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In Silico Molecular Docking Analysis of Potential Anti-Alzheimer's Compounds Present in Occimum Santum

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Abstract

Objective: Alzheimer's disease (AD), a progressive neurodegenerative disorder with many cognitive and neuropsychiatric symptoms, is biochemically characterized by a significant decrease in the brain neurotransmitter Acetylcholine (ACh).

Methods: : In the present insilico study, four plant bioactive compounds of *Ocimum sanctum* were analyzed for their inhibitory role on AChE (Acetylcholinesterase) and BChE (Butyrylcholinesterase) activity by applying the molecular docking studies. Other parameters viz. determination of molecular interaction-based binding affinity values, protein-ligand interactions, Lipinski rule of five, functional properties and biological activities for the above compounds were also calculated by employing the appropriate bioinformatics tools. The active compounds is to reveal its potentiality by molecular docking analysis to find out its potent compound against alzheimer's disease which was done by Lipinski's rule in docking analysis.

Results: A wide range of docking score found during molecular docking analysis. Among the compounds Eugenol, α – Farnesene, Benzene, 1, 2- dimethoxy-4-(1-propenyl) and Cyclohexane, 1, 2, 4-triethenyl is found to be a good inhibitor of 4 well-known drug targets. This is an effective lead molecule that can be used in the treatment of Alzheimer's disease.The results of docking analysis clearly showed that Cyclohexane-1, 2, 4-triethenyl has highest binding affinity with AChE and BChE

Conclusion: Cyclohexane-1, 2, 4-triethenyl and other compounds are inhibiting of both, as it possessed best value in Molecular docking hence these are the potent anti-alzheimer's agent.

Keywords: Ocimum sanctum; Molecular docking; Alzheimer's disease; Eugenol

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Introduction

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by progressive loss (and even death) of structure and function of neurons, and have created great burden to the individual and the society. The actual cause of various neurodegenerative diseases still remains a mystery in healthcare. Some of the commonly studied showed that the causes for neurodegenerative diseases are protein degradation, oxidative stress, inflammation, environmental factor, mitochondrial defects, familial history, and abnormal protein accumulation in neuron. Medicinal plants like Withaniasomnifera (ashwagandha), Ginseng,curcumin,resveratrol, Baccopamonnieri, Ginkgo biloba, and Wolfberry have been applied to prevent or alleviate neurological diseases and relief of neurological symptoms reported in in vivo or in clinical trials [1, 2]. Alzheimer's disease is a life-threatening neurodegenerative disorder. About 50 million people across the globe are affected by this disease. The risk percentage of AD is rising gradually throughout worldwide. As per the recent WHO reports 20 million people are in advanced stage of AD [3]. Acetylcholine, a neurotransmitter released by nerve cells acts as a signal intermediate between two nerve cells [4].Pathological character of acetylcholine depletion in the brain is due to increased levels of Acetycholinesterase (AChE),

