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Research Article

ANTI-PARKINSON POTENTIAL OF *PERSEA AMERICANA* SEED EXTRACTS THROUGH *IN-SILICO* DOCKING STUDY

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ABSTRACT

Objective: The aim of this study is to investigate the potential of *Persea americana* extracts for their Anti-Parkinson application through an *in-silico* docking study.

Methods: PubChem and protein data bank databases were used to retrieve 3D structures. AutoDock4 was used to perform protein-ligand docking analysis. PyMOL was used to visualize the docking results.

Results: Among the 30 ligand, the highest affinity was demonstrated by Hesperidin with a free binding energy of −6.8 kcal/mol and formation of five hydrogen bonds. The second highest significance was demonstrated by Biphenyl 4-(4-diethylaminobenzylidenamino) with a free binding energy of −5.9 kcal/mol with the formation of 2 hydrogen bonds. Among the three sets of phytochemicals from different solvent extracts, water extract demonstrated the highest potential as Anti-Parkinson active.

Conclusion: *P. americana* extracts were analyzed for their Anti-Parkinson potential, and among the three extracts, the aqueous extract was predicted to have significant Anti-Parkinson potential, based on *in silico* docking analysis, due to the presence of active phytochemicals such as Hesperidin and others.

Keywords: *Persea americana*, Hesperidin, Protein-ligand docking, AutoDock 4, PyMOL.

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INTRODUCTION

The avocado (*Persea americana*) also termed as alligator bear or bitter fruit, with its origin in Mexico, Central, or South America ages back to 500 B.C [1,2]. Classified as a member of the flowering plant family Lauraceae, it has long been used as a traditional herbal medicine for the treatment of stomachache, diarrhea, hypertension, and diabetes [3]. A great source of Vitamin C, E, K, B6, riboflavin, niacin, folate, pantothenic acid, magnesium, potassium, lutein, beta-carotene, omega 3, 6, monounsaturated fatty acids, and phytonutrients such as stigmasterol and campesterol, carotenoids, flavonoids, and polyhydroxylated fatty alcohols [4,5] makes it a potential reducer of obesity, cardiovascular disease, and neurodegenerative diseases, respectively. Off lately, neurodegenerative disorders have affected millions of people worldwide, causing a mortality rate of 6.8 million per year [6]. Evidence suggests mitochondrial mutation and reactive oxygen species (ROS) being related to the pathogenesis for any neurological disorders [7], occurring due to the disruption in the balance between free radical formation and the counteractive endogenous antioxidant defense system that includes superoxide dismutase, catalase, and glutathione peroxidase [8-10]. The ROS so formed causes exponential oxidation of essential lipids and protein, resulting in genomic instability and telomere shortening [9-12]. It attacks the post-mitotic glial and neuronal cells contributing to cerebral ischemia, seizure disorders with an ultimatum of apoptosis. Diabetes induced neuropathy has also been involved in macrovascular disease, microangiopathy, cognitive decline, and brain atrophy [13,14]. Another key identified feature for any neurodegenerative disorders is the presence of Lewy bodies; these are proteinaceous deposits in nerve cells of the brain responsible for thinking and motor movement [15]. Amidst it, the alpha-synuclein protein has been a defined constituent responsible for synucleinopathies, Parkinson's disease, and dementia [16]. Although the protein has not been extensively studied, the recent consensus has shown alpha-synuclein to be associated with the modulation of dopamine release and promoting membrane curvature [17,18].

In this context, traditional herbal products found in avocado have long been used to treat memory-related disorders. Neuronal cells require proper electrical impulses and gradient channels for their function which in turn depends on their fatty acid composition. Dietary consumption of avocado that's rich in linoleic acid and alpha-linoleic acid-like fatty acids has proven to improvise membrane fluidity, synaptic plasticity, neural function, and neuroprotection [19]. Combinations of avocados and soybean fats have been shown to prevent oxidation and formation of ROS, elevating the flexibility of neuronal cells when exposed to low-oxygen conditions [20]. The polyphenolic and monounsaturated fatty acids found in avocado have been evident to inhibit fibril and Lewy body formation. Steroids in the form of stigmasterol, sitosterol, brassicasterol, and campesterol have also been shown to reduce amyloidogenic processing that may be advantageous in delaying the progression of Parkinson's disease [21,22]. In addition, the phenolic extracts of avocado seeds have been shown to have high levels of B-type procyanidins and epicatechin exhibiting antioxidant property that may serve the purpose of treating neurodegenerative disorders. It is also found to be rich in Vitamin E and unsaturated fatty acids preventing free radical damage mostly exhibited in such disorders. Rich in extracts such as peptone, B-galactoside, cytochrome P-450, polyuronoids, and volatile oils slow down the process of cellular aging and are anti-inflammatory in nature. Highly rich in amino acids, it is a great source of nutrients that might further aid in treating neuro-related disorders [23,24]. Therefore, the diversity of bio-nutrients and phytochemicals present in avocado plays an important role in the prevention and treatment of various degenerative disorders.

