaminergic neurons in striatum causes imbalance of neurotransmitters like acetylcholine and dopamine, resulting in the Parkinson's disease. Tremor, rigidity, dyskinesia are the primary symptoms and memory loss, sleeps disorders, cognitive impairments are the secondary symptoms of Parkinson's. **Aim:** To investigate the structural changes *in silico* docking was performed with target protein LRRK2 with the following compounds theaflavin, baicalein, sesamol, tenuigenin, gastrodin, phloroglucinol and L-DOPA. **Methods:** The *in silico* docking was carried out using autodock version 4.2. Rasmol tool was used to visualize the protein structures. **Results:** The docking energy of L-DOPA with LRRK2 showed binding energy-4.97 Kcal/mol, theaflavin-7.19 Kcal/mol, baicalein-7.4 Kcal/mol, sesamol-4.99Kcal/mol, tenuigenin-7.9 Kcal/mol, gastrodin-6.02 Kcal/mol and phloroglucinol as binding energy-4.99 Kcal/mol. **Conclusion:** These results indicate that the natural plant compounds have more affinity and interact with LRRK2 in a better manner compared to the L-DOPA the standard drug. Therefore natural plant compounds may be helpful in the treatment of Parkinson's disease.

INTRODUCTION: The aggregation of proteins in the nerve ending of the human brain, known as lewy bodies. This formation of the lewy Bodies leads to the loss of neurons and this cause Parkinson's disease ¹. Parkinson's disease is the most common neurodegenerative disease, which affects life span of the elder people. Parkinson's disease is a chronic neurodegenerative disease caused by loss of dopamine producing neurons in substantianigra.

Among the World wide populations, 1 percent of the above 65 years older people are affected by the Parkinson's disease ². It is slow progressive disease; it affects mainly movements of the body, muscle control, memory and concentration.

Tremor, bradykinesia, rigidity and postural imbalance are primary symptoms of Parkinson's disease. Large fractions of patients with Parkinson's disease have cognitive impairments as the most common primary symptoms. Depression, insecurity, confusion, monotone voice, erectile dysfunction are the common secondary symptoms of Parkinson's disease ³. Parkinson's disease remains poorly understood, although a broad range of studies were conducted over the past few decades. The mutation in LRRK2 causes sporadic late-onset form of Parkinson's diseases ⁴.

	QUICK RESPONSE CODE DOI: 10.13040/IJPSR.0975-8232.9(6).2258-65
	Article can be accessed online on: www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(6).2258-65	

LRRK2 is a large multidomain protein. It contains 2,527 amino acids. The functional domain of LRRK2 are Ank (ankyrin-like), LRR (leucine rich repeat), Roc (Ras-of-complex proteins), Cor (C-terminal of Roc), kinase, wD40 UBL (ubiquitin-like), RING 1, IBR (in-between-ring), RING 2. LRRK2 is the autosomal dominant inherited gene and its mutations may affect the diverse proteins functions⁵. LRRK2 mutations cause early onset of Parkinson's disease, with a clinical profile identical to sporadic late-onset Parkinson's disease.

The putative function of LRRK2 remains unknown. The normal function of LRRK2 is the regulation of kinase and GTPase activities, binding partners, phosphosubstrates. Mutation in LRRK2 leads to enhanced kinase activity and GTP binding that result in cell death⁶. The important pathophysiology of PD are aggregation of alpha synuclein and the formation of lewy bodies⁷. Parkinson's disease is still unclear, because it results due to number of genetic and environmental factors.

