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Research article

Characterization and molecular docking studies of Erucic acid

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ABSTRACT

Neurodegenerative diseases (NDs) are a wide range of neurological conditions characterized by the deterioration of neurons, glial cells, synapses, and other networks. Parkinson's disease is one of the second most common neurodegenerative disorders after Alzheimer's disease. Erucic acid, an omega-9 monounsaturated fatty acid, was reported to be commonly present in mustard oil. Erucic acid was also reported to have neuro protective and antioxidant benefits in a number of pre-clinical trials conducted in the past. In the present study, erucic acid, linoleic acid, and Riluzole were evaluated using a molecular docking-based technique based on their binding affinities and other physicochemical characteristics of the compounds. PYRX 0.8 was used for molecular docking between ligands and the various antioxidant and neurotransmitter-associated proteins, and Discovery Studio Visualizer 2020 was used to create the visualization. Additionally, Lipinski's rule of five was used to forecast whether these compounds would be drug-like. Further absorption, distribution, metabolism, excretion, and Toxicity (ADME-T) profile of the compounds were studied using the pkCSM tool. According to drug-likeness analysis, all of the compounds i.e. erucic acid, linoleic acid, and Riluzole fell within Lipinski's rule of five's acceptable range. The docking studies implied that erucic acid might have anti-parkinsonian effects by binding to molecular targets superoxide dismutase (SOD1) enzyme protein i.e. 5YTU and to 5-Hydroxytrytamine (5H2TC) receptor protein i.e. 6BQH when compared to Riluzole along with good ADME-T properties. However, more research is needed to evaluate the efficacy of erucic acid against additional targets of Parkinson's disease and other neurodegenerative illnesses.

Keywords: Neurodegenerative Disease, Parkinson's disease, Erucic Acid, Riluzole, Linoleic acid, Molecular Docking, ADME-T study

INTRODUCTION

Parkinson's disease is the utmost common neurodegenerative disorder following Alzheimer's disease (AD) [1]. PD is characterized by dopaminergic neuron degeneration in the substantia nigra pars compacta (SNpc) region of the brain [2]. A few of the pathophysiological pathways linked to PD include oxidative stress and neurotransmitters. Oxidative stress can further cause mitochondrial dysfunction, mitochondrial mutations, and oxidative damage [3]. The reported literature is well-educated in reactive oxygen species (ROS) scavenging and also neuron protective properties against oxidative stress-cause damage [4]. Also, it was reported that PD and AD are brought on by low levels of glutathione reductase (GSH), superoxide dismutase (SOD), and catalase (CAT) in the brain [5-7].

Various neurotransmitters involved in the pathogenesis of PD are dopamine (DA); serotonin (5-HT); norepinephrine and glutamate [8]. DA, the most prevalent catecholamine neurotransmitter in the brain, is crucial for several processes, including rewarding behavior, emotion, cognition, movement, and endocrine control [9].5-HT has also been observed to be plentiful in the striatum, medial globus pallidus, substantia nigra pars reticulate, and the basal ganglia's output areas suggesting that it plays a function in PD [10].

Erucic Acid (EA)

22:1-9, consists of omega-9 monounsaturated fatty acid. It is common in wallflower seed with a reported level of 20 to 54 % in rapeseed oil [11] and 42 % in mustard oil.

Recently, EA was reported to have a promising memory-enhancing effect on rats with cognitive impairment induced by scopolamine [12] EA and its amide derivatives erucamide were also proven to have positive cognitive effects [13];used in the treatment of X-linked adrenoleukodystrophy (X-ALD) along with Oleic acid [14]; have Peroxisome proliferator-activated receptors delta)PPARδ interactions [15] and having anti-neuroinflammatory effects by acting as thrombin inhibitor and elastase inhibitor [16]. Due to these observed outcomes in the previous studies, it can be concluded that EA might have a beneficial role in the treatment of PD.

As a result, molecular docking simulations were performedtodiscover how EA binds to oxidative enzymes, dopamine receptors, and serotonin receptors which were compared with the reference ligands – Riluzole (RIL) and Linoleic acid (LA). Further ADME-T properties of EA, LA, and RIL were also studied to explore the pharmacokinetic profile of the compounds.

MATERIALS AND METHODS

LA and EA (analytical grade) were bought from Merck Life Sciences in Gurugram. From TCI Chemicals (India) Pvt. Ltd., RIL was bought.

Drug Likeness Analysis

Lipinski's rule of five parameters was determined using the SwissADME website (http://www.swissadme.ch/) to analyze whether a molecule has the potential to be turned into a drug (drug-likeness)[17].

Molecular Docking Studies

Using PyRx-Virtual Screening Tool (AutoDock Vina) version 8.0, molecular docking was done to ascertain the free binding energy. Discovery Studio Visualizer 2020 was used for Receptor-Ligand Interactions. Ligand and protein preparation were done using the below-mentioned tools: (i) For Ligand Preparation: The 3D structure of the ligand molecules was created using ChemDraw 12.0 software. The structural data format (.sdf) was used to download each of these ligand molecules from PubChem (https://pubchem.ncbi.nlm.nih.gov) (ii) For Protein Preparation: The Research Collaboratory for Structural Bioinformatics' Protein Data Bank (http://www.rcsb.org) was used to find the following proteins that have 3D structures and are linked to (a) Antioxidant enzymes.: human GSH with a xanthene inhibitor protein (PDB ID: 1XAN) with 2.00 Aº resolution; human erythrocyte CAT protein (PDB ID: 1DGB) with 2.20 Aº resolution; human SOD1 complexed with isoproterenol C2221 space group protein (PDB ID: 5YTU) with 1.90 Aº resolution; and rabbit reticulocyte 15-lipoxygenase protein (PDB EA [CH3 (CH2)7CH=CH (CH2)11COOH], identified as ID: 1LOX) with 2.40 Aº resolution (b) D2 receptor: D2 receptor crystal structure bound to the atypical antipsychotic drug risperidone (PDB ID: 6CM4) with 2.87 Aº resolution; the haloperidol-bound D2 receptor crystal structure that led to the discovery of subtype-selectiveligands (PDB ID: 6LUQ) with 3.10 Aº resolution (c) 5-HT2C receptor: crystal structure of 5-HT2C in complex with ritanserin with 2.70 Aº resolution.

