

Original Article

MOLECULAR DOCKING STUDY OF NEUROPROTECTIVE PLANT-DERIVED BIOMOLECULES IN PARKINSON'S DISEASE

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ABSTRACT

Objective: The objective of this study was to explore the therapeutic role of biomolecules in targeting the altered expression of Parkin in PD pathogenesis.

Methods: We employed various *in silico* tools such as drug-likeness parameters, namely, Lipinski filter analysis, Muscle tool for phylogenetic analysis, Castp Server for active site prediction, molecular docking studies using AutoDock 4.2.1 and LIGPLOT1.4.5 were carried out.

Results: Our results show that neuroprotective activity of Quercetin to be most effective and can provide their possible clinical relevance in PD. Further, initial screenings of the molecules were done based on Lipinski's rule of five. CastP server used to predict the ligand binding site suggests that this protein can be utilized as a potential drug target. Finally, we have found Quercetin to be most effective amongst four biomolecules in modulating Parkin based on minimum inhibition constant, Ki and highest negative free energy of binding with the maximum interacting surface area in a course of docking studies.

Conclusion: This research could provide a potential therapeutic window for the treatment of PD.

Keywords: Parkinson's disease, Ubiquitin E3 ligase, Parkin, Molecular docking, Biomolecules

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INTRODUCTION

PD is characterized by progressive loss of dopaminergic neurons in the *substantia nigra*, leading to the loss of motor skills [1-4]. Several risk factors, for instance, genetic polymorphisms, aging and dietary supplements have been reportedly involved in the development and prognosis of PD. Other causative factors that might influence disease outcomes include accumulation of reactive oxygen species (ROS), selective loss of neurons, loss of mitochondrial membrane potential and ATP depletion that are also known to be associated with the PD pathogenesis [5]. However, ubiquitin proteasome system (UPS), which is responsible for the recognition and degradation of damaged proteins, is found to be impaired in case of PD [6]. Parkin is a well-known component of UPS which is having a pivotal role in the protein homeostasis. Conversely, under stress condition, the normal functioning of Parkin is altered or down regulated and thereby leading to the prognosis of PD [7]. Furthermore, the connection between the UPS and neurodegeneration has been supported by the recognition of disease-causing mutations in genes coding for numerous UPS proteins in PD [8].

Importantly, the impaired function of Parkin can be ameliorated by using different biomolecules such as, Naringenin, Quercetin, Resveratrol and Sesamol. These biomolecules are having an antioxidant profile which would be a strong basis for showing neuroprotection within the brain [9]. These biomolecules are natural compounds which are found in many fruits and vegetables and having much stronger antioxidative and neuroprotective activities [10]. The neuroprotective properties of Naringenin Inhibited LPS induced NOS and COX2 expression and suppressed the production of NO in microglial cells. It also inhibited LPS/IFN- γ induced p38 and STAT-1 phosphorylation [11]. However, Quercetin, improved behavioural function, suppressed oxidative stress, brain swelling, and cellular injury both *in vitro* and *in vivo* [12]. Although, Sesamol and Naringenin reversed both the rotenone/MPTP+-induced toxicity in PD rat model [4]. Similarly, Resveratrol (3, 5, 4-trihydroxystilbene) is a naturally-occurring polyphenol found in peanuts, skin and seeds of grapes [13]. It plays a pivotal role in cell proliferation and apoptosis by acting on a variety of signalling

mechanisms such as, Protein kinase B (Akt), Mitogen-activated protein kinase (MAPK), and many other signaling cascades [14]. Most recent reports suggest that resveratrol can induce the Heme Oxygenase-1 (HO-1) expression in dopaminergic neuron and thus can prevent the dopaminergic cell death through autophagic flux. Additionally, resveratrol can also display neuroprotective effects against rotenone-induced neurotoxicity in dopaminergic SH-SY5Y cells by modulating HO-1 dependent autophagy [15].