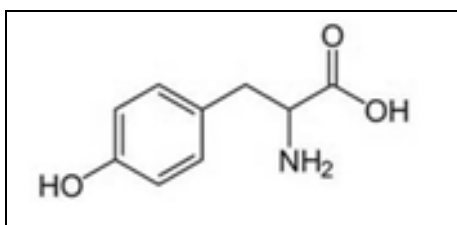


FIG. 1: MOLECULAR STRUCTURE OF L-DOPA

L-Dopa (**Fig.1**) (L-3, 4-dihydroxyphenyl alanine) is a synthetic drug and precursor to the neurotransmitter dopamine, nor-epinephrine and epinephrine. L-DOPA increases the reduced level of neurogenesis, which is caused by the 6-OHDA lesion, in the hippocampal dentate gyrus and in the layer of olfactory bulb⁸. The trade name of L-Dopa is sinemet, stalevo and prolopa. L-Dopa is converted into dopamine by the enzyme DOPA decarboxylase in CNS. Pyridoxal phosphate (Vit B6) is the cofactor for these reactions. Prolonged intake of L-DOPA causes side effects for the Parkinson's disease patients. Over dosage of L-DOPA causes hypertension, extreme emotional states, gastrointestinal bleeding.

L-DOPA gradually increases the abnormal involuntary movements, which is known as dyskinesias⁹. Other than L-DOPA treatment, the genotyping is used to find the impulse control in PD patients and its improvement predicted by the drug ropinirole,

the dopamine agonists¹⁰. Plants are rich in antioxidants and flavonoids may protect neuronal junction and stimulate the neuronal regeneration¹¹.

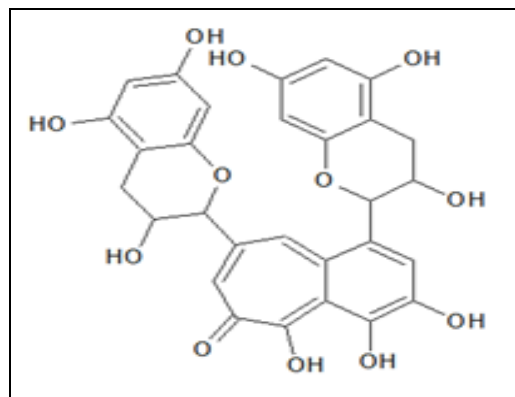


FIG. 2: MOLECULAR STRUCTURE OF THEAFLAVIN

Theaflavin (**Fig. 2**) is formed from the black tea processing methods and it has antioxidant and antimicrobial activity¹². Theaflavin gives colour and flavor to black tea. The chemical structure of theaflavin has four types they are theaflavin (TF1), Theaflavin-3-gallate (TF2A and TF2B), Theaflavin-3, 3'-digallate (TF3)¹³. Theaflavin protects DNA from oxidative damage. The catechins from the processed Green tea have the antioxidant property and it can scavenge the hydroxy radicals¹⁴.

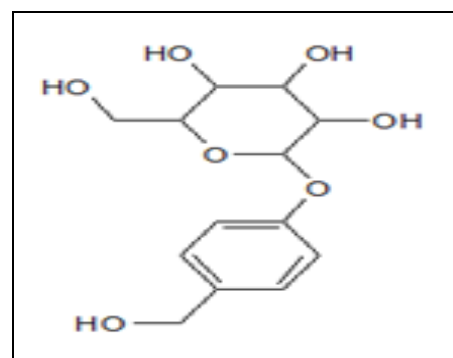


FIG. 3: MOLECULAR STRUCTURE OF GASTRODIN

Gastrodin (**Fig. 3**) is a glucoside of gastrodigenin. It was isolated from the orchid *Gastrodia elata* and from the rhizome of *Galeola faberi*. It has neuroprotective effect. Gastrodin shows neuronal death in the MPTP induced PD models¹⁵. The molecular formula of gastrodin is C₁₃H₁₈O₇. *Rhizoma Gastrodiae*, extract of Tianma, Chinese herb show neuroprotective effects, and it may be due to the attenuated apoptosis pathway¹⁶. Gastrodin improves the cognitive functions in PD patients and also it prevents the increasing level of serotonin transporter¹⁷.