PyMOL Stereo 3D Zalman software 4.30 was used to eliminate the ligands and water molecule-occupying protein.

Pharmacokinetic Characteristics and Toxicity Prediction Studies (ADME-T Profile)

Further, the pkCSM tool (https://biosig.unimelb.edu.au/pkcsm) was used to forecast the compounds' ADME and toxicity profiles [18].

RESULTS

Drug Likeness Analysis of EA, LA, and RIL

As per Lipinski Rule of Five, if there are no more than two rule violations on any of the following mentioned criteria in the table, the molecule has a high likelihood of being developed as a drug (Table 1). Therefore, in light of the findings of this study, we chose all of these compounds for the molecular docking investigation as all compounds are proven to be drug-like.

Table 1: The Lipinski's Rule of Five for EA, LA, and RIL

Compound	Lipinski's Rule of Five					
	MW (≤500 g/mol)	HBD (≤5)	HBA (≤10)	cLog Po/w (≤5)	No. of rule violations (≤2 violations)	Drug-Likeness
EA	338.57 g/mol	1	2	7.14	1	Yes
LA	280.45 g/mol	1	2	5.44	1	Yes
RIL	234.30 g/mol	1	5	2.81	0	Yes

Molecular Docking Studies

Molecular Docking Analysis of Oxidative Enzymes Proteins with EA, RIL & LA

The docking studies revealed the binding ability of the novel compound EA which showed better interaction with the SOD1 enzyme than the other oxidative enzymes when compared with the reference ligand -RIL. With grid widths of 74.40, 71.40, and 61.70 XYZ points, the center of the grid for the GSH enzyme protein (1XAN) was placed at X=68.58, Y=-15.77, and Z=53.60.; CAT enzyme protein (1DGB) has a grid center set at X=18.23, Y=30.12, and Z=59.80 with grid sizes of 80.02, 90.24, and 77.48 XYZ points; grid sizes of 47.00, 43.20, 44.50 XYZ pointswere used for the SOD enzyme protein (5YTU), with the grid center set at X= 81.36, Y= 11.15, and Z= 18.65.; and with a grid size of 86.18, 68.80, 87.18, the grid center for the lipoxygenase enzyme protein (1LOX) was placed

at X=-19.72, Y=144.13, and Z=58.32 by just leaving all docking parameters at their default levels, resulting in 0.5Aº each for the grid spacing.

Molecular docking results showed that the interaction of EA with SOD1 enzyme protein (5YTU) at SER A: 102 was similar to the interaction of RIL with SOD1 enzyme protein (5YTU) at SER A: 102. The molecular docking results of all oxidative enzymes protein with EA; LA, and RIL were depicted in Table 2. The docking poses of antioxidant enzymes protein (SOD1) with EA and RIL were depicted in Figures 1 & 2.

Therefore, based on the above results, one can conclude that EA emerged to have an antiparkinsonian potential that can be linked to its antioxidant activity by binding to the SOD1 enzyme.

Table 2: Molecular Docking Results of Oxidative Enzymes Proteins with EA, RIL & LA

Compounds	**Binding energy (kcal/mol)**				**Hydrogen bonds**			**Interactions**				
	1XAN	1DGB	5YTU	1LOX	1XAN	1DGB	5YTU	1LOX	1XAN	1DGB	5YTU	1LOX
EA	-5	-6.3	-3.5	-4.9	3	4	3	3	TYR A: 364, ASN A: 366, GLY A: 381	ASP A: 128, ASN A: 149, GLN A: 195, GLY A: 204	PRO A: 74, ARG A: 79, SER A: 102	LYS A:189, ASN A: 190, SER A: 592
RIL	-6.5	-6.4	-5.1	-5.7	4	3	5	4	SER A: 51, HIS A: 129, ALA A: 130 (2)	GLN A: 11, ASN A: 321 (2)	ASN A: 26(2), SER A: 102, ASP A: 109, HIS A: 110	ASN A: 359 (2), ASP A:447 (2)
LA	-5.6	-7.5	-4.9	-5.8	4	3	3	3	ILE A: 466, THE A: 469, SER A: 471(2)	ARG A: 72, PHE A: 334, ARG A: 365	ALA A: 4; ASN A: 19, PHE A: 20	ARG A: 136(2), ASP A: 164

Figure 1: (A): 3D Image of Docked Pose of EA with Target Protein- 5YTU.