an enzyme that catalyzes acetylcholine hydrolysis. Another therapeutic target of AD viz. the Butyrylcholinesterase (BChE) also shows significantly more than 50% sequence similarity with AChE [5]. Moreover, the function and location of BChE is very similar to Acetycholinesterase. These two therapeutic targets of AD are essential for termination of nerve impulse transmissions at cholinergic synapses by rapid hydrolysis of acetylcholine and this can be counteracted by using therapeutically and biologically active compounds. As per the cholinergic hypothesis, AChE and BChE hydrolytic enzymes detected in neurofibrillary tangles and neuritic plaques in the brain, act on ACh and Butyrylcholine to terminate its actions in the synaptic cleft by cleaving the neurotransmitter to choline and acetate. It was suggested that AChE predominated in the healthy brain, whereas BChE considered playing a minor role in regulating brain ACh levels. However, BChE activity progressively increases in patients with AD, while AChE activity remains unchanged or declines. Although no successful therapies are currently available that can modify the disease. The major application is computeraided drug design, in which structure-based drug design (SBDD) plays a very important role in identification of new drugs against the selected therapeutic targets. SBDD requires knowledge on biological therapeutic target, aims to discover small molecules (ligands) with desired chemical or drug properties. This approach provides an idea regarding interaction of target and ligands by creating biological environment computationally. Ocimum sanctum (Tulsi) is a member of family Lamiaceae. Literally Tulsi means “Matchless one”. Also, known as “Queen of Herbs”[6]. (Incomparable one) (Babita Labh Kayastha). Tulsi (Ocimum sanctum Linn.), commonly known as Holy Basil, is an herbaceous plant found throughout the south Asian region. Different parts of plant are used in ayurveda and siddha systems of medicine for prevention and cure of many illnesses [7, 8].From literature; it is known that Tulsi has been utilized therapeutically since 400-500 BC. Earliest references of Tulsi were found in Rigveda (3500-1600 BC). Therapeutically it is used in anticancer, anti-oxidant, anti-diabetic, radiations, infertility and for many other major and minor diseases [9, 10]. Being adaptogenic, Tulsi is used to improve health. Extract of Tulsi is used in ayurvedic treatments for common cold, heart diseases, and stomach disorders, poisoning cases, convulsions, epilepsy, malaria, fever, bronchitis and certain inflammatory problems [11,12]. Therefore, extract of Tulsi is also known as “Extract of Life” and considered to grant longevity. Thus in view of this, the present study was carried out to evaluate the anti alzhemers properties of Ocimum sanctum.

Materials and Methods

In silico analysis Molecular docking analysis of isolated compounds

Molecular docking studies on the above mentioned selected compounds against AChE and BChE was done in auto dock vina in PyRx software, which is freely accessible and designed for molecular docking studies. PyRx includes docking wizard with an easy-to-use user interface which makes it a valuable tool for computer-aided drug design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for rational drug design [13]. The selected drug targets were energy minimized, and converted them into pdbqt format in PyRx. The selection of phytocompounds was based on their inhibiting properties against target. Based on the above-mentioned search criteria, we found four compounds namely Eugenol, α – Farnesene, Benzene, 1, 2- dimethoxy-4-(1-propenyl) and Cyclohexane,1,2,4-triethenyl. To find out the pharmacokinetic properties of selected compounds, we carried out Lipinski's rule of 5. According to this rule, a compound might be capable of showing drug-like behaviour if it satisfies a minimum of four of the five characteristics. The characteristics followed by Lipinski’s rule of 5 are, molecular weight < 500, 65 hydrogen bond donors, SIO hydrogen bond acceptors, lipophilicity 65, and molar refractivity between 40 and 130. The tool used for the validation of all four compounds was swissADME, which is a convenient tool in drug discovery. Compounds that meet all the conditions of Lipinski's rule of 5 were chosen as ideal drug candidates [14,15].

Protein Preparation

Auto dock vina generated docking pair of protein and ligands was saved in pdb format, and were visualized in PyMOL [16] visualization tool i.e. python-enhanced molecular graphics tool. It excels at three-dimensional visualization of proteins, small molecules, density, surfaces and trajectories. It also includes molecular editing, ray tracing, and movies. The ligand binding sites and surrounding amino acids of ligands were also visualized. Molecular interactions in the form of hydrogen bonds between proteins and ligands were characterized and the distance of hydrogen bonds was also calculated. Proteins have specific sites, the amino acid residue side chains that form an active cavity or cleft where the ligands or atoms or other proteins are capable to bind and are called active sites. The active sites of the AChE and BChE proteins were identified by using supercomputing facility for bioinformatics and computational biology, IIT Delhi. Identified active sites were visualized in PyMOL molecular visualization tool.