Therapeutic interferences in neurodegenerative conditions using biomolecules are a seemingly new prospect. Therefore, a mature understanding of the mechanism impacting biomolecules mediated therapeutics could contribute towards fostering neuroprotective strategies. Here, we have focused our study towards impaired Parkin activity by using various *in silico* approaches including molecular docking analysis. Further, these biomolecules such as Naringenin, Quercetin, Resveratrol and Sesamol were selected and screened via lipinski filter analysis followed by molecular docking of the screened molecules towards their clinical aspects in PD. Finally, in this paper, we have reported the active site of Parkin protein for a potential target of these biomolecules by molecular docking that may further provide their probable clinical relevance in PD biology.

MATERIALS AND METHODS

Retrieval of ubiquitin E3 ligase Parkin and their function recognition

The amino acid sequence of Ubiquitin E3 Ligase Parkin with accession numbers 4I1H_A was retrieved from NCBI database and was used for homology search using Basic Local Alignment Search Tool. Protein functional elucidation was done using Interproscan server (<http://www.ebi.ac.uk/interpro/search/sequence-search/>) [16].

Phylogenetic relationship and physicochemical properties

For multiple sequence analysis Muscle Software (<http://www.ebi.ac.uk/Tools/msa/muscle/>) was used and a phylogenetic tree was constructed using Muscle Software based on NJ (Neighbor

joining) plot without distance correction [17]. ProtParam (<http://web.expasy.org/protparam/>) was used to predict physicochemical properties. The parameters computed by ProtParam included the molecular weight, theoretical PI, aliphatic index and grand average of hydropathicity (GRAVY).

Homology modelling, visualization and quality assessment of 3D structure of Ubiquitin E3 Ligase Parkin

Homology modeling was used to determine the 3D structure of Parkin isoforms. A BLASTP search with default parameters was performed against the Brookhaven Protein Data Bank (PDB) to find suitable templates for homology modeling. Templates with PDB ID: 411H was retrieved for Parkin proteins from Protein Data Bank (PDB). The Protein Structure Prediction Server Swiss model (<http://swissmodel.expasy.org/>) was used for homology model construction. Once the 3D structure of proteins was generated, structural evaluation and stereochemical analysis were performed using RAMPAGE (<http://www.mordred.bioc.cam.ac.uk/~rapper/rampage.php>) [18]. Errat server (<http://nihserver.mbi.ucla.edu/ERRATv2/>) was used to find the accuracy of the structure and visualization of determined structures was performed using Pymol viewer.

Ligand optimization

Reported ligand molecules (*Naringenin*, *Quercetin*, *Resveratrol* and *Sesamol*) along with their physical and chemical properties were retrieved from PubChem Compound Database (<http://www.pubchem.ncbi.nlm.nih.gov/>). SDF files of Ligands were converted in PDB file with the help of Open Babel tool that could be used for docking study. Visualization of Molecular Structure of compounds was done using Pymol viewer.

Lipinski filter analysis of screened drugs

An online tool Lipinski Filter (http://www.scfbio-iitd.res.in/software/drug_design/lipinski.jsp) was used to retrieve the information about drug likeness of drugs with the help of Lipinski Rule of five [19]. Lipinski rule (or Lipinski rule of five) helps to differentiate drug and non-drug like molecules. It is used to identify the possibility of success or failure due to drug likeness for molecules fulfilling with two or more of the following rules: (a) Molecular Mass should be less than 500 Dalton, (b) High

Lipophilicity (expressed as log P less than 5), (c) Less than 5 hydrogen bond donors, (d) Less than 10 hydrogen bond acceptors, and (e) Molar refractivity should be between 40-130.

Active site prediction

Castp Server (<http://www.sts.bioe.uic.edu/castp/>) was used to predict the active sites of the protein. It could also be used to measure area, the circumference of mouth openings of each binding site in a solvent and molecular accessible surface [20]. PDB file of protein was upload in the server and it showed the ligand binding sites present in protein and the site with maximum surface area and maximum surface volume was selected and all the amino acid residues involved in binding with ligands were retrieved.