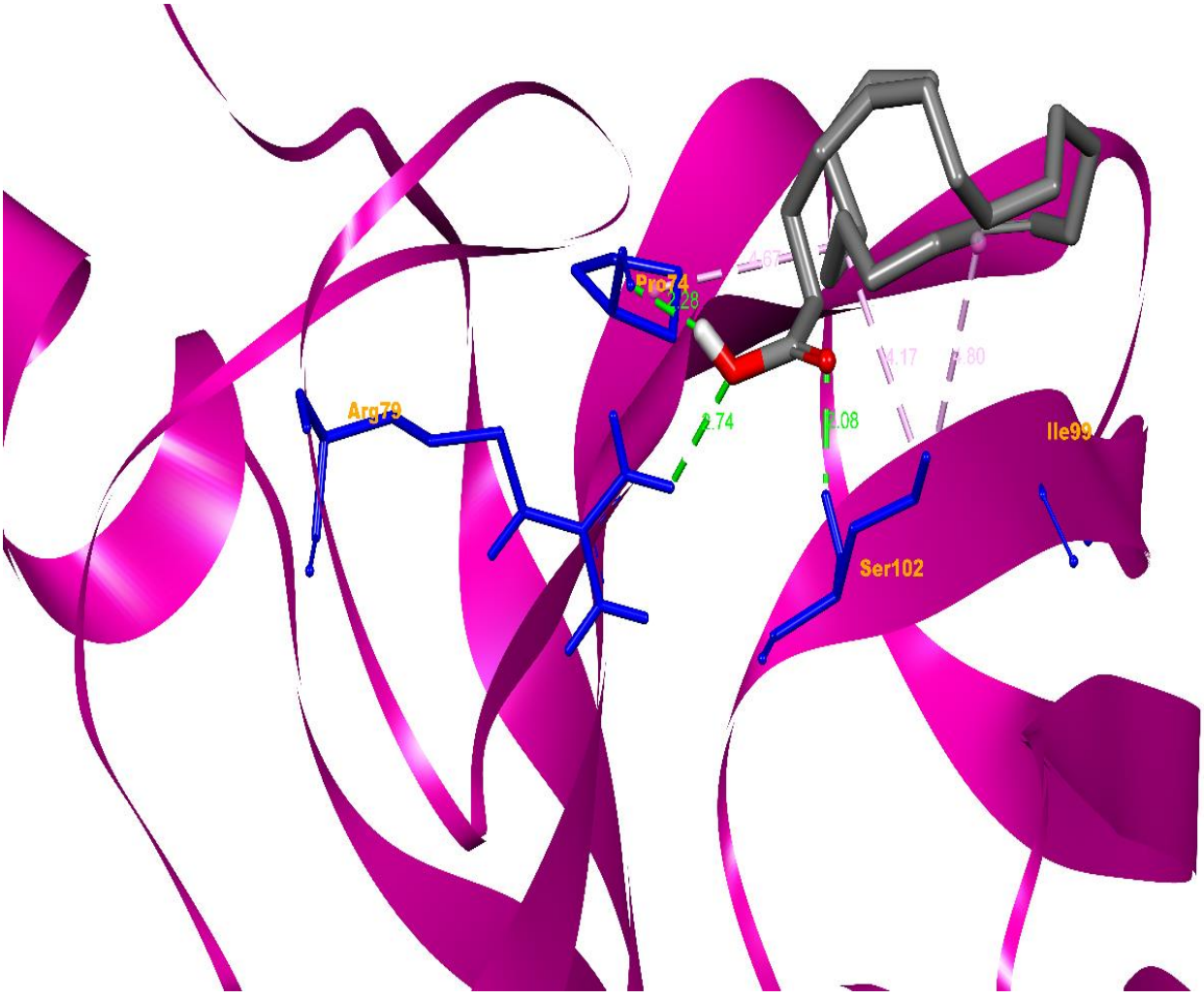


Figure 1: (B): 2D Image of Docked Pose of EA with Target Protein- 5YTU.

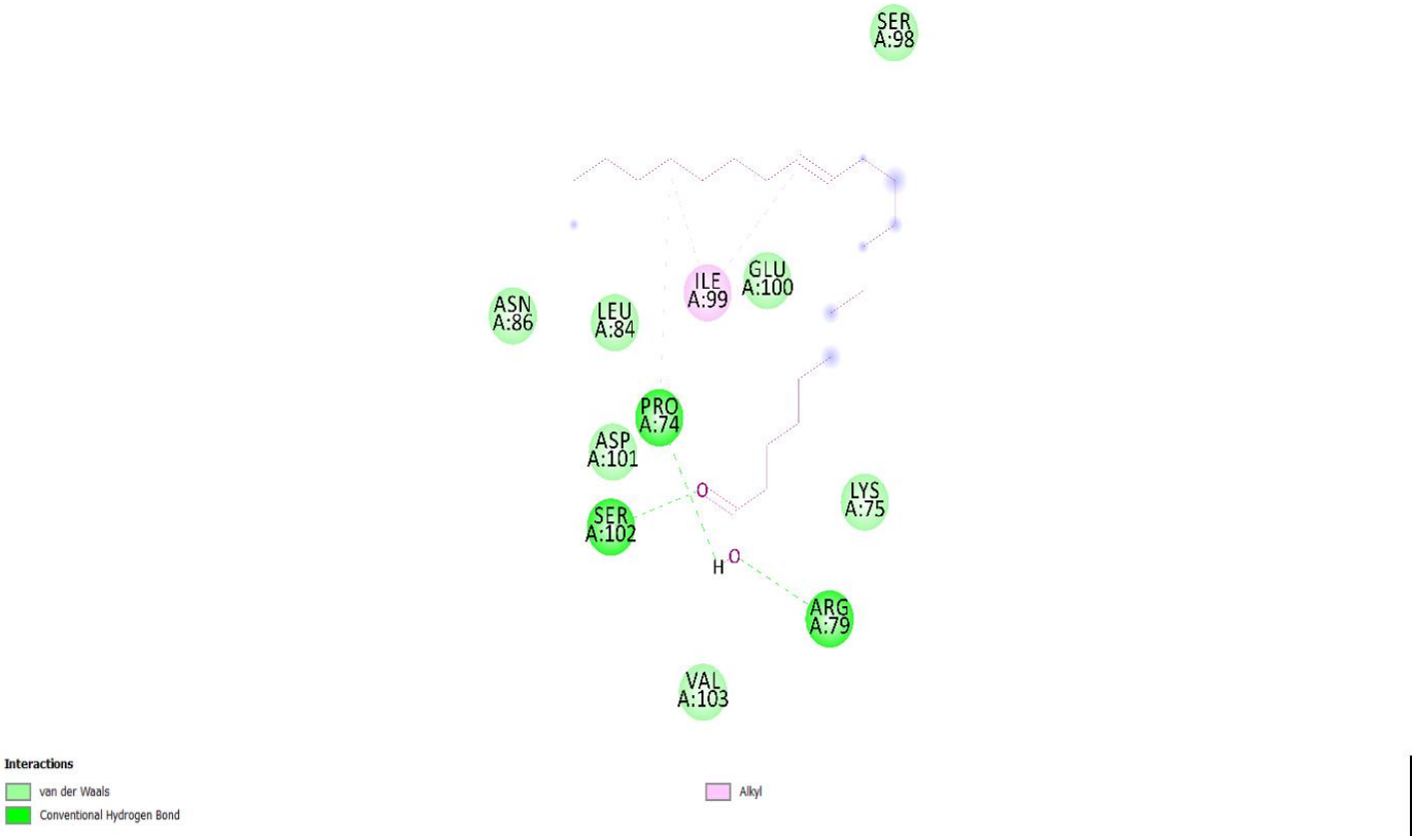


Figure 2: (A): 3D Image of Docked Pose of RIL with Target Protein- 5YTU.