Ligand Preparation

Compounds were retrieved from PubChem databases, i.e. Eugenol, α – Farnesene, Benzene, 1, 2- dimethoxy-4-(1-propenyl) and Cyclohexane, 1, 2, 4-triethenyl. Then Ligands are prepared by AutoDockTools-1.5.6 by adding charges (Gastegier) to it.

Active Site Selection and Grid Box Preparation

The active sites of the target protein, were retrieved from a webserver CASTp 3.0 as it is a focused docking where we’re aware of our site of bindings. Then fix the active sites by preparation of Grid (with the help of coordinates) for Rigid docking.

After the grid-preparation, started the process of docking with the help of AutodockVina 4.2 with MGL Tools by giving the commands in the command prompt. Then, the interation study can be shown in the AutoDockTools-1.5.6.

Docking [17]

After the grid-preparation, started the process of docking with the help of AutodockVina 4.2 with MGL Tools by giving the commands in the command prompt. Then, the interaction study can be shown in the AutoDockTools-1.5.6.

Visualization

The result page was analysed in PYMOL 2.5 and BIOVIA Discovery Studio Visualizer b21.1.0.20298. Pymol shows the site of binding i.e., where ligand binds to protein and the DSV shows the particular amino acids of our target protein where the ligand binds.

Reults and Discussions

Based on Insilico Docking, the ligand with the name Eugenol, α – Farnesene, Benzene, 1, 2- dimethoxy-4-(1-propenyl) and Cyclohexane,1,2,4-trietheny is found to be good inhibitor of 4 well-known drug targets. However, Cyclohexane-1,2,4-triethenyl has highest binding affinity score with targets. The in silico findings on Tulsi indicated that it has potential neuroprotective properties due to its ability to bind to specific protein targets for AD. Tulsi exhibited comparatively higher than standard drugs used against both AD. Tulsi is enriched with alkaloids , flavonoids and steroidalsaponins , which are helpful against neuro degeneration and mental disorders.Compound which has low bio-availability are less effective against disease.To solve this problem predicting the bioavailability, properties before the drug development will be a great advantage. By using certain computer based methods such as molecular docking it can be studied. Increased hydrogen bond interaction and high binding affinity scores express the strong binding of constituents with the selected receptor. In table-1, it is observed that based on lipophilicity of Alpha-farnesene showed highest that is 5.01 followed by Cyclohexane-1,2,4-triethenyl showed 3.63 followed by Benzene,1,2-dimethoxy-4-(1-propenyl) showed 2.72 followed by Eugenol 2.25. On basis of **Table 2**,it is obsereved that on the basis of the binding energy or docking energy of Cyclohexane-1,2,4-triethenyl shows the highest negative value which is the best dock-score i.e -5.8 followed by Alpha-farnesene -5.6 , followed by Benzene,1,2-dimethoxy-4-(1-propenyl) -5.2 and Eugenol -5.2.

In **Table 1**, it is observed that basing on lipophilicity of Alpha-farnesene showed highest i.e., 5.01 followed by Cyclohexane-1,2,4-triethenyl showed 3.63 followed by Benzene, 1, 2-dimethoxy-4-(1-propenyl) showed 2.72 followed by Eugenol showed 2.25. Also, on the basis of Molar Refractivity of Alpha-farnesene showed highest i.e., 72.8 followed by Cyclohexane-1,2,4-triethenyl showed 56.26 followed by Benzene, 1, 2-dimethoxy-4-(1-propenyl) showed 54.01 followed by Eugenol which is lowest i.e., 49.06.

Molecular Docking Analysis

In this study, the binding mode of Amyloid Precursor Protein was investigated by doing computational analysis, Rigid Docking. The results of docking analysis were described in **Table 1** and the docking figures showed in **Figures 1-6**. Among all the compounds,Cyclohexane, 1,2,4- triethenylshowed well docking

Table 1.

