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Molecular Docking, In-Silico Admet Screening Of Farnesol as Alpha Synuclein, Uchl-1 and Comt Inhibitors

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ABSTRACT: Objective: To perform molecular docking studies of farnesol with various targets such as alpha synuclein, UCHL-1, COMT inhibitors and in-silico ADMET screening of the selected compound.**Methods:** In the present in-silico study, bioactive compound farnesol were analysed for their inhibitory role on alpha synuclein, UCHL-1 and COMT activity by applying the molecular docking studies. The molecular docking and ADMET screening were carried out by using Accelrys Discovery Studio 4.1 client.**Results:** The docking energy of farnesol with alpha synuclein showed binding energy level -53.70 kcal/mol whereas clenbuterol(S) showed binding energy 5.32 kcal/mol. Farnesol with UCHL-1 showed binding energy -32.0 kcal/mol whereas L-Dopa(S) showed binding energy 30.33 kcal/mol. Farnesol with COMT showed binding energy -32.06 kcal/mol whereas Tolcapone(S) showed binding energy 31.67 kcal/mol. The compound Farnesol has excellent binding energy with good ADMET properties.**Conclusion:** These results clearly revealed that the bioactive compound farnesol have good binding interactions with alpha synuclein, UCHL-1, COMT when compared to the standard drugs.

KEYWORDS: Parkinson's disease, Molecular docking, Alpha synuclein, UCHL-1, COMT, ADME/Tox.

I.INTRODUCTION

Neurodegenerative diseases affect millions of people worldwide, in which progressive loss of structure and functions of neurons including neuronal death is observed. Alzheimer's and Parkinson's disease are the most common type in which parkinson's disease progresses slowly as small clusters of neurons in the midbrain die. The gradual loss of these neurons reduces level of chemical called dopamine, which is responsible for transmitting messages to the part of the brain that coordinate muscle movement. Common symptoms includes tremors or shaking in hands, arms, legs, jaw and face; rigidity or stiffness of the limbs and trunk; bradykinesia or slowness of movement; and difficulties with balance, speech and coordination. Symptoms of Parkinson's disease begin gradually and typically worsen over time.

The genes responsible for the cause of disease includes alpha synuclein, ubiquitin carboxy-terminal hydrolase-1 (UCHL-1), catechol-o-methyltransferase (COMT). Alpha synuclein is a protein that, in humans, is encoded by the SNCA gene. It is found abundant in the brain, mainly at the tip of nerve cells called neurons in specialized structures called presynaptic terminals. They go on to accumulate in large masses termed 'Lewy bodies' and these clumps are now associated with brain cell death; the process involved in the aggregation of these misfolded proteins may be a trigger of parkinson's disease. The UCHL-1 enzyme is involved in the ubiquitin proteasome system, a cellular pathway responsible for the degradation of misfolded and damaged proteins. The ubiquitin proteosome system play an important role in the etiology of parkinson's disease. UCHL-1 protein is especially abundant in the brain and has been localized to Lewy bodies and other inclusion characteristic of human neurodegenerative diseases. UCHL-1 protein expression is specific to neurons, cells of the neuroendocrine system. COMT is an enzyme that metabolizes or degrades neurotransmitters such as dopamine. The motor symptoms of Parkinson's disease are caused by the reduction in dopamine, which transmits signals in the brain to produce smooth, purposeful movement.

Farnesol is a natural 15-carbon organic compound which is an acyclic sesquiterpene

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alcohol. Farnesol is produced from 5-carbon isoprene compounds in both plants and animals. Farnesol is present in many essential oils such as citronella, neroli, cyclamen, lemon grass, tuberose, rose, musk, balsam and tolu. It is used in perfumery to emphasize the odors of sweet floral perfumes. Farnesol has several beneficial activities such as anti-inflammatory, antioxidant, and anti-allergic properties.

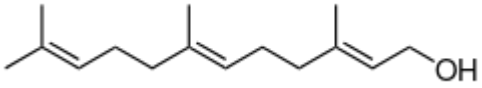

Figure 1. Structure of (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode of a ligand with a protein of known three-dimensional structure. The main objective of the study was to perform molecular docking of farnesol with alpha synuclein, UCHL-1, COMT to determine its binding efficacy and the ADMET properties of the selected compound.