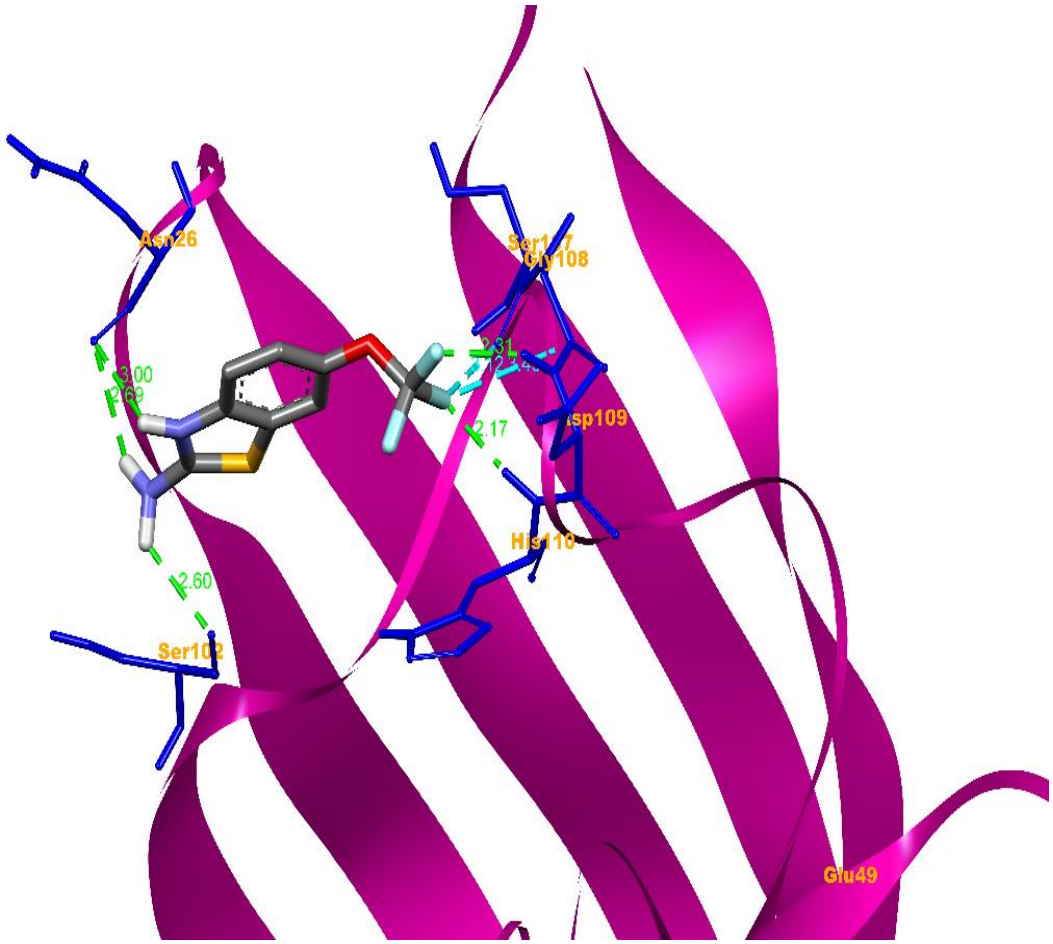
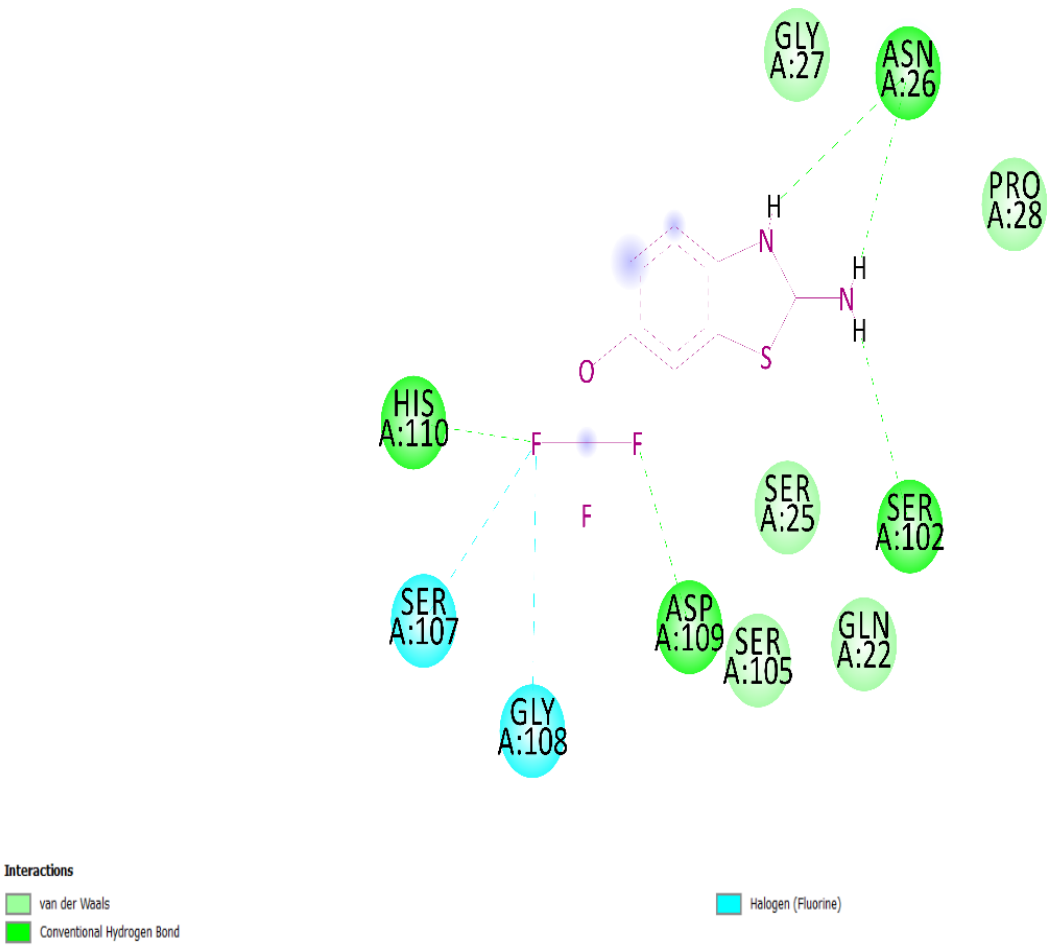


Figure 2: (B): 2D Image of Docked Pose of RIL with Target Protein- 5YTU.