SL. NO.	Name of the Compounds	Molecular Weight	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Molar Refractivity	Lipophilicity
1	Eugenol	164.2	1	2	49.06	2.25
2	α – Farnesene	206.37	1	2	72.8	5.01
3	Benzene, 1, 2- dimethoxy-4-(1-propenyl)	180.24	0	2	54.01	2.72
4	Cyclohexane,1,2,4- triethenyl	162.27	0	0	56.26	3.63

Table 2. Docking result.

Sl.no	Compound Name	PubChem CID	Docking Energy
1	α – Farnesene	5281516	-5.6
2	Benzene, 1, 2- dimethoxy-4-(1-propenyl)	637776	-5.2
3	Cyclohexane,1,2,4- triethenyl	96529	-5.8
4	Eugenol	3314	-5.2

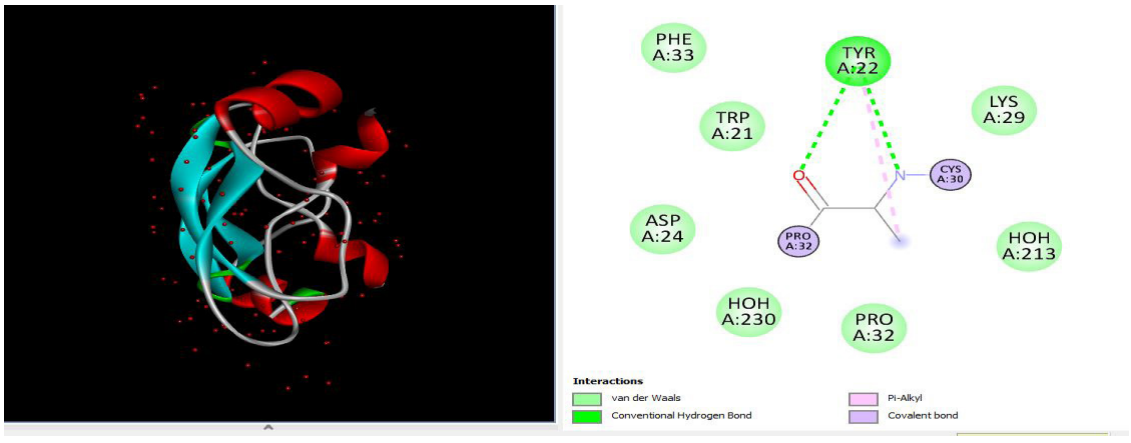

Figure 1 α – Farnesene with 1AAP Biovia Visualization

score Amyloid Precursor Protein.

Docking result

Docking results with, α – Farnesene, Benzene, 1, 2- dimethoxy-4-(1-propenyl) and Cyclohexane,1,2,4-triethenyl in the Amyloid Precursor Protein (PDBID: 1AAP) (**Table 2**).

Discussion

Treatment and prevention of Alzheimers is very much essential. Plants are natural reservoir of many medicinal value added components helps to overcome many chronic disorder.Hence herbal medicines are considered to be an excellent remedy for treatment of dibetes. Molecular docking is an important computational tool to predict the possible interactions between the drug and protein in a non-covalent fashion. Extensive in silico docking procedures have been carried out to examine whether the compound is a good ligand with diabetic targets.Screening of anti amylogenic therapeutics is very important and essential for the effective management of AD. Many resesrchers have worked on extraction, isolation , characterization of extracts and bioactive fractions from medicinal plant also they have established profile and data of interaction of active components against various targets and enzymes of AD using in silico molecular docking tools. Some medicinal plants contains appreciative quantities of flavo noids,alkaloids,glycosanonins and polyphenolic compounds that are considered to be effective against oxidative stress-induced neurotoxicity. Tulsi is enriched with alkaloids, flavonoids and steroidalsaponins, which are helpful against neuro degeneration and mental disorders.Compound which has low bio-availability are less effective against disease.To solve this problem predicting the bioavailability, properties before the drug development will be a great advantage. By using certain computer based methods such as molecular docking it can be studied. Increased hydrogen bond interaction and high binding affinity scores express the strong binding of constituents with the selected receptor. In **Table**

