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Structural Prediction and Comparative Molecular Docking Studies of L-DOPA, Gastrodin, Baicalein, Tenuigenin on LRRK2 and Hsp90

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KEYWORDS

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A B S T R A C T

Parkinson's disease is one of the neurodegenerative diseases. It is mainly due to the loss of dopaminergic neurons in the substantia nigra. Prolonged usage of L-dopa shows severe side effects in PD patients. PD patients may be treated with natural plant compounds to avoid side effects. *Insilico* docking study was performed to investigate the structural changes and binding configuration between target proteins such as LRRK2 and Hsp90 with L-DOPA, gastrodin, baicalein, tenuigenin. The *insilico* docking study was carried out using autodock version 4.2. Rasmol tool used to visualize the protein structures. The target protein LRRK2 with L-DOPA showed binding energy -4.97Kcal/mol, gastrodin -6.02Kcal/mol, baicalein -7.4Kcal/mol, tenuigenin -7.9Kcal/mol. Hsp90 with L-DOPA -4.8Kcal/mol, gastrodin -5.06Kcal/mol, baicalein -6.24Kcal/mol, tenuigenin -6.06Kcal/mol. These results shows the plant compounds possess high affinity for LRRK2 and Hsp90 proteins, than L-DOPA, the standard drug. Therefore natural plant compounds may be helpful in the treatment of Parkinson's disease.

Introduction

Neurodegenerative disorder is the progressive death of neurons and also loss of structures of neurons. There are four major types of neurodegenerative disorder such as Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic lateral sclerosis. Parkinson's disease is caused by the aggregation of proteins in the brain regions. The pathology of Parkinson's disease is formation of lewybodies in the nerve endings and loss of dopaminergic neurons in the substantia nigra. There are many reasons for the pathology of Parkinson's disease. The main reason may be improper protein folding due to the molecular chaperones, improper mechanism of ubiquitin-proteosomal system and misleading LRRK2 gene regulation. LRRK2 (Leucine Rich Repeat Kinase 2) is a multi-domain protein (West *et al.*, 2007). The LRRK2 domains involved in multiple enzymatic and protein interactions. It is

linked with autosomal dominant Parkinsonism (Mata *et al.,* 2006). LRRK2 belongs to ROCO super family (Ras of Complex Proteins (Roc)) with a C-terminal of Roc domain). LRRK2 contains many functional domains such as leucine rich repeat, Ras of complex proteins, Ankyrin-like, C-terminal of Ras of complex protein (Guo *et al.,* 2006). It contains 2,527 amino acids. The putative function of LRRK2 is unknown (Paison *et al.,* 2004). It causes early-onset Parkinson's disease and identical to the sporadic late onset Parkinson's disease clinical profile (Smith *et al.,* 2006). Hsp90 is one of the molecular chaperones. It has three different domains such as N-terminal, middle domain, C-terminal (Kelley and Georgopoulous. 1992). Hsp90 is one the main component to form the molecular chaperone system. The mechanism of Hsp90 is poorly understood.

Hsp90 binds with the set of cochaperones to regulate the tyrosine kinases and hormone receptors (Picard. 2006). The molecular chaperone Hsp90 is essential for cell viability in eukaryotes and it makes up 1-2% of cytosolic proteins (Krukenherg *et al.,* 2011). L-DOPA (L-3, 4-dihydroxyphenyl alanine) is the standard drug for Parkinson's disease. Neurotrophic factor released by the brain and CNS are mediated by the L-DOPA (Hiroshima *et al.,* 2014). Prolonged usage of L-DOPA leads to hypotension, anxiety and dyskinesis and also tardive dyskinesias (Klawans. 1973). Tenuigenin is an active component of *polygala tenuifolia willd*. Tenuigenin was added to differentiation medium of neural stem cells, it increased the number of newly formed neurospheres, and hence it is involved in proliferation and differentiation of hippocampal nerve cells (Chen *et al.,* 2012). Tenuigenin may have the beneficial effects on cognitive functions by increasing the expression of brain derived neurotrophic factor (BDNF) and its receptor tyrosine protein kinase (TrKB) (Chen *et al.,* 2014). Baicalein is isolated from *scutellaria rivularis*. It scavenges superoxide radicals and inhibits the xanthine oxidase (Shieh *et al.,* 2000). Baicalein has an anti-oxidant property (Goa *et al.,* 2001). It prevents the neuronal death, which is induced by cerebral ischemia (Wang *et al.,* 2011). Gastrodin was isolated from *gastrodia elata*. It has antioxidant property and also increases the expression of antioxidant protein genes (Yu *et al.,* 2005). Gastrodin regulates the balance of endothelin and nitric oxide in plasma for older people (Zhang *et al.,* 2003). Preliminary step of drug designing is *Insilico* docking studies. Further research and studies are made, depending on the binding energy of docked compounds. The present study shows the binding energy between the plant compounds and the target proteins such as LRRK2 and Hsp90. Mutation in these genes, results in Parkinson's disease. By binding to proteins their activity may reduce the Parkinson's disease without any side effects.