Preparation of protein and ligand molecules

Preparation of protein involves the addition of polar hydrogen atoms, the addition of charge and removal of any miscellaneous structures from the protein molecule by Autodock 4.2.1 whereas; ligand preparation involves the addition of charge.

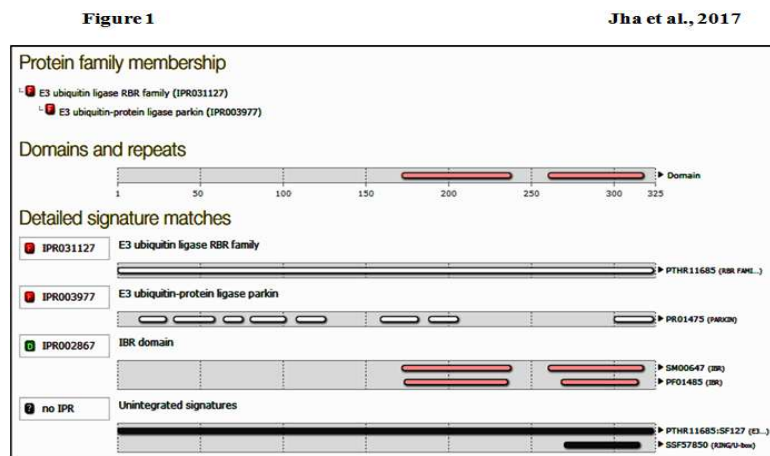
Molecular docking analysis

Prepared and optimized structures of ligands and proteins were ultimately used for molecular docking using Autodock 4.2.1 for predicting the possible protein–ligand interactions and the results that include the understanding of the association that involves H-bonding and hydrophobic interactions were analyzed using LIGPLOT1.4.5, a program to generate schematic diagrams of protein–ligand interactions [21].

RESULTS

Retrieval of ubiquitin E3 Ligase Parkin and their functional elucidation

Based on functional domain sequence of well-characterized gene/protein, a homology search was done using Basic Local Alignment Search Tool (BLAST). We have successfully hunted 5 isoforms of Parkin (table 1) on the basis of families and domains identified from Interproscan results. Interproscan study revealed that all homologues proteins for Parkin were belonging to E3 ubiquitin ligase RBR family (IPR031127), E3 ubiquitin-protein ligase Parkin family (IPR003977) and IBR domain (IPR002867) (fig. 1).



Retrieval of Ubiquitin E3 Ligase (Parkin) related Proteins and their functional elucidation

Fig. 1: Interproscan result for Parkin

Table 1: Hunted parkin related proteins

S. No.	Accession	Protein	Score	Identity	E Value
1	AGH62057.1	PARK2 splice variant	686	100%	0
2	BAA25751.1	Parkin	680	99%	0
3	ABN46990.1	Parkin 2	679	99%	0
4	4K95_A	Chain A, Crystal Structure Of Parkin	624	90%	0
5	Q9JK66.1	E3 ubiquitin-protein ligase Parkin	623	89%	0

Phylogenetic relationship and physicochemical properties

For multiple sequence analysis, *Muscle software* was used and found that amino acid residues were conserved in most of the isoforms of the Ubiquitin E3 ligase Parkin. A phylogenetic study of Parkin hunted proteins revealed that Parkin and PARK2 splice variant were different from others (fig. 2 (a and b)).

However, another Chain A, Crystal Structure of Parkin and E3 ubiquitin-protein ligase Parkin were in the same cluster as share more homology while Parkin 2 was in another cluster. ProtParam showed that Mol. wt. of Parkin was 36393.5 Daltons and an isoelectric point was 7.06 which indicate that Parkin had slightly positive charged respectively. The GRAVY index of-0.372 for Parkin is indicative of hydrophilic (table 2).