Previous docking studies have unraveled the antibacterial activity of ethanolic extracts of avocado where rutin present in it binds to

PBP2a of the bacterial cell wall serving as an antibacterial drug [25]. Further *in-vitro* and *in-silico* studies have shown the hydroxyl group of proanthocyanidins in avocado chelating with the catalytic center of the enzyme tyrosine inhibiting its activity further laying a foundation in agriculture, food and nutrition industries [26]. With this context, this paper aims in taking an *in-silico* approach for understanding the interaction of various phytochemicals present in avocado to the oxidation pathways and amyloid formation in neurodegenerative Parkinson's disease; serving the possibility of therapeutics to treat it, respectively.

METHODS

The chemical structures of the phytochemicals identified from the extracts of *P. americana* were retrieved from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/). The protein structure of alpha-synuclein was retrieved from the protein data bank (PDB) website (www.rcsb.org) with a PDB ID: 1XQ8. The protein-ligand docking study was performed using AutoDock 4 software and the results are visualized using the PyMOL tool [27-32].

RESULTS

Phytochemicals of *P. americana*

Based on the previous study by Rachael *et al*. (2020) (unpublished data), the list of phytochemicals present in the ethanol, water, and ethyl acetate extract of *P. americana* seed was obtained and the chemical structures of these list of chemicals were retrieved from PubChem database. A total of 30 ligands were identified and retrieved from the PubChem database and were used for docking analysis.

Anti-Parkinson's docking analysis

The 30 ligand molecules were subjected to protein-ligand docking study to predict their Anti-Parkinson potential by inhibition of alpha-synuclein protein. AutoDock-4 was used for this purpose. The free binding energy of all the retrieved phytochemicals against the alpha-synuclein protein is tabulated in Table 1. Among the 30 ligand molecules, the highest significance was exhibited by Hesperidin with a free binding energy of −6.8 kcal/mol and formation of five hydrogen bonds (Lys-043, Lys-032, Val-040). The graphical representation of the interaction between Hesperidin and alpha-synuclein is shown in Fig. 1. The second highest significance was demonstrated by Biphenyl 4-(4-diethylaminobenzylidenamino) with a free binding energy of −5.9 kcal/mol with the formation of 2 hydrogen bonds (Val-040, Lys-043). Interactions of Biphenyl 4-(4-diethylaminobenzylidenamino) with alpha-synuclein are shown in Fig. 2. The third highest significance was demonstrated by the aldosterone molecule with a free binding energy of −5.8 kcal/mol. The interaction between aldosterone and alpha-synuclein is shown in Fig. 3. All three analyzed ligands show the same binding site interaction with the alpha-synuclein protein. Among the three extracts that are analyzed in this protein-ligand docking study, it is predicted that the aqueous extract of *P. americana* has the potential to be applied as an Anti-Parkinson agent, by inhibition of alpha-synuclein.

DISCUSSION AND CONCLUSION

Molecular docking is a frequently used approach in molecular drug designing, providing easy access to understand ligand-receptor interaction. Previous studies have shown these computation techniques to unravel and design potent new drugs by understanding the mechanism of drug-receptor interaction. Computer-aided drug design aids in recognizing small molecules by orienting and scoring them in the active binding site of the protein [33,34]. The protein alpha-synuclein has its active binding site for the formation of Lewy bodies and synucleinopathies. Three forms of extracts taken from *P. americana* were studied through docking for its potential binding affinity to the active site of the protein and inhibition of Synuclein activity. The highest significant value was evaluated for Hesperidin in the aqueous extract of the plant with a binding energy of −6.8 kcal/mol. It was found to be a more suitable ligand, confounding a greater ability to bind to the active site of the synuclein protein, thus preventing its aggregation and serving as a potential drug to treat Parkinson's. Moreover, previous reports have shown lower solubility of the drug

Table 1: The binding energy of phytochemicals from *Persea americana* with alpha-synuclein protein

