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Short Communication

Exploring the Interaction of E3 Ubiquitin-Protein Ligase Parkin with Natural Compound Amentoflavone: Implications for Parkinson's Disease Therapy

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Abstract

Parkinson's disease is a neurodegenerative disorder resulting from progressive damage to specific brain regions. Key symptoms encompass involuntary movements (tremor), slowness of movements (bradykinesia), and muscle rigidity. Although the precise cause remains uncertain, a combination of genetic and environmental factors is believed to contribute to its development. This study focuses on the interaction of the E3 ubiquitin-protein ligase parkin with natural compounds. Docking investigations revealed that Amentoflavone exhibited an excellent binding energy score of approximately -10 kcal/mol. The E3 ubiquitin-protein ligase parkin displayed a robust binding affinity with docked amentoflavone, evident from a high binding energy of -10 kcal/mol. Nonetheless, additional biological studies are crucial not only to validate its potential efficacy against Parkinson's and assess safety in terms of toxicity but also to perform further computational analyses confirming these preliminary assessments.

INTRODUCTION

Parkinson's disease is a specific subtype of Parkinsonism, and Parkinsonism is a more general term that includes various conditions with similar motor and non-motor symptoms. It's crucial for healthcare professionals to carefully evaluate and diagnose the specific cause of Parkinsonism in an individual to determine appropriate treatment and management strategies [1-3].

Parkinson's Disease (PD) is a chronic neurodegenerative disorder that predominantly affects the motor system. It is characterized by the progressive loss of dopamine-producing neurons in the substantia nigra, a region of the brain. Dopamine serves as a vital neurotransmitter, playing a pivotal role in the regulation of movement and coordination [4-7]. While the precise cause of Parkinson's disease remains unclear, it is thought that a combination of genetic and environmental factors contributes to its development. Presently, there is no cure for Parkinson's disease; however, diverse treatment options exist with the goal of symptom management and enhancing quality of life. Depending on the severity of symptoms, healthcare professionals may recommend medications, physical therapy, or, in certain cases, surgical interventions like deep brain stimulation [4-7].

The present work focused on the protein Parkin and its potential role in finding compounds to combat Parkinson's disease. Parkin is a protein associated with the regulation of cellular processes, and mutations in the Parkin gene have been linked to a familial form of Parkinson's disease [8,9]. Parkin, acting as a RING-between-RING E3 ligase, operates in the covalent binding of ubiquitin to particular substrates.

Mutations in Parkin have associations with Parkinson's disease, cancer, and mycobacterial infection [8,9]. This investigation was performed by Molecular Docking studies [10-12]. Molecular docking plays a pivotal role in drug design by pinpointing potential therapeutic compounds. This technique is essential in the drug development journey as it forecasts the affinity and binding capabilities of novel molecules to specific target proteins, thereby facilitating the synthesis and refinement of promising drug candidates [10-12]. General speaking, A more negative binding energy indicates a stronger affinity between the ligand and the protein target, a desirable characteristic in drug discovery and design. Consequently, researchers typically prioritize ligand poses or conformations with the lowest negative binding energies when analyzing docking results, as they represent potential drug candidates with high binding affinity to the target protein [10-12].

MATERIAL AND METHODS

E3 ubiquitin-protein ligase parkin (Chain A) was taken by Protein Data Bank, (PDB Code 4I1H**).**

Grid box for Blind Docking analysis was performed by Pyrx program [13]: center_x = 60.2823; center_y = 22.4819; center_z = -12.0064; size_x = 52.1553899384; size_y = 65.1767790318; size_z = 86.6129901886.

RESULTS AND DISCUSSION

Parkinson's disease is a neurodegenerative disorder caused by the progressive damage of certain parts of the brain [1-7]. The main symptoms include:

-Involuntary movements of one or more parts of the body (tremor)

-Slowness of movements (bradykinesia)

-Muscle rigidity

The exact cause of Parkinson's disease remains uncertain, it is believed that a combination of genetic and environmental factors plays a role in its development [1-7].

Molecular docking is a computational technique widely used in drug design and discovery to predict the binding modes and affinities of small molecule ligands to target proteins. This process plays a crucial role in guiding the selection and optimization of drug candidates by providing insights into their potential therapeutic activity and interaction mechanisms [10-13].

General speaking, a lower (more negative) binding energy suggests a stronger affinity between the ligand and the protein target, which is generally considered desirable in drug discovery and design. Therefore, when analyzing docking results, researchers often prioritize ligand poses or conformations with the lowest negative binding energies as potential drug candidates with high binding affinity to the target protein [10-13].