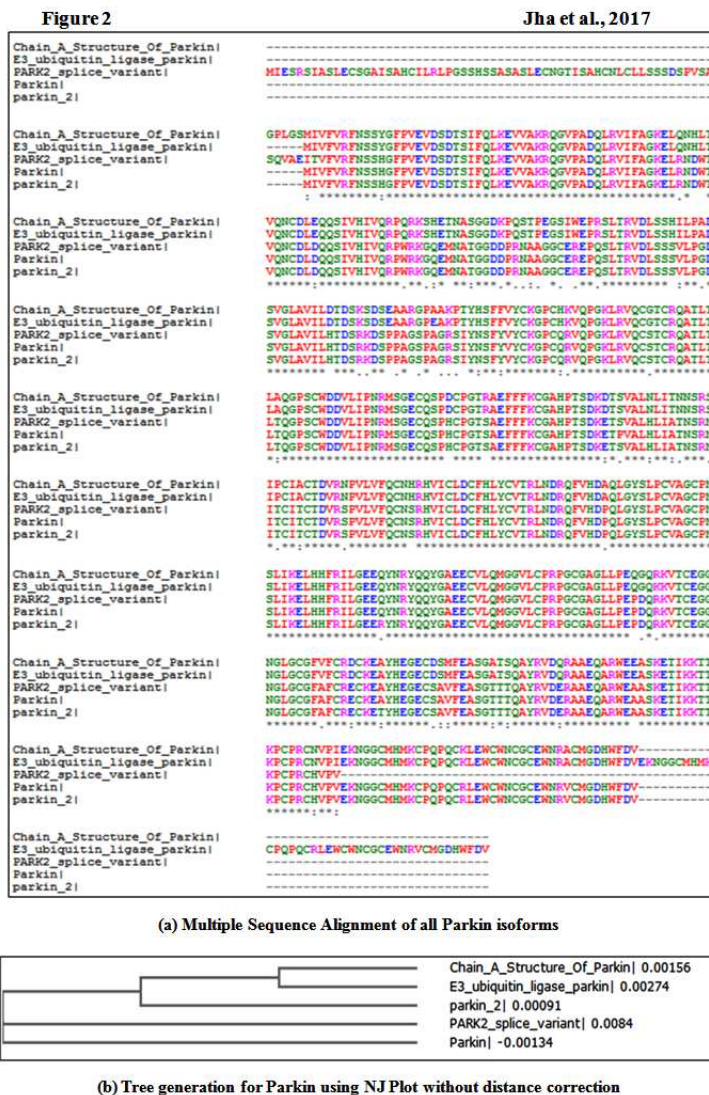


Fig. 2: (a) Multiple sequence alignment of all Parkin isoforms and (b) tree generation for parkin using NJ plot without distance correction

Table 2: Physico-chemical properties of parkin

Properties	Parkin
Molecular Formula	C ₁₅₆₈ H ₂₄₂₀ N ₄₅₈ O ₄₆₈ S ₃₈
Molecular Weight (Daltons)	36393.5
Theoretical PI	7.06
Aliphatic Index	60.28
Grand Average of Hydropathicity (GRAVY)	-0.372

Homology modeling 3D structure visualization and quality assessment of retrieved proteins

Prediction of 3D structure of proteins provides us precise functional information of how proteins interact and localize in their stable conformation. Homology modelling is one of the most common structure prediction tools in proteomics and genomics. The best

matching template was selected for the target protein on the basis of sequence homology using PDB Advance Blast. The template is experimentally determined 3D structure of a protein that share sequence similarity with the target sequence. Template showed a sequence identity of 100% for Parkin isoforms. 3D structure of Parkin was generated using Swiss Model Server. The Z-score is indicative of overall model quality and is used to check whether the

input structure is within the range of scores typically found for native proteins of similar size. SWISS MODEL has provided Z score

of the template and query model. Z score of Parkin has been shown in (table 3), suggesting a high-quality structure for docking studies.

Table 3: Swiss model server result showing template structure used in homology modelling, sequence Identity and quality score of the model generated

Gene name	Modeled residue range	Based on template	Sequence identity	Q mean Z-score
Parkin	1-325	4I1H	100%	-0.81

3D structure of Parkin was generated. Even though there were no steric clashes in the structure generated, these were assessed for geometric and energy aspects (fig. 3(a)). Ramachandran plot was used to check the reliability of predicted 3D structure of Ubiquitin E3 Ligase Proteins Parkin. RAMPAGE checks the stereo chemical quality of a protein structure by analyzing residue-by-residue geometry and overall structure geometry.