Molecular Docking Analysis of D2 Receptor Proteins and 5HT2C Receptor Protein with EA, RIL & LA:

D2 receptor proteins- 6CM4 protein had a grid center set at X= 24.01, Y= 0.58, and Z= 11.22 with grid sizes of 89.63, 59.62, and 87.61 XYZ points, and 6LUQ protein had a grid center set at X= 23.93, Y= 1.58, Z= 13.71 with grid sizes 78.24, 68.96, 87.84 XYZ points, with 0.5Aº of grid spacing each by keeping all parameters in defaults for docking. However, the grid center for 5HT2C receptor protein (6BQH) was set at X= 47.38, Y= 33.85, Z= 35.31 with grid sizes 64.46, 58.25, 94.34 XYZ points with grid sizes 78.24, 68.96, 87.84 XYZ points, by just leaving all docking parameters at their default levels, resulting in grid spacing of 0.5Aº each.

Molecular docking results revealed that the interaction of EA and RIL with proteins (6CM4; 6LUQ) was not found to be analogous. The molecular docking results of proteins with EA, RIL, and LA (Table 2).

However, further molecular docking study revealed that the interaction of EA and RIL with 6BQH protein was found to be analogous i.e. they both bound to the same amino acids- SER A: 219 & VAL A: 215 (Table 3 & Figure 3&4). Since EA and the 5HT2C receptor interacted, molecular docking studies may have indicated that EA's anti-parkinsonian efficacy is derived from this connection.

Table 3: Molecular Docking ResultsofD2 Receptor Proteins and 5HT2C Receptor Protein with EA, RIL & LA

Compounds	Binding energy (kcal/mol)			Hydrogen bonds			Interactions		
	6CM4	6LUQ	6BQH	6CM4	6LUQ	6BQH	6CM4	6LUQ	6BQH
EA	-4.7	-4.6	-5.7	1	2	2	VAL A: 417	TYR A:239, GLU A: 232	SER A:219, VAL A: 215
RIL	-5.6	-5.8	-7.1	3	3	2	TYR A: 1088, ARG A: 220, ALA A: 1093)	GLY A:98 (2), THR A: 433	SER A: 219, VAL A: 215
LA	-4.7	-4.5	-5.8	1	1	1	LEU A: 40	THR A: 433	ASP A:134

Figure 3: (A): 3D Image of Docked Pose of EA with Target Protein- 6BQH.

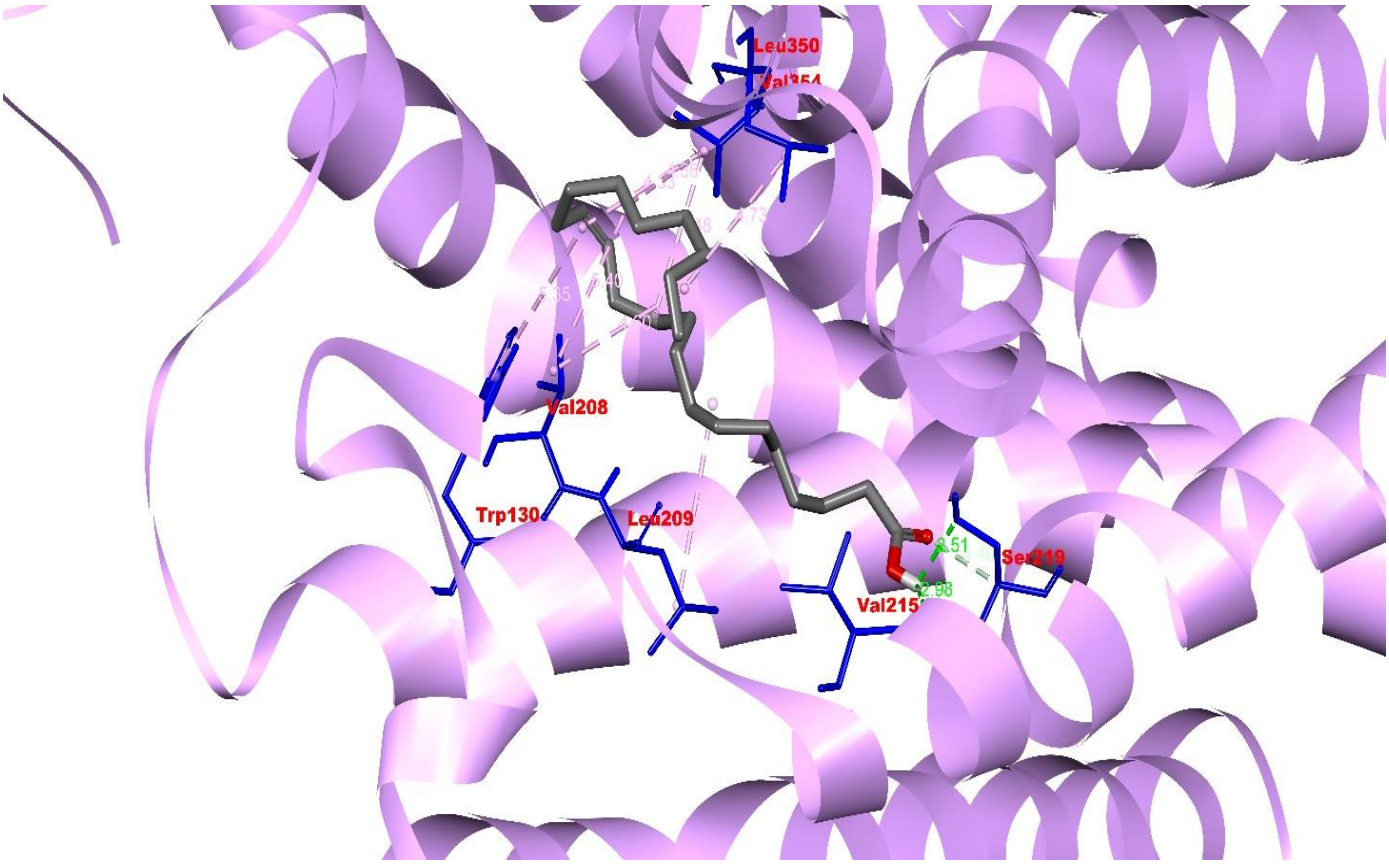


Figure 3: (B): 2D Image of Docked Pose of EA with Target Protein- 6BQH.