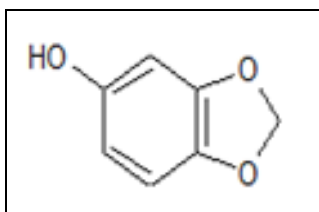


FIG. 4: MOLECULAR STRUCTURE OF SESAMOL

Sesamol (Fig. 4) is a water soluble lignin. It has antioxidant and anti cancer property¹⁸. Its molecular formula is C₇H₆O₃. Its molecular mass is 38.12g/mol. Sesame oil is used in Ayurvedic medicine. Sesamol is a derivative of phenol and it is soluble in water. It has antioxidant property and also antifungal property. Sesamol has anti photo activity. Administration of sesamol with folic acid shows neuroprotective effect in the 6-OHDA parkinsonian animals¹⁹. Sesamol prevents the cognitive impairments in Alzheimer's disease animal models and also prevents neuroinflammation²⁰.

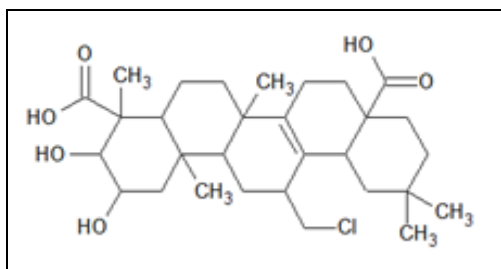


FIG. 5: MOLECULAR STRUCTURE OF TENUIGENIN

Tenuigenin (Fig. 5) is an active component extracted from achinese herb *Polygala tenuifolia* root. It is used to treat memory loss and cognitive function in Chinese medicine²¹. Tenuigenin protects the PC 12 cells from Mpp⁺ induced neuronal death²². Tenuigenin shows neuroprotective effect on neuro inflammation from a single intranigral dose of LPS in adult male rat. Tenuigenin protects the neurons by inhibiting the LPS-induced inflammation in microglia cells²³.

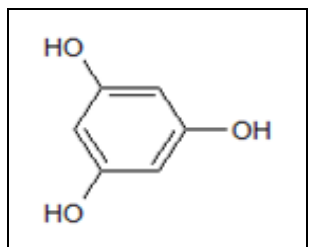


FIG. 6: MOLECULAR STRUCTURE OF PHLOROGLUCINOL

Phloroglucinol (Fig. 6) are secondary metabolites that occur naturally in certain plant species. It is

also produced by organisms that are not plants, such as algae or bacteria. Phlorotannin is one of the forms of phloroglucinol and it is abundantly present in *Ecklonia cava* (edible brown algae). Phloroglucinol treated cells shows attenuation of H₂O₂ induced cell damage through an activation of antioxidant system inside the cell²⁴. Phloroglucinol has anti-inflammatory activity. Phlorotannins have acetylcholinesterase inhibitory activity²⁵.

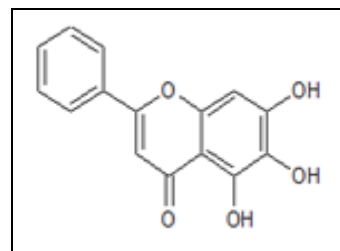


FIG. 7: MOLECULAR STRUCTURE OF BAICALEIN

Baicalein (Fig. 7) is type of flavanoid, isolated, from the root of *Scutellaria baicalensis* and *Scutellaria lateriflora*. It is used in Chinese medicine and has antiallergic, anticarcinogenic and antioxidant activity²⁶. Baicalein interacts with alpha-synuclein and form quinones during oxidation and it inhibits fibrillation. Baicalein prevents damage made by 6-OHDA or MPTP in both *in-vivo* and *in-vitro* models of Parkinson's disease. Roteone induced mitochondrial damage, production of ROS, swelling of brain mitochondria is prevented by baicalein²⁷.

The new drug development and its designing are most challenging tasks. In advance science, production of new and effective drugs is more important. Docking studies helps to find out effective drug interactions before they are tested with human. The known structure of protein (LRRK2) and ligands are docked using Autodock 4.0. In this study, we have docked the plant compounds and L-DOPA with LRRK2.