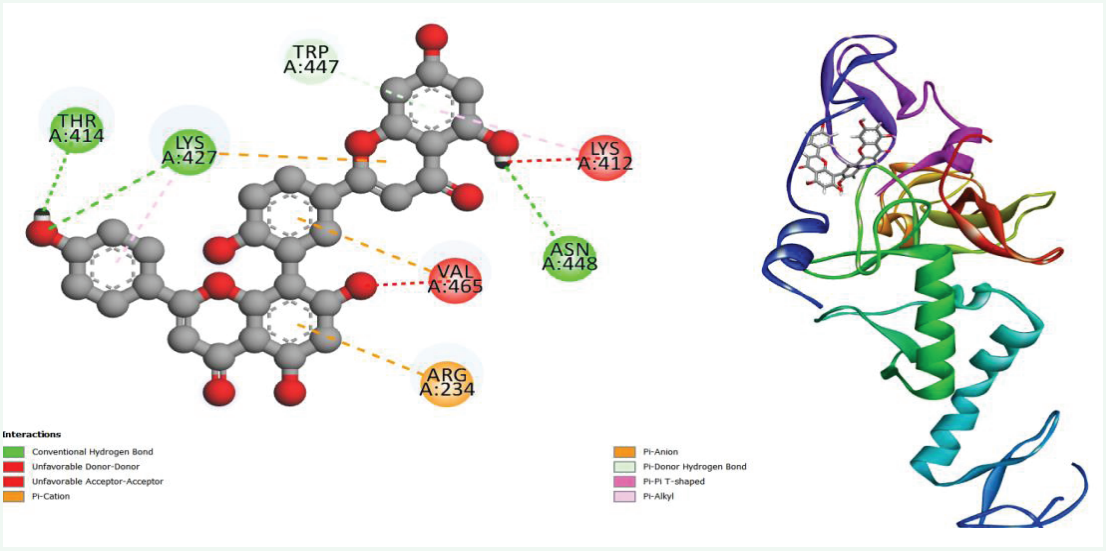

Figure 1 Displays the docking outcomes of E3 ubiquitin-protein ligase parkin (in conjunction with Amentoflavone -10 kcal/mol within the potential Ligand Binding Site, as analyzed by Autodock Vina through the pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Amentoflavone.

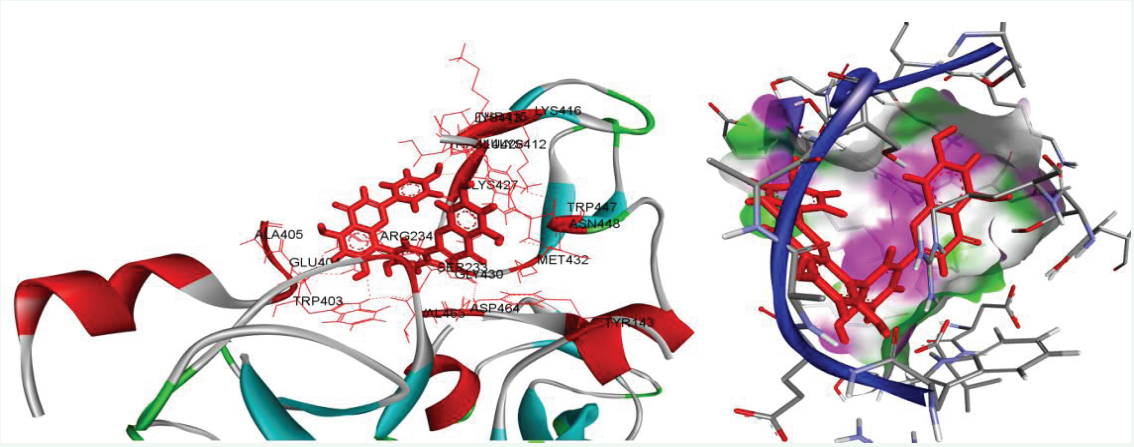

Figure 2 Displays the characterization of E3 ubiquitin-protein ligase parkin (in conjunction with Amentoflavone -10 kcal/mol within the potential Ligand Binding Site.

Table 1: Shows of predicted toxicity parameters by pKCSM Server with Amentoflavone evaluated.

Compounds	AMES Toxicity	Max. Tolerated Dose(human) (logmg/kg/day)	hERG I Inhibitor	hERG II Inhibitor	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity
Amentoflavone	no	0.438	no	yes	2.527	3.572	no

The present work focused on E3 ubiquitin-protein ligase parkin with natural compounds. From docking investigations Amentoflavone showed excellent binding energy score of about -10 kcal/mol. Indeed, The E3 ubiquitin-protein ligase parkin demonstrates a strong binding affinity with docked amentoflavone, evidenced by a high binding energy of -10 kcal/mol.

Nevertheless, additional biological studies are imperative not only to validate its potential efficacy against Parkinson's and assess its safety concerning toxicity but also to conduct further computational analyses capable of confirming these initial assessments.

Further investigations were conducted to further reduce the number of potential compounds, with particular emphasis on predicting the toxicity of Amentoflavone are applied with pKCSM server [14]. Based on the results presented in Table 1, it has been confirmed that amentoflavone, a naturally occurring biflavonoid compound found in various plants such as Ginkgo biloba and Hypericum perforatum (St. John's wort), exhibits low toxicity effects.

CONCLUSION

This computational study focused on exploring the interaction between the E3 ubiquitin-protein ligase parkin and natural compounds, with Amentoflavone demonstrating a notable binding energy score (-10 kcal/mol). The strong binding affinity observed during docking suggests a potential therapeutic role for Amentoflavone in Parkinson's disease. However, it is crucial to underscore that further biological studies are imperative to validate the efficacy of Amentoflavone against Parkinson's and to assess its safety in terms of toxicity.

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