Materials and Methods

Preparation of target proteins and ligands

Gene sequence of target proteins are collected from PFam, PDB, Uniprot, Pubchem data bases. The ligand structures are collected in the form of smiles. The Protein Data Base (PDB) files should be corrected, before the autodock step and save it in'pdb' format.

Preparing the Ligand and macromolecules

Before docking partial atomic charges are applied to each atom of the ligand. Ligands distinguish between aliphatic and aromatic carbons. The receptor file of macromolecule used by AutoDock must be in "pdbqs"

format which is pdb plus 'q' charge and's' solvation parameters.

Auto Dock

AutoGrid and AutoDock must be run in the directories where the macromolecule, ligand, gpf and dpf files are to be found. The key results in a docking log are the docked structures found at the end of each run, the energies of these docked structures and their similarities to each other. AutoDock 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 templates (chang *et al.*, 2010). According to the docking poses, the calculation docking energy was carried out.

Results and Discussion

The plant compounds were docked with the LRRK2 and Hsp90, the target proteins. All the plant compounds had higher affinity towards both LRRK2 and Hsp90. The results of binding poses and binding energy are listed below. The ligands and the proteins are visualized in the ball and stick model. The docking binding energy of Hsp90 with L-DOPA (Fig 1) - 4.87Kcal/mol and LRRK2 (Fig 5) - 4.97Kcal/mol. Prolonged usage and over dosage of L-DOPA leads to L-DOPA induced dyskiinesias (LID),as reported by Jenner, 2008. Baicalein with Hsp90 (Fig 2) shows binding energy as -6.24Kcal/mol and LRRK2 (Fig 6) -7.4Kcal/mol. Cheng *et al.*, 2008 reported that baicalein improved its protective effect by increasing the dopamine and number of dopaminergic neurons. This may be useful as an effective anti-parkinson drug. Gastrodin binding energy with Hsp90 (Fig 3) is -5.06Kcal/mol and LRRK2 (Fig 7) -6.02Kcal/mol. Gastrodin prevents the SH-SY5Y cells from death by activating the p38 MAPK/Nrf2 signaling pathway.

It also induces Ho1 gene expression in the cell reported by Jiang *et al.*, 2014. Tenuigenin shows binding energy with Hsp90 (Fig 4)-6.06Kcal/mol and LRRK2 (Fig 8) -7.91 Kcal/mol. Lv *et al.*, 2009 suggested that tenuigenin and one of its form, tenuifolin are Chinese herbal medicines and used to treat the memory loss. Tenuigenin may be helpful in the treatment of neurodegenerative disorder.

Table.1 Binding Energy of L-DOPA with Hsp90

HSP 90		**L-DOPA**	**DISTANCE (Å)**	**DOCKING ENERGY (KCAL/MOL)**
RESIDUE	**ATOM**			
LYS204	NZ	OXT	2.85	–4.87
LYS204	NZ	O	3.15	
GLU200	OE1	H2	2.17	
GLU200	N	O	2.89	
ARG201	N	O	3.08	
GLU199	OE1	H	1.71	
GLU199	OE1	H	1.69	
LYS84	NZ	O	3.02	

Table.2 Binding Energy of Baicalein with Hsp90

HSP 90		BAICALEIN	DISTANCE (Å)	DOCKING ENERGY (KCAL/MOL)
RESIDUE	ATOM			
ILE214	O	H	1.89	–6.24
ILE214	O	H	1.75	
ILE214	N	O	2.76	

Table.3 Binding Energy of Gastrodin with Hsp90

HSP 90		GASTRODIN	DISTANCE (Å)	DOCKING ENERGY (KCAL/MOL)
RESIDUE	ATOM			
ILE214	N	O	2.98	–5.06
ILE214	O	H	1.80	
SER211	O	H	1.98	
SER211	O	H	1.92	
ILE218	N	O	2.92	
ILE218	O	H	2.20	
LEU220	N	O	2.90	