Extract	Compound name	Protein data bank ID	Binding energy (kcal/mol)
Ethanol extract	Androsta-1,4-dien-3-one, 17-hydroxy-17-methyl-	6300	−5.7
	Isopropyl myristate	8042	−3.4
	Tricaprylin	10850	−3.3
	Glyceryl palmitate	14900	−3.1
	Benzene, 1,2,4-trimethyl-5-(3-methylbutyl)	583850	−4.7
	Retinal	638015	−5.4
	Methyl oleate	5364509	−3
Aqueous extract	1-Eicosanol	12404	−3.2
	1-Heptacosanol	74822	−3
	Aldosterone	5839	−5.8
	Biphenyl 4-(4-diethylaminobenzylidenamino)	628682	−5.9
	Hesperidin	10621	−6.8
	Methyl 14-methylpentadecanoate	21205	−3.1
	Octadecanoic acid	5281	−3.3
	Oleic acid	445639	−3.5
	Palmitic acid	985	−3
	Phorbol 12,13-dibutyrate	37783	−5.6
	Phorbol 12-myristate 13-acetate	27924	−4.4
Ethyl acetate extract	11,14-Eicosadienoic acid, methyl ester	5365566	−3.8
	2,3,4-Trimethyl-5-hexen-3-ol	141427	−3.4
	Cyclohexane, 1-ethenyl-1-methyl-2,4-bis (1methylethenyl)	641756	−4.8
	Cyclopropanecarboxylic acid, pentadecyl ester	560133	−3.5
	Methacrylic acid, hexadecyl ester	17235	−3.5
	n-Dodecyl methacrylate	8906	−2.8
	n-Hexadecanoic acid	985	−2.9
	Octadecanoic acid	5281	−2.9
	Palmityl oleate	5377655	−2.8
	Saponarin	441381	−5.9
	Tridecanediol	544162	−3.5
	Z, Z-4,15-Octadecadien-1-ol acetate	5363119	−3.6

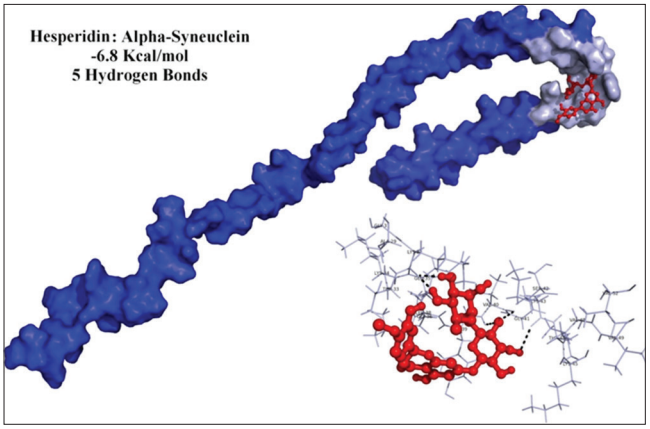

Fig. 1: Interaction between Hesperidin and alpha-synuclein

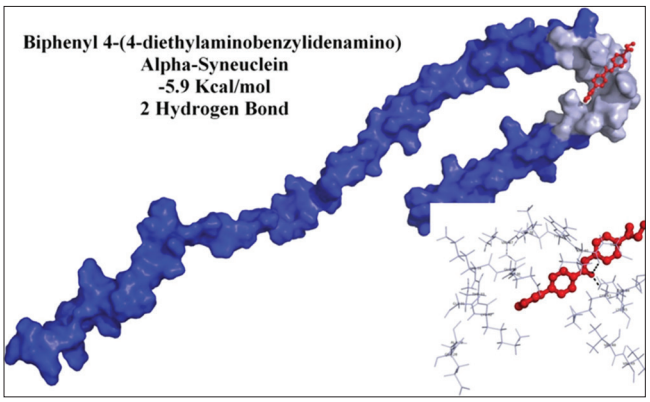

Fig. 2: Interaction between biphenyl 4-(4-diethylaminobenzylidenamino) and alpha-synuclein

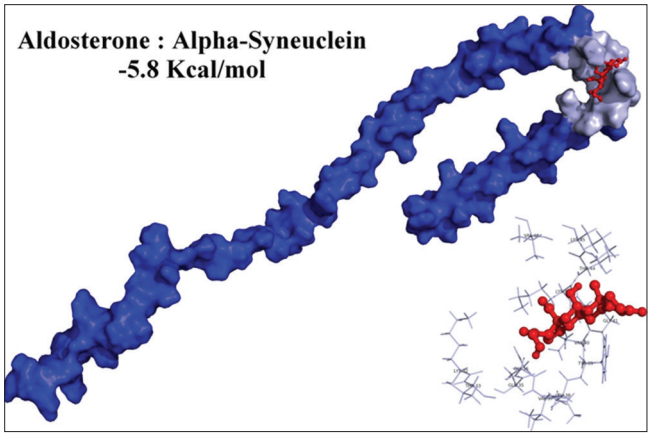

Fig. 3: Interaction between aldosterone and alpha-synuclein

being favorable towards good and complete oral absorption. Thus, in relation to the above context, aqueous extracts of *P. americana* are bound to have lower solubility index and Hesperidin being one of them makes it a potential candidate for a good and complete absorption for effective dosage [34]. Henceforth, this *in-silico* study has given us a comprehensive insight into the structure of the alpha-synuclein protein and the potential phytochemicals present in *P. americana* that could serve as a therapeutic drug to treat the neurodegenerative disorder.

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AUTHORS' CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTEREST

No known conflicts of interest.

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