II.MATERIALS AND METHODS

Preparation of ligand

The chemical structure of farnesol were downloaded from Pubchem database with possible structure definition file format for docking studies.

Preparation of protein target

The crystal structure of alpha synuclein (2KKW), UCHL-1(3IRT), COMT (4XUE) was downloaded from RCSB PDB and the protein was prepared for molecular docking using the protocol. The protein was prepared by eliminating the unessential water molecules, heteroatoms present, small ions, and alternate confirmations; completing the structure by modelling the missing loop, inserting the missing atoms. Checking the potential energy, Vander Waals energy, electrostatic energy and RMS gradient of the complex before and after protein minimization and then fully merging the hydrogen to the target molecule using Accelrys discovery studio 4.1 client.

Prediction of binding site

The binding sites of preferred target protein alpha synuclein (2KKW), UCHL-1 (3IRT), COMT (4XUE) were analysed using Accelrys discovery studio 4.1 to predict the ligand-binding site.

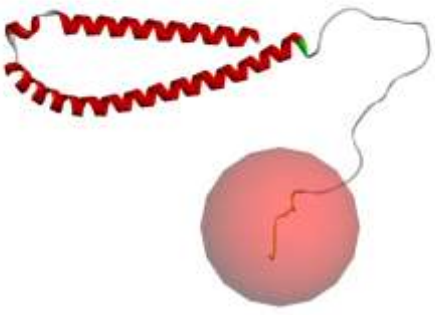

Figure 2. Binding site of Alpha synuclein

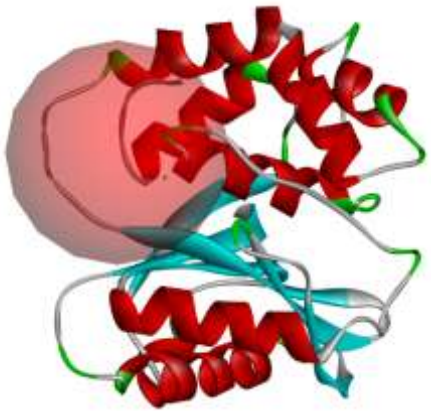

Figure 3.Binding site of UCHL1

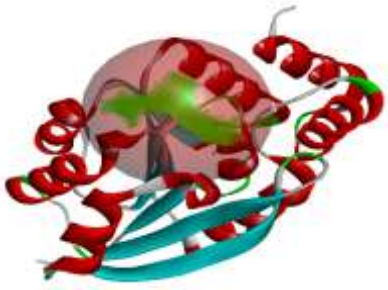

Figure 4. Binding site of COMT

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Molecular docking simulation

Molecular docking analysis of alpha synuclein, UCHL-1, COMT, was performed by Accelrys discovery studio 4.1 client. CDOCKER and ADMET studies were carried out and TOPKAT values were calculated for the compound.

CDOCKER studies

Interaction of ligand with many protein were treated to be fully flexible and protein rigid was evaluated. The compound were minimized and used as input ligand in the protocol explorer of CDOCKER. Molecular dynamic protocol was used to generate various conformations for ligand and the initially generated structures were refined using simulated annealing protocol. The type of interaction to be existed between the ligand and proteins were predicted.

ADMET studies

ADME properties of the compound were calculated using Accelrys Discovery studio 4.1 client. Solubility of the drugs in water at 25^{o}C, human intestinal adsorption level after oral administration, metabolism of the administered drug by the inhibition enzyme cytochrome P450 2D6 (CYP2D6) using 2D input, hepatotoxicity of the drug, Plasma protein binding extent, 95% and 99% confidence ellipses in the ADMET_PSA_2D, ADMET_AlogP98 plane were calculated.

TOPKAT studies

One widely used system to determine the carcinogenicity of the compound is TOPKAT (Oxford Molecular, Beaverton, OR). The predictions of carcinogenicity on descriptors of one- and two-atom fragment electro topological states. TOPKAT is designed to predict the carcinogenicity of chemicals independently in each of four rodent models: male rat, female rat, male mouse, and female mouse.