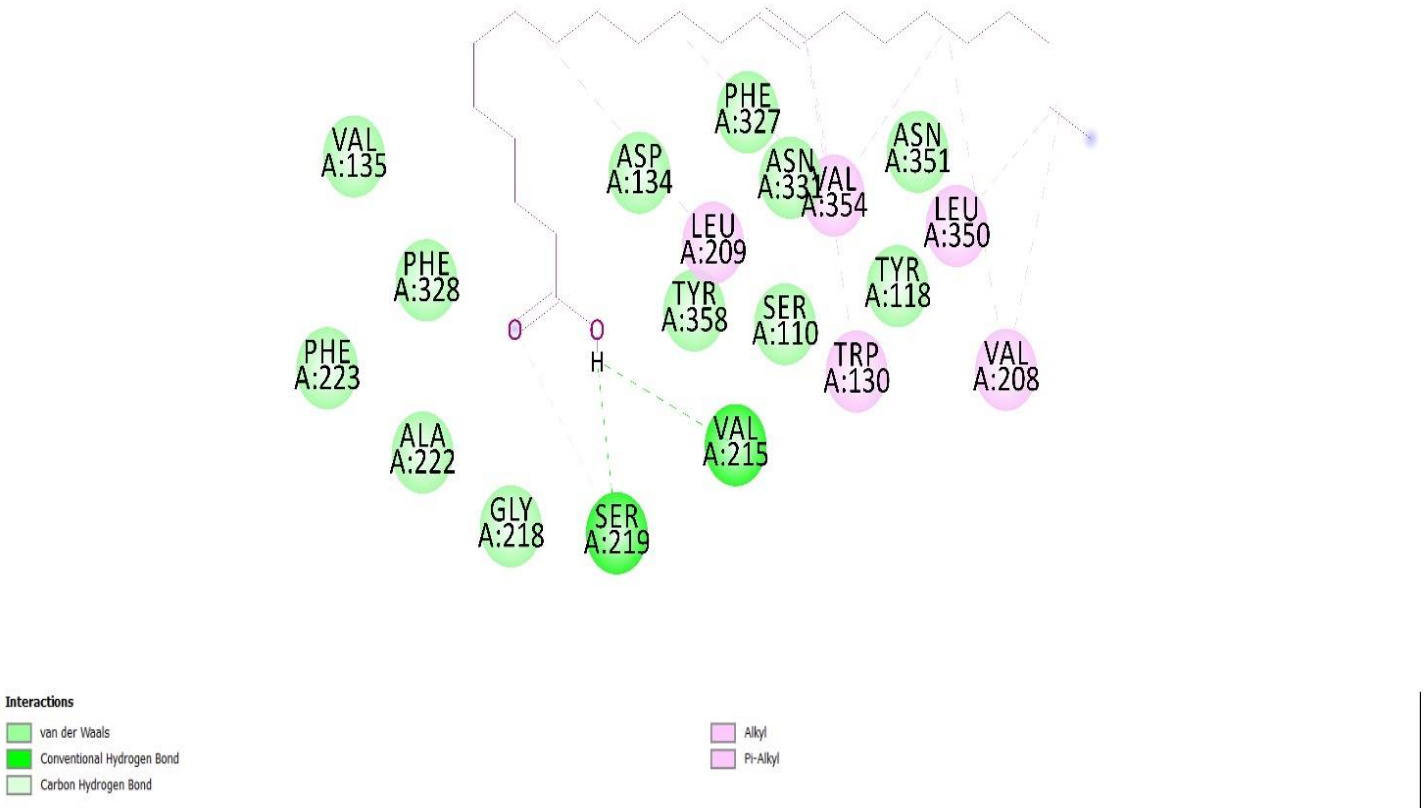


Figure 4: (A): 3D Image of Docked Pose of RIL with Target Protein- 6BQH.