Further, Ramachandran plots were obtained for Parkin for quality assessment (fig. 3(b)). RAMPAGE displayed 97% of residues in the most favoured regions, 3% residues in additionally allowed and no residues in disallowed regions in the case of Parkin protein. Errat server was used to find the accuracy of the model. The result of Errat showed 93.262% accurate structure for Parkin proteins.

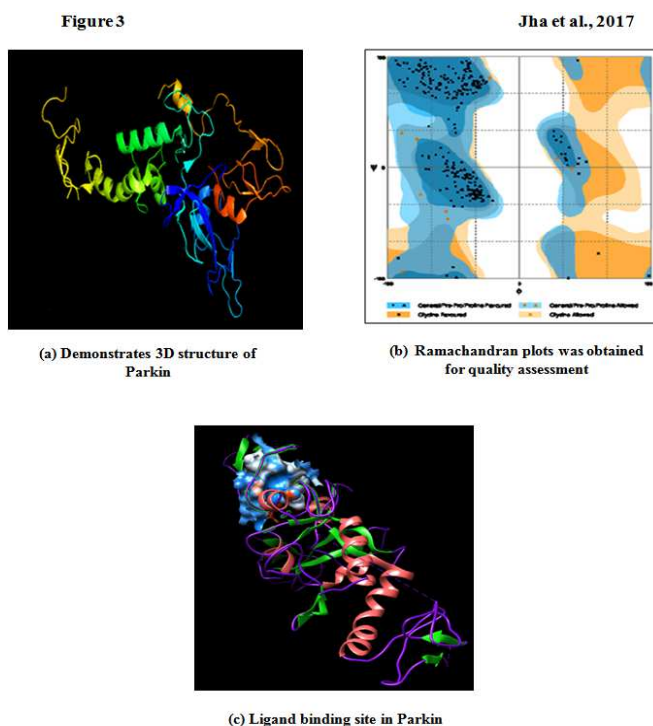


Fig. 3: 3D structure, Ramachandran plot and active site of parkin models

Initial screening of the molecules was done on the basis of Lipinski's rule of five (fig. 4). Lipinski filter analysis revealed that all these

molecules (Naringenin, Quercetin, Resveratrol and Sesamol) could act like a drug as they meet the criteria of Lipinski Rule of five.

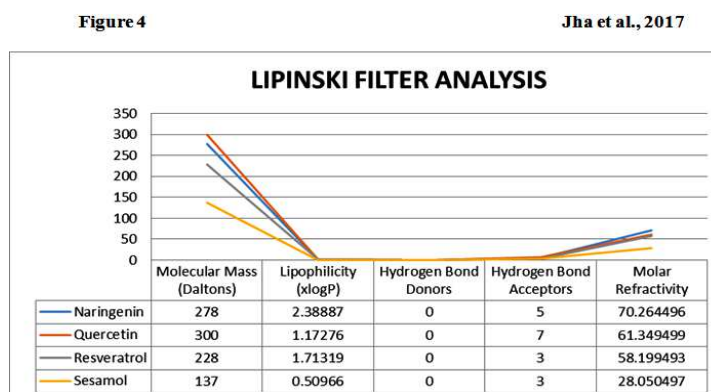


Fig. 4: Drug likeness prediction using lipinski filter analysis

Active site prediction and molecular docking analysis of Parkin with identified molecules

CastP server was used to predict the ligand binding site. This server calculates the possible active sites from the 3D atomic coordinates of the proteins. For Parkin, residues involved in ligand binding site, site volume and volume of protein for thirty active sites were predicted. Among the thirty binding sites obtained from CastP for Parkin, site 30 was highly conserved within the active site of the protein (fig. 3(c)).

The Predicted site 30 consisted 1058.8 Cubic angstroms site volume out of the 3741 Cubic Angstroms of protein volume. The residues in site 30 are illustrated in (table 5).