Docking

Drug compound that qualify the tests are docked with the receptors 2KKW, 3IRT, 4XUE using CDOCKER available on Accelrys Discovery studio 4.1 client. 30 poses were obtained (10 for each receptor). One with the minimum CDOCKER energy is considered to the best binding fit. Interaction of drug with that particular receptor is visualized and analysed.

III.RESULTS

The selected sesquiterpene farnesol and the synthetic drug Clenbuterol, L-Dopa, Tolcapone (standards) were docked in the active site of optimized and energy minimized Alpha synuclein, UCHL-1, COMT respectively. The results were analysed to identify natural compound with good inhibitory activity considering the interactions binding energy. The compound had very good interactions with active site residues. The interactions of Farnesol and Clenbuterol, L-Dopa, Tolcapone with their specific targets are shown in the figures.

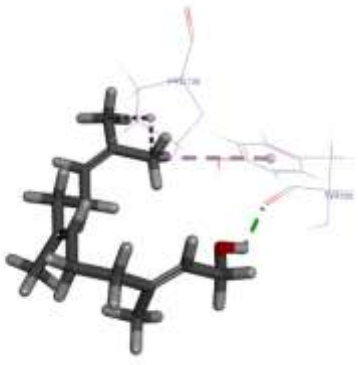

Figure 5
Interactions between alpha synucle in

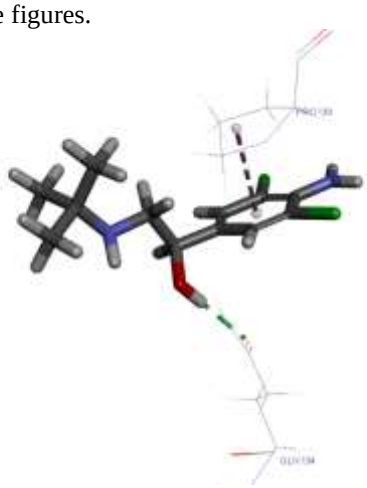

Figure 6
Interactions between alpha synuclein Farnesol and clenbuterol (S)

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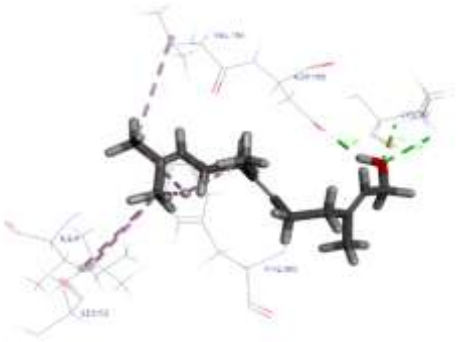

Figure 7
Interactions between UCHL-1 and L-Dopa (S)

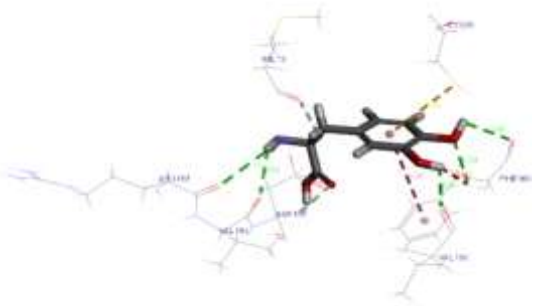

Figure 8
Interactions between UCHL-1 andFarnesol

Figure 9
Interactions between COMT and Farnesol

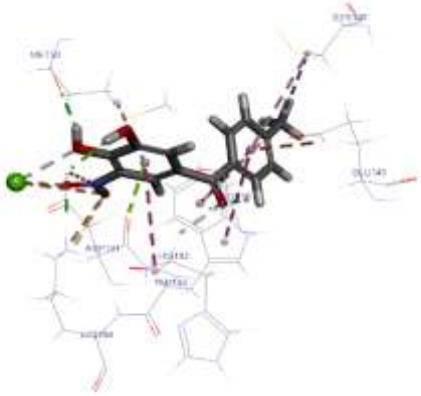

Figure 10
Interactions between COMT and Tolcapone(S)

Similarly, interactions of amino acid, H bond distance and CDOCKER energies of alpha synuclein, UCHL-1, COMT with Farnesol and standards Clenbuterol, L-Dopa, Tolcapone respectively are shown in the table 1-3.