Table.4 Binding Energy of Tenuigenin with Hsp90

HSP 90		TENUIGENIN	DISTANCE (Å)	DOCKING ENERGY (KCAL/MOL)
RESIDUE	ATOM			
TYR216	O	H	1.84	–6.06
LYS208	NZ	O	2.51	

Table.5 Binding Energy of L-DOPA with 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	

Table.6 Binding Energy of Baicalein with LRRK2

ROC DOMAIN OF LRRK2		BAICALEIN	DISTANCE (Å)	DOCKING ENERGY (KCAL/MOL)
RESIDUE	ATOM			
GLU1427	O	H	1.94	–7.4
GLU1427	O	H	1.85	
LYS1432	N	O	3.06	

Table.7 Binding Energy of Gastrodin with LRRK2

ROC DOMAIN OF LRRK2		GASTRODIN	DISTANCE (Å)	DOCKING ENERGY (KCAL/MOL)
RESIDUE	ATOM			
LEU1414	O	H	1.77	–6.02
VAL1418	O	H	1.94	
GLU1427	O	H	1.69	
GLU1427	O	H	1.76	

Table.8 Binding Energy of Tenuigenin with LRRK2

ROC DOMAIN OF LRRK2		TENUIGENIN	DISTANCE (Å)	DOCKING ENERGY (KCAL/MOL)
RESIDUE	ATOM			
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	

Table.9 Number of Hydrogen Bonds and Docking Scores of the Compounds

Compounds	Molecular Formula	Proteins	Docking Energy (KCAL/MOL)	No of Hydrogen Bonds
L-DOPA	$C_9H_{11}NO_4$	LRRK2	-4.97	2
		Hsp90	-4.87	3
Tenuigenin	$C_{30}H_{45}ClO_6$	LRRK2	-7.91	1
		Hsp90	-6.06	1
Baicalein	$C_{15}H_{10}O_5$	LRRK2	-7.4	2
		Hsp90	-6.24	2
Gastrodin	$C_{13}H_{18}O_7$	LRRK2	-6.02	4
		Hsp90	-5.06	4