MATERIALS AND METHODS:

Preparation of Target Protein: The sequence of LRRK2 protein was taken from PDB files. The receptor file used by AutoDock must be in "pdbqs" format which is pdb plus 'q' charge and 's' solvation parameters, AtVol, the atomic fragmental volume, and AtSolPar, the atomic solvation parameter which are used to calculate the energy contributions of desolvation of the macromolecule by ligand binding.

Preparation of Ligand Structure: Before docking partial atomic charges are laid to each atom of the ligand. We also distinguish between aliphatic and aromatic carbons, names for aromatic carbons start with 'A' instead of 'C'. Auto Dock ligands are written in files with special keywords recognized by Auto Dock. The root is a rigid set of atoms, while the branches are rotatable groups of atoms connected to the rigid root. The TORSDOF for a ligand is the total number of possible torsions in the ligand minus the number of torsions that only rotate hydrogens. TORSDOF is used in calculating the change in free energy caused by the loss of torsional degrees of freedom upon binding. After all the above conditions are set the ligand is saved in "pdbq" format.

AutoDock 4.0-Running: AutoDock Tool was used for creating PDBQT files from traditional PDB files. The preparation of the target protein (unbound target) with the Auto Dock Tools software involved adding all hydrogen atoms to the macromolecule, which is a step necessary for correct calculation of partial atomic charges. Gasteiger charges are calculated for each atom of the macromolecule in Auto Dock 4.2 instead of Kollman charges which were used in the previous versions of this program.

Auto Dock was run several times to get various docked conformations, and used to analyze the predicted docking energy. The binding sites for these molecules were selected based on the ligand-binding pocket of the templates²⁸. AutoDock Tools provide various methods to analyze the results of docking simulations such as, conformational similarity, visualizing the binding site and its energy and other parameters like intermolecular energy and inhibition constant. Discovery Studio Visualizer was used to visualize the structure. Molecular visualization is a key aspect of the analysis and communication of modeling studies.

RESULTS AND DISCUSSION: The plant compounds were docked with the target protein LRRK2 and the best docking poses were identified. Majority of the plant compounds had greater binding affinity with target protein. The best binding configuration measured in Kcal/mol. The binding configuration and their docking energy are listed below.



FIG. 8: THREE DIMENSIONAL STRUCTURE OF LEUCINE RICH REPEAT KINASE 2 USING RASMOL

TABLE 1: L-DOPA AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		L-DOPA	Distance (Å)	Docking Energy (Kcal/mol)
Residue	Atom			
LEU1474	O	H	2.04	-4.97
LYS1476	N	O	3.10	
ILE1482	N	O	2.66	
ASN1475	O	H1	1.96	
ARG1477	N	O	2.99	
ARG1477	NH1	OXT	2.66	

Binding Configuration and Statistical Docking Results of L-DOPA with LRRK2:

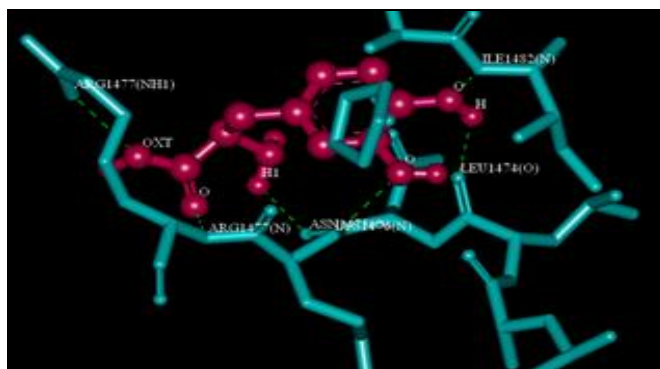


FIG. 9: INTERACTIONS BETWEEN L-DOPA AND ROC DOMAIN OF LRRK2

Binding Configuration and Binding Docking Results of Tenuigenin with LRRK2:

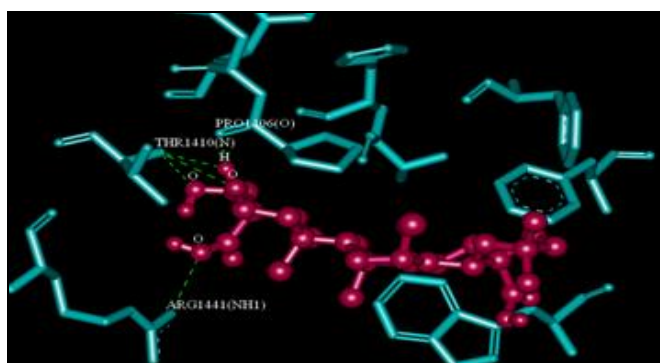


FIG. 10: INTERACTIONS BETWEEN TENUIGENIN AND ROC DOMAIN OF LRRK2

TABLE 2: INTERACTIONS BETWEEN TENUIGENIN AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		Tenuigenin	Distance	Docking Energy
Residue	Atom		(Å)	(Kcal/mol)
PRO1406	O	H	2.06	-7.91
THR1410	N	O	2.38	
THR1410	N	O	3.06	
THR1410	N	O	2.61	
ARG1441	NH1	O	2.90	

Binding Configuration and Docking Results of Baicalein with LRRK2:



FIG. 11: INTERACTIONS BETWEEN BAICALEIN AND ROC DOMAIN OF LRRK2

TABLE 3: INTERACTIONS BETWEEN BAICALEIN AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		Baicalein	Distance	Docking Energy
Residue	Atom		(Å)	(Kcal/mol)
GLU1427	O	H	1.94	-7.4
GLU1427	O	H	1.85	
LYS1432	N	O	3.06	

Binding Configuration and Docking Results of Theaflavin and LRRK2:

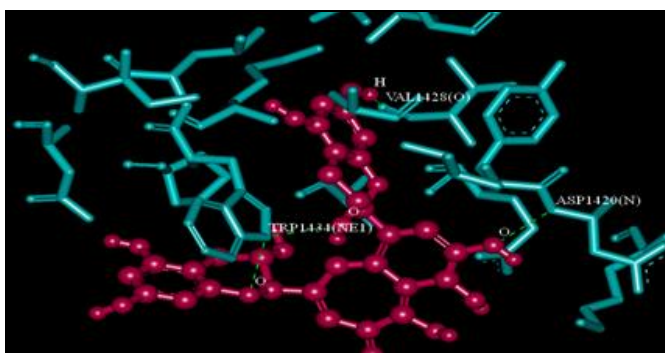


FIG. 12: INTERACTIONS BETWEEN THEAFLAVIN AND ROC DOMAIN OF LRRK2

TABLE 4: INTERACTIONS BETWEEN THEAFLAVIN AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		Theaflavin	Distance	Docking Energy
Residue	Atom		(Å)	(Kcal/mol)
ASP1420	N	O	2.63	-7.19
VAL1428	O	H	1.85	
TRP1434	NE1	O	2.94	
TRP1434	NE1	O	3.04	

Binding Configuration and Docking Results of Gastrodin and LRRK2:

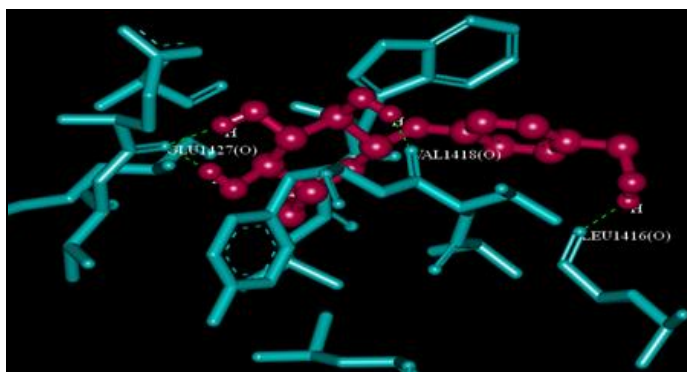


FIG. 13: INTERACTIONS BETWEEN GASTRODIN AND ROC DOMAIN OF LRRK2

TABLE 5: INTERACTIONS BETWEEN GASTRODIN AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		Gastrodin	Distance	Docking Energy
Residue	Atom		(Å)	(Kcal/mol)
LEU1414	O	H	1.77	-6.02
VAL1418	O	H	1.94	
GLU1427	O	H	1.69	
GLU1427	O	H	1.76	