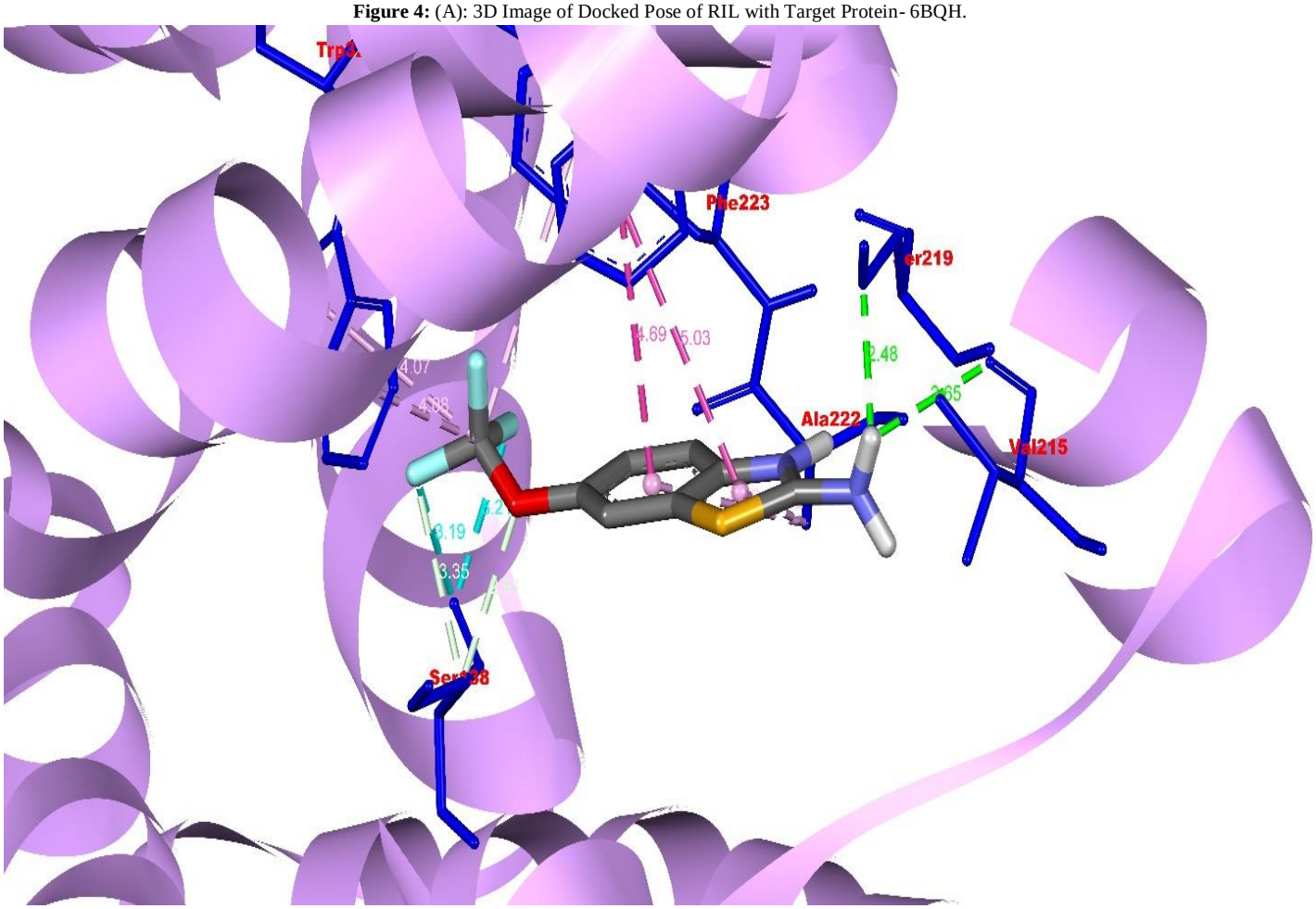


Figure 4: (B): 2D Image of Docked Pose of RIL with Target Protein- 6BQH.ADME-T Study of EA, LA & RIL

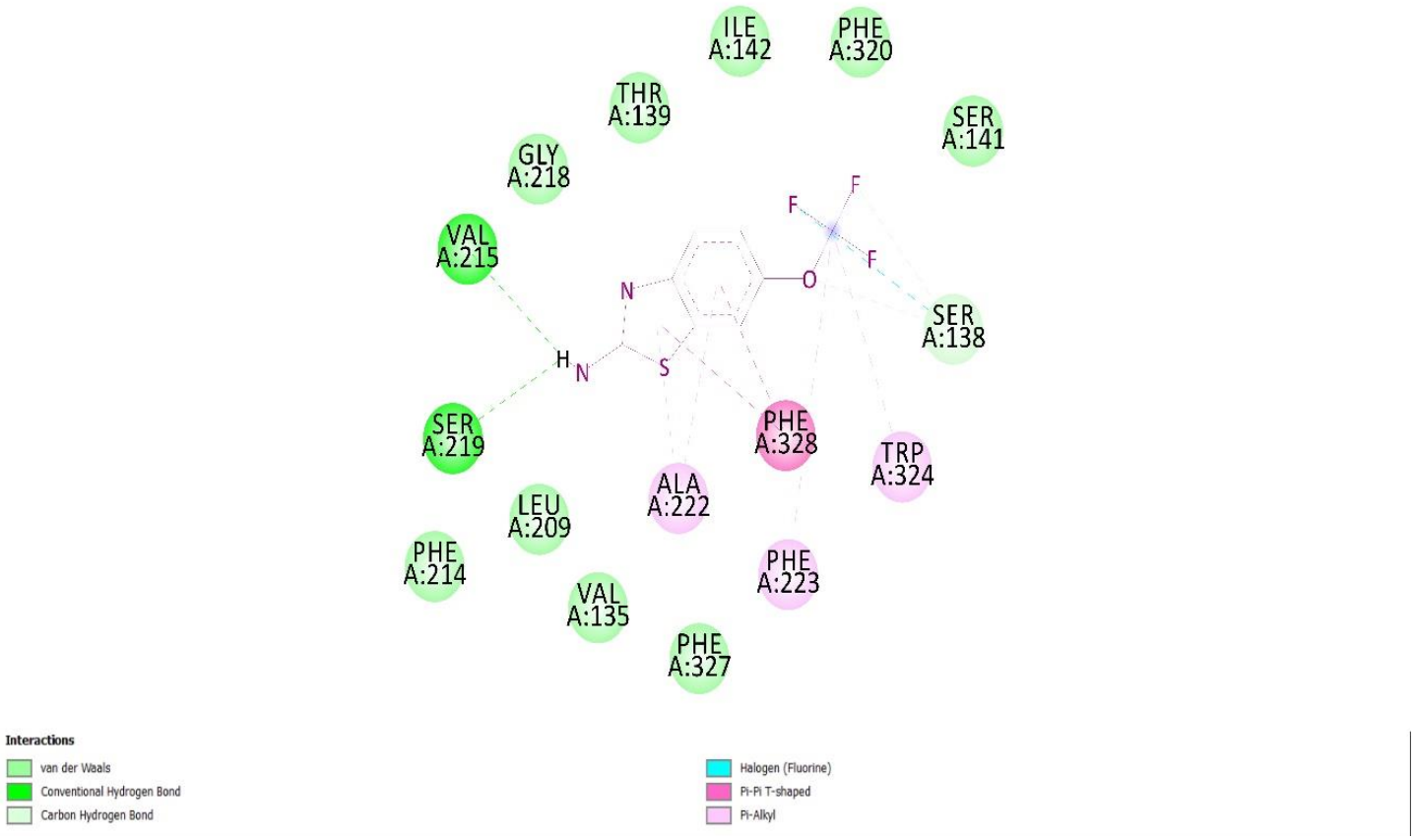


Table 4: ADME-T study of EA, LA & RIL

Parameters assessed	Compounds		
	EA	**LA**	**RIL**
Intestinal absorption	87.886	92.329	90.475
Skin permeability	-2.727	-2.723	-2.883
Caco-2-permeability	1.286	1.57	1.333
Volume of distribution	-0.497	-0.587	0.143
BBB permeability	-0.52	-0.142	0.153
CNS permeability	-0.832	-1.6	-2.489
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	Yes	Yes	No
Total clearance	2.012	1.936	0.259
AMES	No	No	Yes
Hepatotoxicity	No	Yes	Yes
LD_{50}	2.953	1.429	2.569
Class	5	3	5