Table No: 1 Interaction of amino acids, H-bonds distance and CDOCKER energies of Alpha synuclein with Farnesol and Clenbuterol

S. No	Ligand	Interaction of amino acids	Bond length(Å)	CDOCKER energies kcal/mol
1	Farnesol	TYR136, PRO138, PRO138, TYR136	2.05, 3.91, 5.06, 4.91	-53.70
2	Clenbuterol (S)	GLN134, PRO138	2.12, 5.02	5.32

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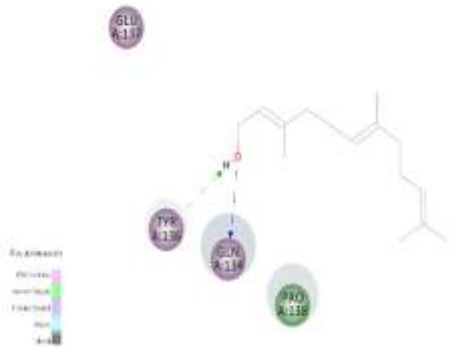

Figure 11
2D diagram for the binding site of Farnesol with alpha synuclein

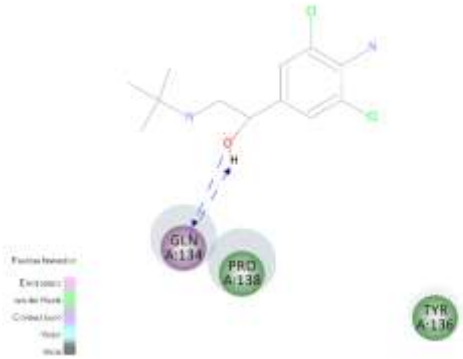

Figure 12
2D diagram for the binding site of clenbuterol with alpha synuclein

Table No: 2 Interaction of amino acids, H-bond distance and CDOCKER energies of UCHL-1 with Farnesol and L-Dopa

S. No	Ligand	Interaction of amino acids	Bond length(Å)	CDOCKER energies kcal/mol
1	Farnesol	LYS157, LYS 157, ASP155, ILE8, LEU52, VAL154, PHE 160, PHE 160, PHE160	2.15, 2.54, 1.96, 4.79, 5.22, 5.07, 4.90, 4.74, 5.37	-32.0
2	L-Dopa (S)	PHE160, ARG153, VAL154, VAL158, PHE160, ASP155, MET6, CYS90, PHE160	2.39, 3.09, 2.50, 2.28, 2.87, 2.75, 2.63, 5.34, 5.99	30.33

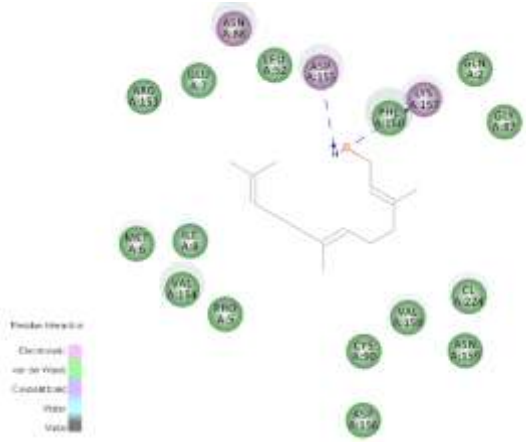

Figure 13
2D diagram for the binding site of Farnesol with UCHL-1

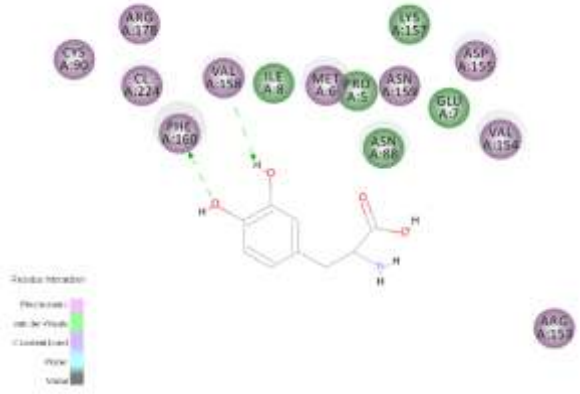

Figure 14
2D diagram for the binding site of L-Dopa with UCHL-1

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Table No: 3 Interaction of amino acids, H-bond distance and CDOCKER energies of COMT with Farnesol and Tolcapone