Binding Configuration and Docking Results of Sesamol and LRRK2:

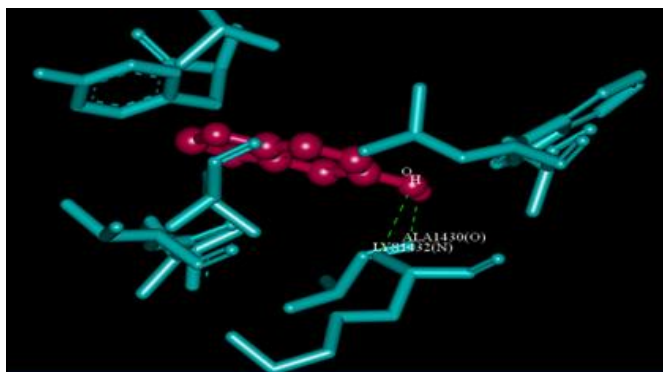


FIG. 14: INTERACTIONS BETWEEN SESAMOL AND ROC DOMAIN OF LRRK2

TABLE 6: INTERACTIONS BETWEEN SESAMOL AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		Gastrodin	Distance	Docking Energy
Residue	Atom		(Å)	(Kcal/mol)
LYS1432	N	O	2.92	-4.99
ALA1430	O	H	2.05	

According to the docking results, the docking energy of L-DOPA with LRRK2 showed binding energy as -4.97Kcal/mol. L-DOPA was found to be the standard drug in reducing the symptoms of Parkinson's disease.

Binding Configuration and Docking Results of Phloroglucinol and LRRK2:

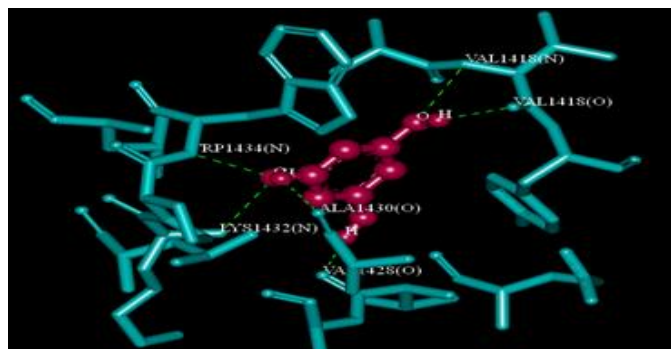


FIG. 15: INTERACTIONS BETWEEN PHLOROGLUCINOL AND ROC DOMAIN OF LRRK2

TABLE 7: INTERACTIONS BETWEEN PHLOROGLUCINOL AND ROC DOMAIN OF LRRK2

ROC domain of LRRK2		Phloroglucinol	Distance (Å)	Docking Energy (Kcal/mol)
Residue	Atom			
VAL1428	O	H	2.00	-4.99
VAL1418	O	H	2.07	
VAL1418	N	O	3.02	
LYS1432	N	O	2.82	
ALA1430	O	H	1.99	
TRP1434	N	O	3.18	

Voon *et al.*, 2017 suggested that chronic treatment of L-DOPA induces the L-DOPA induced dyskinesias (LID) in nearly 80 % of PD patients²⁹. Tenuigenin with LRRK2 showed binding energy as -7.9Kcal/mol, Wei *et al.*, 2015 suggested that tenuigenin improves cognitive functions and enhances the basic synaptic transmission by stimulating the pre-synaptic intracellular calcium³⁰. Baicalein with LRRK2 showed binding energy as -7.4 Kcal/mol. Sownd-harajan *et al.*, 2017 reported that baicalein has neuroprotective effects and it may be used as therapeutic agent to treat the neurotoxicity-mediated diseases³¹. Theaflavin with LRRK2 showed binding energy as -7.19 Kcal/mol. Dhivya *et al.*, 2015 suggested that black tea and increases the neuroprotective activity³².