ADME-T Study of EA, LA & RIL

All the drugs were well absorbed, distributed, and, excreted as anticipated by ADME-T tests using the pkCSM tool (Table 4). For example- (i) intestinal absorption was confirmed to be 87.886%, 92.329 %, and 90.475 % for EA, LA, and RIL respectively with maximum intestinal absorption of LA; skin permeability (log K_p) ranged from -2.727 to -2.883 cm/h (<-2.5); (iii) The compounds' Caco-2 permeability values (log Papp) ranged from 1.286 to 1.57 cm/s. (> 0.90 cm/s) with LA having the highest Caco-2 permeability; (iv) Volume of distribution (VDs) for all the compounds vary from -0.587 to 0.143 [log VDs > 0.45 is classified as high, while log VDs <-0.15] is classified as low]; (v) log BB values of the compounds ranged from -0.52 to 0.153 which is >-1 [19], indicating that all of the compounds were projected to substantially pierce the blood-brain barrier (BBB); (vi) the compounds log PS values ranged from -2.489 to -0.832. Compounds with a log PS > -2 are believed to be permeable to the central nervous system (CNS), whereas those with a log PS >-3 are believed to be impenetrable [19]. Therefore, EA and LA with log PS values of -0.832 and -1.6 respectively can easily permeate the CNS; (vii) None of the compounds affected or inhibited the CYP2D6 enzyme, but EA and LA do so for the CYP3A4 enzyme; (viii) the CL_{tot} value of the studied compounds ranged from 0.259 to 2.012 ml/min/kg, and it forecasts drug excretion rates in the order shown below: EA>LA>RIL; (ix) RIL has mutagenic effects while EA and LA did have mutagenic effects; (x) the range of predicted LD_{50} values for the compounds was between 1.429 kg/mol - 2.953 kg/mol. The acute toxicity class of chemicals is often divided into six categories: category 1 (LD_{50} = ≤ 5mg/kg), category 2 (LD_{50} = > 5 ≤ 50 mg/kg), category 3 (LD_{50} = > 50 ≤ 300 mg/kg), category 4 (LD_{50} = >300 ≤ 2000 mg/kg), category 5 (LD_{50} = > 2000 ≤ 5000 mg/kg), category 6 (LD_{50} = > 5000 mg/kg) [19]. On this basis, EA and RIL belong to category 5, which indicated that they were relatively low acute toxic compounds when compared to LA which belongs to category 3.

DISCUSSION

Omega-3 and omega-6 PUFAs are involved in a variety of biochemical processes, which contribute to the well-established positive effects on neurodegenerative diseases (NDs). Similar to this, it has been proposed that omega-9 MUFAs, such as oleic acid, play a part in the metabolism of essential fatty acids and the control of anti- and pro-inflammatory mechanisms.

Mustard oil, Rapeseed oil, and canola oil all contain EA as one of their major components and these oils serve as important global sources of vegetable oil for dietary needs. Mustard oil is the most preferred cooking oil among the rural population in north and east India due to its high smoke point (250°C), and nutty, and sour flavor [20]. EA was reported to have cardiac toxic effects in some countries and therefore its permissible limit was fixed by many regulatory agencies across the world. For instance, EA was designated as a natural toxin under the Joint Food Standards Code of Australia and New Zealand, and the maximum quantity in edible oils was established at 20 g/kg (2%) [21].Additionally, 7.5 mg/kg body weight of EA was established as the acceptable daily dosage [22].The maximum level of EA has also been set by the European Union at 5% of all fatty acids (Council Directive 76/621/EEC, 1976). However, India does not have such a law. Contrarily, epidemiological studies carried out among Indians show that ingesting mustard oil can reduce the incidence of coronary heart disease [20]. Also, many studies were conducted earlier which revealed the neuro protective nature of EA. Therefore, exploring different molecular targets of EA for its anti-parkinsonian properties is very necessary.

Drug-likeness analysis, which focuses on assessing the solubility, absorption, and permeability of medications taken orally, cannot be separated from drug research and discovery despite the fact that metabolic processes might alter the physicochemical features of therapeutics. The most frequently applied rule in the drug-likeness analysis is Lipinski's rule of five. According to the five-point rule of Lipinski, EA, LA, and RIL were all found to be similar drugs.

In our study, oxidative enzyme proteins and neurotransmitter receptor proteins were explored as molecular targets for EA for its anti parkinsonian potential using molecular docking studies.

According to the outcomes of molecular docking investigations with oxidative enzymes as target proteins, EA and the common medicine RIL exhibited antioxidant action by binding to the same amino acid, SER A: 102, of the SOD1 enzyme.

Similarly, molecular docking investigations with D2 receptors as target proteins were carried out. The results obtained from these molecular docking studies revealed that the interaction between EA and D2 receptor proteins (6CM4 and 6LUQ) was not matching with the interaction between RIL and D2 receptor proteins. However, the binding interaction of EA and RIL with 5HT2C receptor protein

(6BQH) was found to be analogous to EA and RIL as they both bound to the same amino acids i.e. SER A: 219 and VAL A: 215.

A chemical that enters the human bloodstream at least 90% of the time has proven to be absorbed well [23]. Additionally, absorption by oral medicines is also influenced by the Caco-2 permeability parameter across the intestinal epithelium [24].After being absorbed, medications are subsequently dispersed throughout the body. The drug's capacity to cross the BBB indicates that compounds can enhance the physiological activity and regeneration in the brain, which can help the brain fight off neurodegenerative disorders. [23]Following the distribution, the medication is metabolized. Most of the compounds get quickly metabolized by appropriate CYP450 enzymes [25]. The proportionality constant measures the amount of drug clearance that is primarily a combination of renal and hepatic clearance.

Therefore, based on the two molecular docking studies conducted, one can link that EA might show its anti-parkinsonian potential as an antioxidant via binding to SOD1 or via binding to the 5HT2C receptor. Additionally, a favorable ADME-T profile can help in the development of anti-parkinsonian drugs, and all of the compounds under investigation met the criteria for pharmacological similarity.

CONCLUSION

India is fortunate in having a wide range of oilseed crops grown in its different agro climatic zones. Mustard-rapeseed oil has long been one of the most consumed edible oil in India especially in rural areas. Erucic acid obtained from mustard oil was recently reported to have memory enhancing effect on scopolamine-induced cognitive impairment in rats. Therefore, we hypothesis that erucic acid might have a positive health benefit in Parkinson's disease in which cognitive impairment is a common non-motor complication associated with Parkinson's disease. So, molecular docking studies and ADME-T profile to observe the anti-parkinsonian activity of erucic acid was conducted in this study.

Erucic acid was shown to have an affinity for the protein targets superoxide dismutase (SOD1) and to 5-Hydroxytrytamine (5H2TC) when compared to Riluzole (Reference drug), along with good ADME-T properties. However, erucic acid may be effective against additional targets of Parkinson's disease and other neurodegenerative diseases, but more research is required to determine this.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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