S. No	Ligand	Interaction of amino acids	Bond length(Å)	CDOCKER energies kcal/mol
1	Farnesol	ASN220, GLU249, ASN220, MG302, MET90, ILE141, ILE141, HIS192, TRP193	2.22, 1.87, 2.57, 2.31, 4.56, 4.54, 4.04, 5.05, 4.99	-32.06
2	Tolcapone (S)	LYS194, MG302, ASP191, LYS194, ASP191, MET90, GLY116, GLY116, HIS192, LYS194, MG302, MG302, GLU140, ASP191, TRP193, TRP193, HIS192, CYS145, TRP193, MET90, CYS145	3.60, 5.15, 5.17, 1.99, 2.06, 2.04, 2.39, 2.46, 2.36, 2.83, 2.79, 3.01, 3.60, 2.70, 5.34, 4.21, 5.11, 4.68, 5.19, 4.35, 4.99	31.67

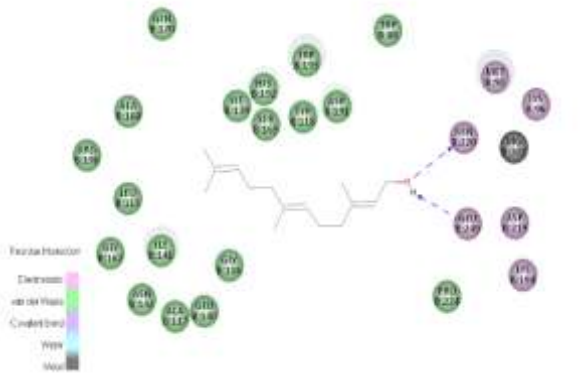

Figure 15
2D diagram for the binding site of Farnesol with COMT

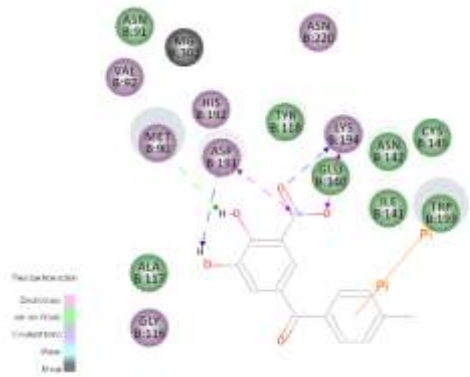

Figure 16
2D diagram for the binding site of Tolcapone with COMT

ADMET studies

The pharmacokinetic and pharmacodynamic properties of the selected compound are predicted through ADMET study; Adsorption, distribution, metabolism, excretion, and toxicity. Results are also gathered from the ADMET plot. The studies help in predicting and excluding compounds which may be toxic or may be unable to cross membrane. The predictions made through the studies are given in the following tables.

Table No: 4 Predicted values of log S, QP log w, QP log BB for farnesol

Compound	ADME solubility	ADME solubility level	ADME Alogp98	ADME BBB	ADME BBB level	Absorption level	ADME TPSA 28
Farnesol	-3.917	Good	4.76	0.988	Very high	Good	20.81

Table No: 5 CYP2D6 values for the compound

Compound	ADMET EXT CYP2D6	ADMET EXT CYP2D6 prediction	ADMET EXT CYP2D6 applicability
Farnesol	-0.315	FALSE	11.634

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Table No: 6 Hepatotoxicity prediction of the compound

Compound	ADMET EXT hepatotoxicity	ADMET EXT hepatotoxicity prediction	ADMET EXT hepatotoxicity applicability
Farnesol	-11.416	FALSE	8.954

Table No: 7 QP log PPB of the compound

Compound	ADMET EXT PPB	ADMET EXT PPB prediction	ADMET EXT PPB applicability
Farnesol	0.561	TRUE	10.55

TOPKAT values

After the ADMET studies the compound was screened further for prediction of toxicity using TOPKAT tool in discovery studio is to check its safety drugs approval and rejection by regulatory agencies which is decided after screening for mutagenicity which is performed in-vitro by Ames test. Ames test is to access the genotoxicity of the drugs which is related to direct (mutation inclusions involved in carcinogenesis) and indirect effects (surrogate events) in DNA there by leading to its mutations.