Fig.1 Binding configuration of L-DOPA with Hsp90

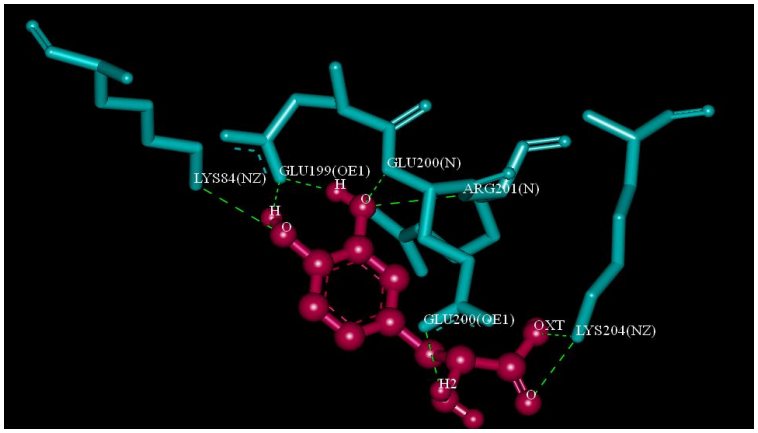


Fig.2 Binding configuration of Baicalein with Hsp90

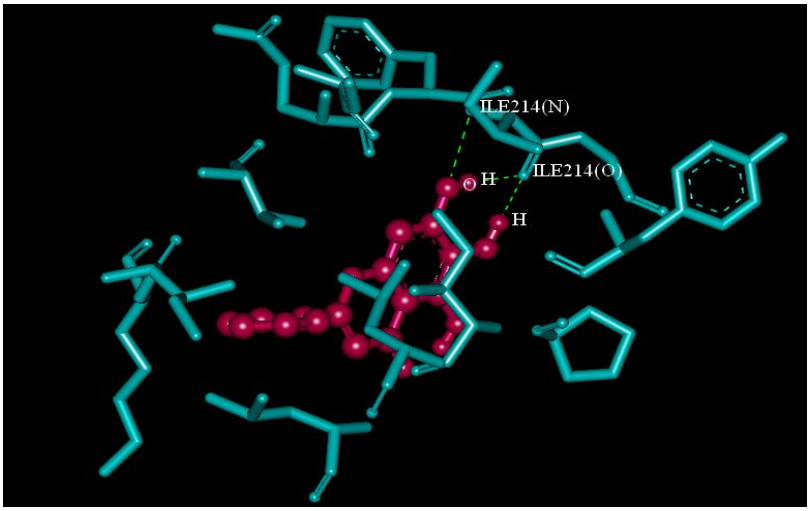


Fig.3 Binding configuration of Gastrodin with Hsp90

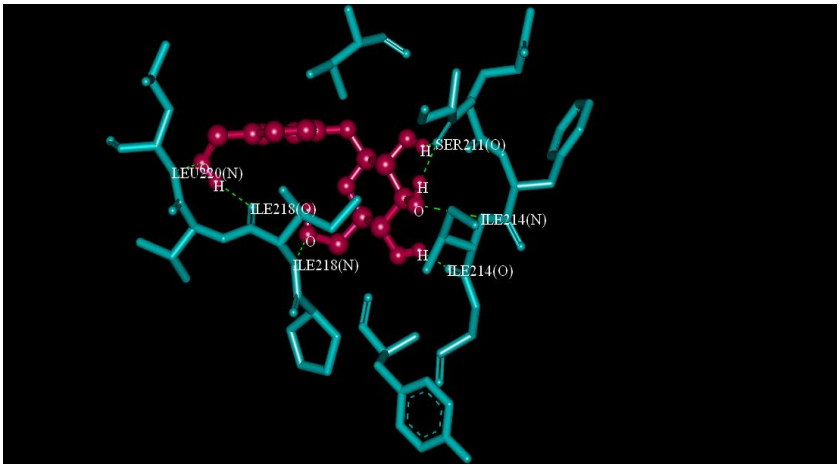


Fig.4 Binding configuration of Tenuigenin with Hsp90

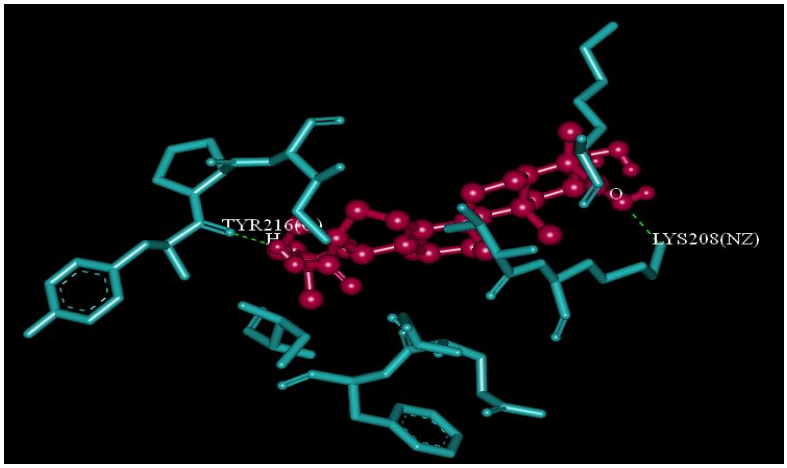


Fig.5 Binding configuration of L-DOPA with LRRK2

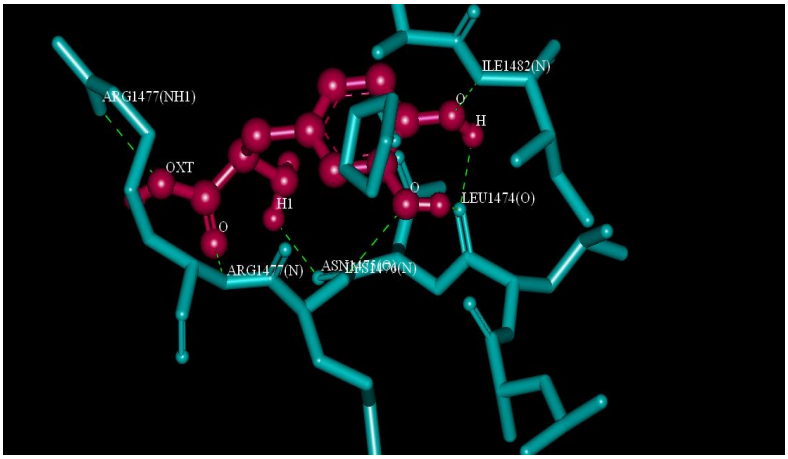


Fig.6 Binding configuration of Baicalein with LRRK2

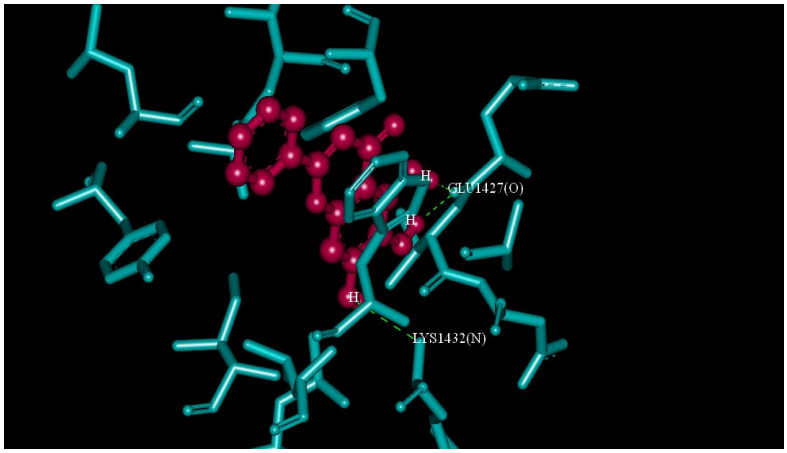


Fig.7 Binding configuration of Gastrodin with LRRK2

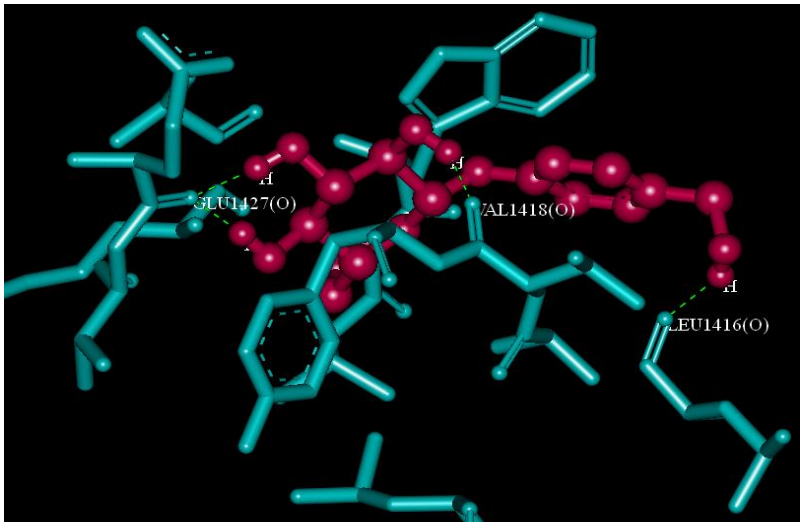
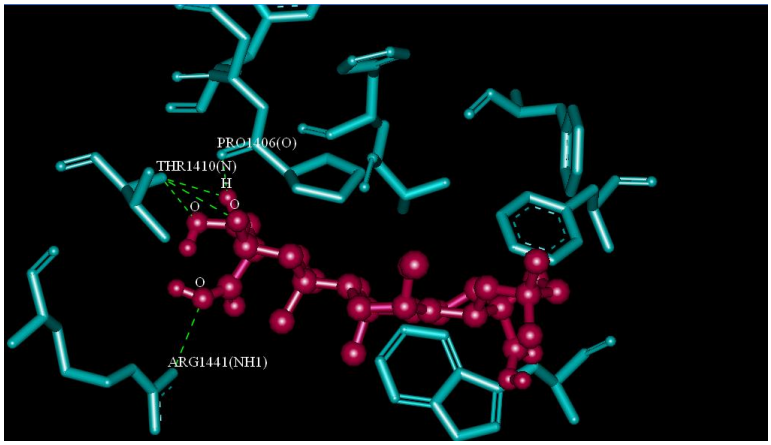


Fig.8 Binding configuration of Tenuigenin with LRRK2



According to the results, comparing the LRRK2 and Hsp90, the target proteins interactions with the plant compounds, LRRK2 shows higher affinity than Hsp90.

All the plant compounds with LRRK2 have higher binding energy than Hsp90. Eventhough, ROC domain of LRRK2 having higher binding energy, the number of hydrogen bond interactions of all compounds with both the proteins are same. Gastrodin shows higher number of interactions of hydrogen bonds than other compounds.

L-DOPA and all plant compounds having binding configuration and hydrogen bond interactions with the both target proteins. Therefore plant compounds may have anti-parkinson activity. This may be confirmed via *invivo* studies. Further studies may be helpful to understand the mechanism of new anti-parkinson drugs.

Parkinson's disease is the neurological disorder. All the synthetic drugs of Parkinson's disease cause severe side effects. Plant compounds cause no side effects as L-DOPA and other synthetic drugs. From this study, we can understand that all the plant compounds are having interactions with LRRK2 and Hsp90. Therefore, these plant compounds may be useful in the treatment of Parkinson's disease.

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