Molecular docking pattern of Parkin with screened molecules (Naringenin, Quercetin, Resveratrol and Sesamol) have been identified and depicted in (fig. 5). On the basis of docking analysis, interacting compounds with minimum binding constant and highest negative free energy of binding are most effective. Docking calculation of Parkin has been presented in (table 4).

Table 4: Docking calculation of compounds with parkin

Compound name	Est. free energy of binding	Est. binding constant	Est. intermolecular energy	vdW+Hbond+desolv Energy	Electrostatic energy	Est. internal energy	Torsional free energy
Naringenin	-7.12 (kcal/mol)	6.08 μ M	-8.31 (kcal/mol)	-8.19 (kcal/mol)	-0.12 (kcal/mol)	+9.71 (kcal/mol)	+1.19 (kcal/mol)
Quercetin	-7.60 (kcal/mol)	2.67 μ M	-9.39 (kcal/mol)	-9.15 (kcal/mol)	-0.25 (kcal/mol)	+9.67 (kcal/mol)	+1.79 (kcal/mol)
Resveratrol	-6.69 (kcal/mol)	12.43 μ M	-8.48 (kcal/mol)	-8.47 (kcal/mol)	-0.02 (kcal/mol)	+17.26 (kcal/mol)	+1.79 (kcal/mol)
Sesamol	-4.99 (kcal/mol)	221.78 μ M	-5.28 (kcal/mol)	-5.17 (kcal/mol)	-0.11 (kcal/mol)	+0.34 (kcal/mol)	+0.30 (kcal/mol)