Table No: 8 TOPKAT values for the compound

Compound	Mouse F NTP	Mouse M NTP	Rat F FDA	WOE	Rat oral LD50	Rat inhalational LC50	Carcinogenic potency TD50 mouse	Chronic LOAEL	Daphnia EC50
Farnesol	NC	C	SC	C	5.48	5,981.7	53.18	0.149	3.262

Table No: 9 TOPKAT Values

Compound	Skin sensitization	Ocular irritancy	Ames prediction
Farnesol	None	None	Non mutagen

IV.DISCUSSION

The docked pose of Alpha synuclein, UCHL-1, COMT with Farnesol and Clenbuterol, L-Dopa, Tolcapone is shown in figures 5-10. This clearly revealed the binding positions of the ligand with their targets. In most of the potent therapeutic target, hydrophobic and H-bond interactions plays an important role for mediating the biological activity.

Table 1: The compound showed CDOCKER energy -53.70 Kcal/mol when compared to the standard Clenbuterol (5.32Kcal/mol). Further, the compound Farnesol exhibited hydrogen bond, and hydrophobic bond interactions with alpha synuclein. The H bond interactions are similar between the compound and the standard whereas there are one more hydrophobic interaction has been observed between farnesol and TYR136 and PRO 138. Whereas, Clenbuterol (S) exhibited hydrogen bond and hydrophobic interactions with alpha synuclein. H bond interactions were seen between clenbuterol and GLN134. Hydrophobic bond interactions were seen between clenbuterol and PRO138.

Table 2: The Compound showed CDOCKER energy -32.0 Kcal/mol when compared to the standard levodopa (30.0 Kcal/mol). Further, the compound Farnesol exhibited hydrogen bond, hydrophobic bond interactions with UCHL-1. H bond interactions were seen between Farnesol and LYS157, ASP155. Hydrophobic bond interactions were seen between Farnesol and ILE8, LEU52, VAL154, PHE160. Whereas, Levodopa (S) exhibited hydrogen bond, hydrophobic bond, and other interactions with UCHL-1. H bond interactions were seen between levodopa and PHE160, ARG153, VAL154, VAL158, PHE160, ASP155, MET6. Hydrophobic bond interactions

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were seen between levodopa and PHE160, and other interactions were seen between levodopa and CYS 90. Whereas, Levodopa (S) exhibited hydrogen bond, hydrophobic bond, and other interactions with UCHL-1. Hydrogen bond interactions were seen between levodopa and PHE160, ARG153, VAL154, VAL158, PHE160, ASP155, MET6. Hydrophobic bond interactions were seen between levodopa and PHE160. Other interactions were seen between levodopa and CYS 90.

Table 3: The Compound showed CDOCKER energy -32.06 Kcal/mol when compared to the standard Tolcapone (31.67 Kcal/mol). Further, the compound Farnesol exhibited hydrogen bond, hydrophobic bond and other interactions with COMT. H bond interactions were seen between Farnesol and ASN220, GLU249, ASN220. Hydrophobic interactions were seen between Farnesol and MET90, ILE141, ILE141, HIS192, TRP193. And other interactions were seen between Farnesol and MG302. Whereas, Tolcapone (S) exhibited hydrogen bond, hydrophobic bond, electrostatic bond and other interactions with COMT. H bond interactions were seen between Tolcapone and LYS194, ASP191, MET90, GLY116, GLY116, HIS192, LYS194. Hydrophobic interactions were seen between Tolacapone and TRP193, HIS192, CYS145, TRP193, MET90, CYS145. Electrostatic bond interactions were seen between Tolcapone and LYS194, MG302, ASP191, GLU140. Other interactions were seen between Tolcapone and MG302, ASP191.