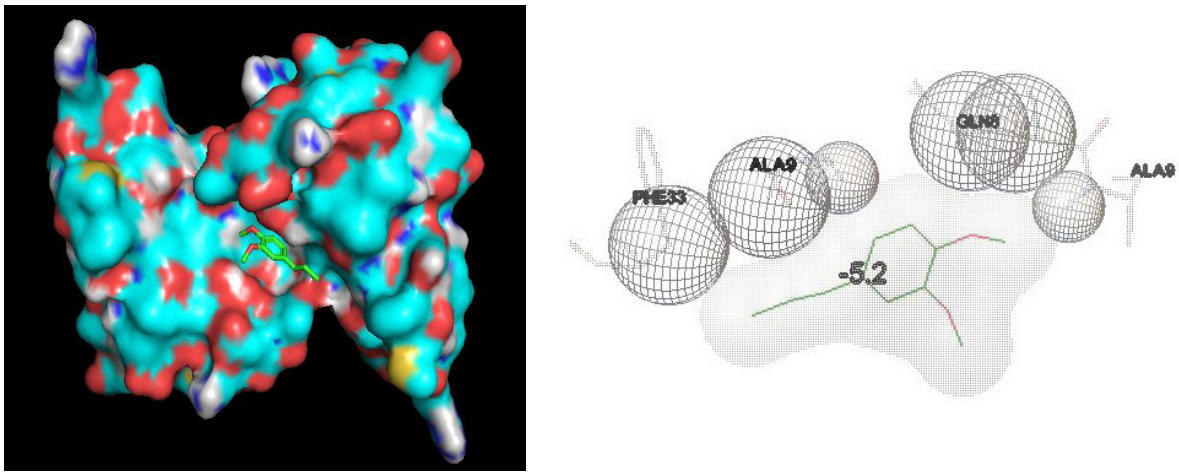

Figure 2 Benzene, 1, 2- dimethoxy-4-(1-propenyl) with Pymol Visualization; Benzene, 1, 2- dimethoxy-4-(1-propenyl) with AutoDockVisualization