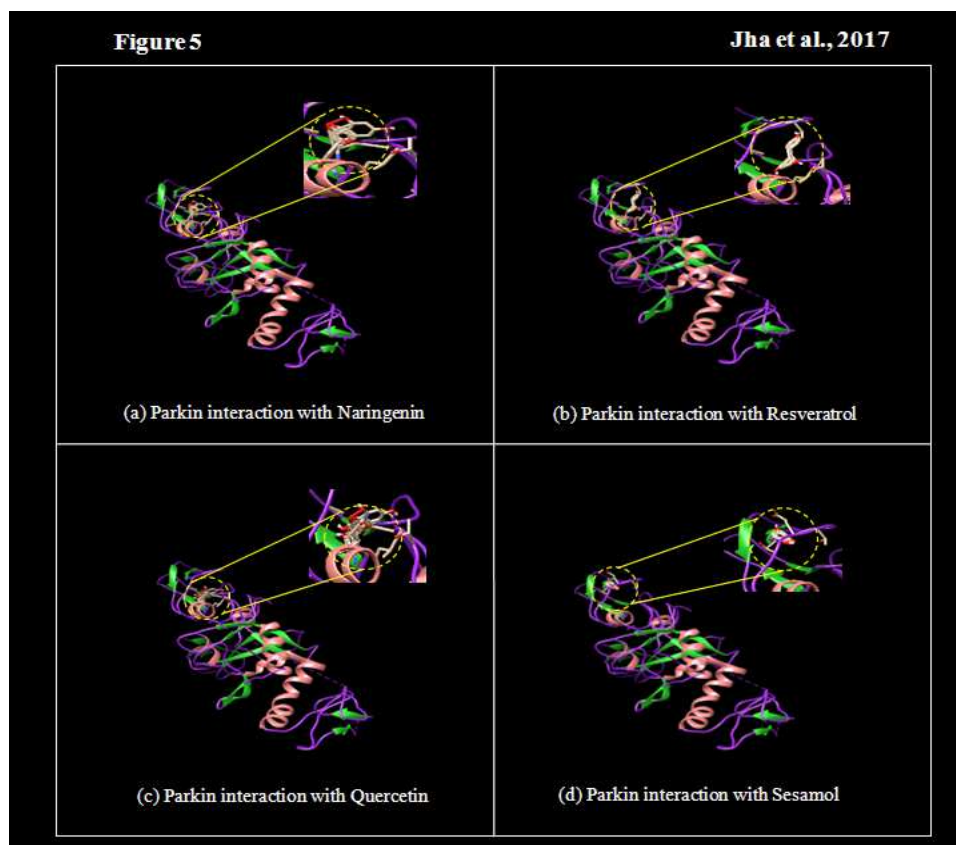


Fig. 5: Docking study of parkin protein with selected compounds

Table 5: Parkin known binding site and selected compounds interacting residues

Compound	Interacting residues
Reported catalytic Site	TYR ¹⁴³ , THR ²³¹ , ASN ²³² , SER ²³³ , ARG ²³⁴ , ASN ²³⁵ , ILE ²³⁶ , THR ²³⁷ , ARG ²⁵⁶ , GLN ⁴⁰⁰ , ARG ⁴⁰² , TRP ⁴⁰³ , GLU ⁴⁰⁴ , ALA ⁴⁰⁵ , ALA ⁴⁰⁶ , SER ⁴⁰⁷ , LYS ⁴⁰⁸ , GLU ⁴⁰⁹ , THR ⁴¹⁰ , LYS ⁴¹² , LYS ⁴¹³ , THR ⁴¹⁴ , LYS ⁴¹⁶ , LYS ⁴²⁷ , GLY ⁴²⁹ , GLY ⁴³⁰ , MET ⁴³² , TRP ⁴⁴⁷ , ASN ⁴⁴⁸ , ASP ⁴⁶⁴ and VAL ⁴⁶⁵ .
Naringenin	ARG ²³⁴ , ASN ²³⁵ , ILE ²³⁶ , THR ²³⁷ , GLN ⁴⁰⁰ , ARG ⁴⁰² , TRP ⁴⁰³ , GLU ⁴⁰⁴ , ALA ⁴⁰⁵ , ALA ⁴⁰⁶ , SER ⁴⁰⁷ and LYS ⁴⁰⁸ .
Quercetin	ARG ²³⁴ , ASN ²³⁵ , ILE ²³⁶ , THR ²³⁷ , GLN ⁴⁰⁰ , ARG ⁴⁰² , TRP ⁴⁰³ , ALA ⁴⁰⁵ , ALA ⁴⁰⁶ and SER ⁴⁰⁷ .
Resveratrol	ARG ²³⁴ , ASN ²³⁵ , ILE ²³⁶ , THR ²³⁷ , GLN ⁴⁰⁰ , SER ⁴⁰⁷ , LYS ⁴⁰⁸ and THR ⁴¹⁰ .
Sesamol	GLU ⁴⁰⁹ , THR ⁴¹⁰ , LYS ⁴¹² , LYS ⁴¹³ and THR ⁴¹⁴ .