As per in silico ADME result, the compound obey Lipinski rule of five. Hence, the compound can reach its target site by crossing Blood Brain Barrier and doesn't show toxicity for the compound. Molecular docking studies of Farnesol exhibited better binding interactions with alpha synuclein, UCHL-1 and COMT.

V.CONCLUSION

The results of the present study clearly revealed that Farnesol had good inhibitory activity against Alpha synuclein, UCHL-1, COMT than the standards Clenbuterol, L-Dopa, Tolcapone respectively. Hence, Farnesol showed better binding affinity with all the three targets namely Alpha synuclein, UCHL-1 and COMT when compared to the standards. Further investigations on the compound Farnesol are necessary to develop potential entities for the treatment of Parkinson's disease.

REFERENCES

[1]. Frederico F Ribeiro, Francisco J B Mendonca Junior Jahn B Ghasemi, Hamilton M Ishiki, Marcus T Scotti, Luciana Scotti. Docking of natural products against neurodegenerative diseases: General Concepts. Bentham Science Publishers. 2018; 21: 1-9.

[2]. A Jagan Mohan Reddy, T Parthasarathy. Designing of potent drug to Target Alpha Synuclein in Parkinson's Disease. Journal of Applied Chemistry. 2017; 10: 15-18.

[3]. Clemens R Scherzer. β2- Adrenoreceptor is a regulator of the alpha synuclein gene driving risk of Parkinson's Disease. Science. 2017; 357(6354): 891–898.

[4]. David A Boudreaux, Tushar K Maiti, Christopher W. Davies, Chittaranjan Das. Ubiquitin vinyl methyl ester binding orients the misaligned active site of ubiquitin hydrolase UCHL-1 into productive conformation. Proceedings of the National Academy of Sciences. 2010; 107: 9117-9122.

[5]. Scott E Wolkenberg. Synthesis and Evaluation of heterocyclic catechol mimics as inhibitors of catechol-o-methyltransferase. Medicinal Chemistry Letters. 2015; 6: 318−323.

[6]. Ruchi Yadav, Akanksha. Molecular docking studies of Resveratrol against neurodegenerative diseases. Journal of Chemical and Pharmaceutical Sciences. 2016; 4: 43-48.

[7]. Priya Nagappan, Vijayalakshmi Krishnamurthy. Structural prediction and comparative molecular docking studies of hesperidin and L-Dopa on A-synuclein, MAO-B, COMT and UCHL-1 inhibitors. International Journal of Pharmaceutical and Clinical Research. 2015; 7(3): 221-225.

[8]. Youssef Moutaouakkil, Ilham Kandousi, Youness Boukharsa, Ahmed Bennana, Yahia Cherrah, Yassir Bousliman et al., Docking of novel reversible monoamine oxidase-B inhibitors and their Anti-Parkinsonian efffect. Journal of Chemical and Pharmaceutical Research. 2017; 9(11): 216-219.

[9]. Michel Geodert, Masami Masuda-Suzukake, Benjamin Falcon. Like prions: the propagation of aggregated tau and alpha synuclein in neurodegeneration. A Journal of Neurology. 2017; 140: 266-278.

[10]. Carole J Proctor, Paul J Tangeman, Helen C Ardley. Modelling the role of UCHL-1 on protein aggregation in age-related neurodegeneration. Public Library of Sciences. 2010; 5(10): 1-12.
[11]. Mizuno Y, Hattori N, Kitada T, Matsumine H, Mori H, Shimura H, Kubo S, Kobayashi H et al. Familial Parkinson's disease. Alpha synuclein and Parkinson. Advances in Neurology. 2001; 86: 13-21.
[12]. Nagatsu T and Sawada M. L-Dopa therapy for Parkinson's disease: Past, present, and future. Parkinsonism and related disorders. Elsiever. 2009; 15(1): 3-8.
[13]. Schulz-Schaeffer WJ. The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathologica. 2010; 120(2): 131-143.
[14]. Leroy E, Boyer R, Auburger G, Leube B, Ullm G, Mezey E et al. The ubiquitin pathway in Parkinson's disease. Nature. 1998; 395(6701): 451-452.