TABLE 8: NO. OF HYDROGEN BONDS AND DOCKING SCORES OF THE COMPOUNDS

Compounds	Molecular Formula	Protein	Docking Energy (Kcal/mol)	No of Hydrogen Bonds
L-Dopa	C ₉ H ₁₁ NO ₄	LRRK2	-4.97	2
Tenuigenin	C ₃₀ H ₄₅ ClO ₆	LRRK2	-7.91	1
Baicalein	C ₁₅ H ₁₀ O ₅	LRRK2	-7.4	2
Theaflavin	C ₂₉ H ₂₄ O ₁₂	LRRK2	-7.19	1
Gastrodin	C ₁₃ H ₁₈ O ₇	LRRK2	-6.02	4
Phloroglucinol	C ₆ H ₆ O ₃	LRRK2	-4.99	3
Sesamol	C ₇ H ₆ O ₃	LRRK2	-4.99	1

CONCLUSION: Parkinson's disease is a multifactorial pathological disease. Currently available

Gastrodin with LRRK2 showed binding energy of -6.02 Kcal/mol. This suggests that gastrodin may increase GABA concentration by inhibiting GABA shunt.

Kumar *et al.*, 2013 reported that Gastrodin prevents the Mpp⁺ induced neurotoxicity in SH-SY5Y cells by regulation of free radicals and capcase 3 pathway³³. Sesamol has protected the neurons from neuronal degeneration by regulating the antioxidant profile and improves behavioral activity of rats. Hassanzadeh *et al.*, 2014 suggested that sesamol shows ameliorative effects in experimental models of epilepsy and prevent the oxidative drugs and also it may be beneficial to produce antiepileptic drugs³⁴. Sesamol with LRRK2 showed binding energy as -4.99 Kcal/mol. Phloroglucinol with LRRK2 showed binding energy of -4.99 Kcal/mol. Phloroglucinol reduces ROS (reactive oxygen species) levels. Kadam *et al.*, 2013 suggested that phloroglucinol extracted from marine algae and it has neuroprotective effect³⁵.

The docking results of plants compounds compared to L-DOPA, the standard drug shows that tenuigenin, theaflavin, baicalein, gastrodin have higher docking score than L-DOPA, sesamol and phloroglucinol have equal score to L-DOPA. All plant compounds having hydrogen bond interaction with LRRK2 the target protein.

Comparing all the plant compounds, gastrodin (Fig. 13) and phloroglucinol (Fig. 15) having more hydrogen bond interactions with LRRK2 protein than other compounds. These results show clearly that like L-DOPA, the plants compounds also have effective binding capacity with ROC domain of LRRK2 protein. The plant compounds may have anti-Parkinson's effect. However *in-vivo* studies may be carried out to confirm the same.

conventional treatments are not able to prevent the pathomechanisms.

The standard drugs L-DOPA cannot be used for prolonged period and over dosage may be produced. Along with L-DOPA these plants compounds may given to the patients. It may reduce the side effects and thereby increase the anti-Parkinson's effect.

ACKNOWLEDGEMENT: This study was technically supported by the Mrs. Shoba, Assistant Professor, Department of Biochemistry and Bioinformatics, MGR Janaki college of Arts and Science for Women, Chennai.

CONFLICT OF INTEREST: We declare that we have no conflict of interest.

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How to cite this article:

Jayanthi P and Vijayalakshmi K: Comparative molecular docking studies and structural prediction of plant compounds on LRRK2. *Int J Pharm Sci Res* 2018; 9(6): 2258-65. doi: 10.13040/IJPSR.0975-8232.9(6).2258-65.

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