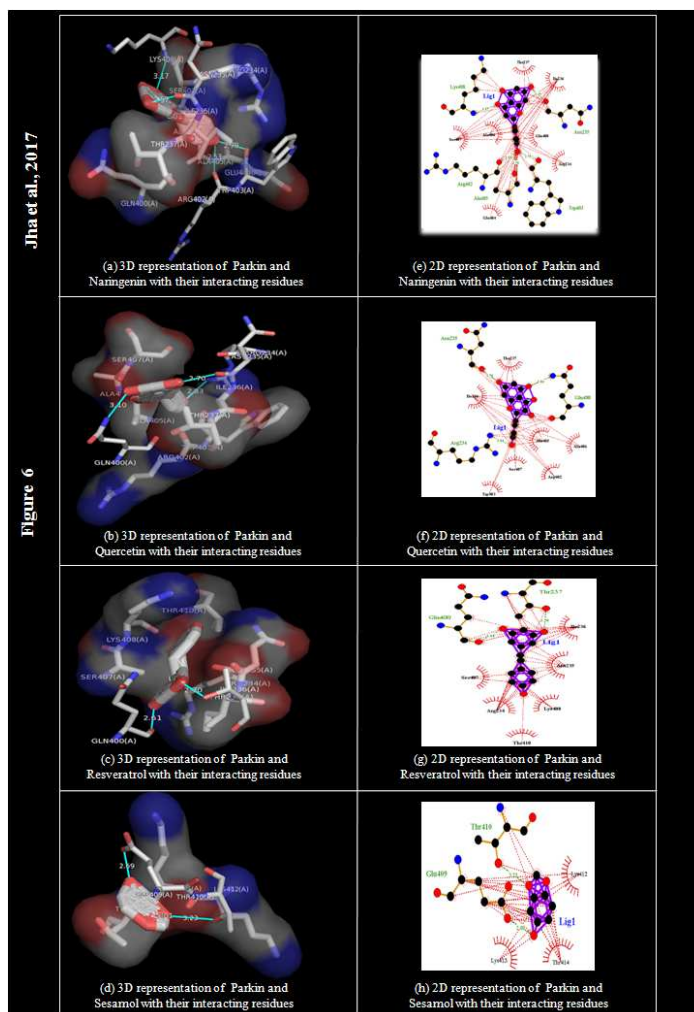


Fig. 6: Binding site of Parkin with selected compounds along with its reported catalytic site

Binding site residues of Parkin interacting with Naringenin, Quercetin, Resveratrol and Sesamol were found to be the same as the residues involved in their respective catalytic sites. Interacting residues of Parkin with Naringenin, Quercetin, Resveratrol and Sesamol along with their identified catalytic sites have been shown in (table 5) and their 2D and 3D pattern of interaction is presented in (fig. 6).

DISCUSSION

This research introduced the novel potential of biomolecules, which could be applied for therapeutic intervention in PD progression. Mutations in PD associated genes such as Parkin potentially lead to autosomal recessive PD [22]. Moreover, this gene displays characteristic ubiquitin E3 ligase activity. Parkin is ubiquitously expressed in a number of pathways associated with PD pathogenesis and has ubiquitin E3-ligase activity which also reduces α -synuclein aggregation [23]. Thus, it seems imperative to design therapeutic strategies aimed at elevating the level of Parkin to improve neuronal survival in PD. Further, various studies have advocated that several compounds of plant origin possess neuroprotective properties, however, their mode of action has not been clearly defined. Based on docking study analysis, the present study provides scientific evidence that given four biomolecules namely Naringenin, Quercetin, Resveratrol and Sesamol are interacting at the reported binding site of Parkin. Further, Binding Constant, K_b of Naringenin, Quercetin, Resveratrol and Sesamol for Parkin were found to be 6.08 μ M, 2.67 μ M, 12.43 μ M and 221.78 μ M respectively, suggesting that all the selected compounds were effective as Ubiquitin E3 Ligase activators. Investigation of active binding sites within Parkin protein

gives a better idea for a valuable drug target site and drug interaction with the highest affinity. In this study the most effective compound was found to be Quercetin is having minimum binding Constant, K_b and highest negative free energy of binding with a maximum interacting surface area with reported highly conserved active site within Parkin protein in course of docking studies [24-27].

Hence, this manuscript is showing for the first-time neuroprotective effect of Quercetin with Parkin in PD pathogenesis.

CONCLUSION

The future of neurodegenerative therapies depends on the researchers' ability to adjust actions of circumstances and have a clear projection relating to the aberrant mechanisms that ultimately decides the fate of neurons and henceforth degeneration. Despite, tremendous advancements in the field of neurotherapeutics, still the future of such therapies hangs on morbid conjecture and fragile hopes the biomolecules present us an interesting avenue to exploit in PD. Interrupting critical interactions of the biomolecules can solve the "targeted therapy crisis" problem in neurodegeneration. In conclusion, we have found Parkin protein for a potential target of Quercetin by molecular docking studies, which will be useful for the design of novel and highly efficient drug for the treatment of PD therapeutics.

AUTHORS' CONTRIBUTION

P. K designed the manuscript. S. K. J performed the experiments and software analysis for the target molecules. S. K. J performed the docking software analysis. P. K and S. K. J analyzed, coordinated and

drafted the manuscript. Authors read and approved the final manuscript.

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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