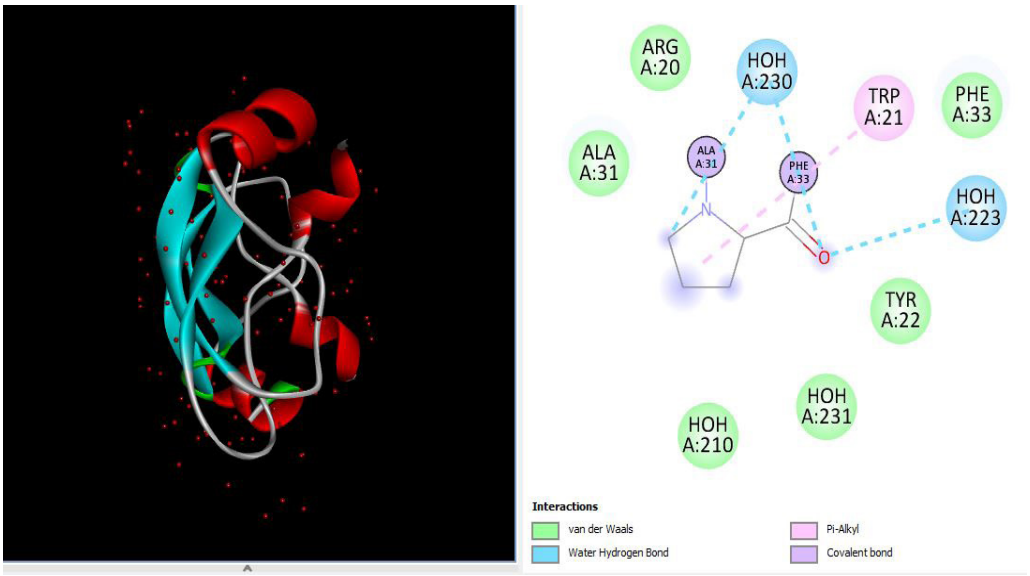

Figure 3 Benzene, 1, 2- dimethoxy-4-(1-propenyl) with Biovia Visualization

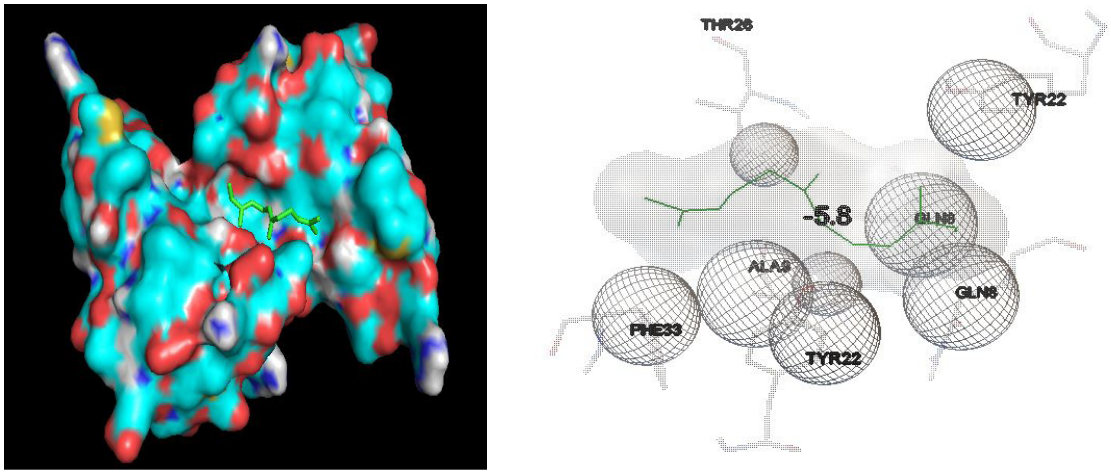

Figure 4 Cyclohexane,1,2,4- triethenyl with 1AAP Pymol Visualization; Cyclohexane,1,2,4- triethenyl with 1AAP Autodock Visualization

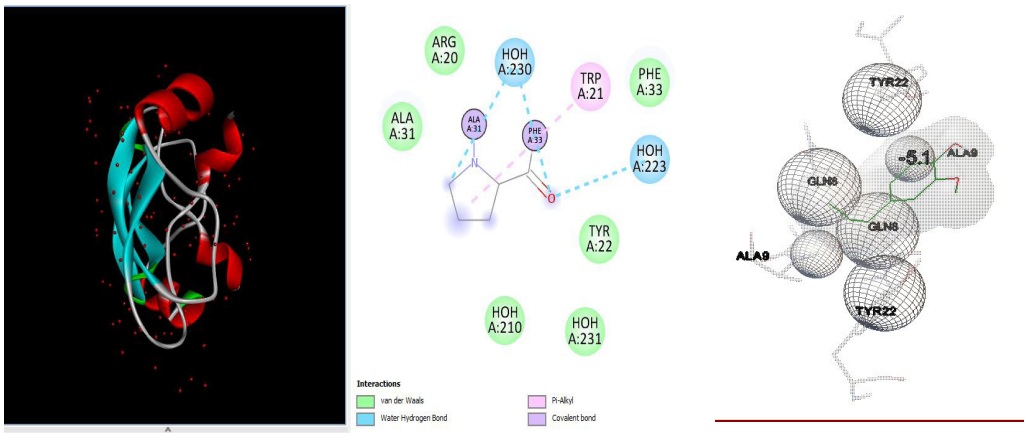

Figure 5 Cyclohexane,1,2,4- triethenyl with 1AAP Pymol Visualization; Cyclohexane,1,2,4- triethenyl with 1AAP Autodock Visualization

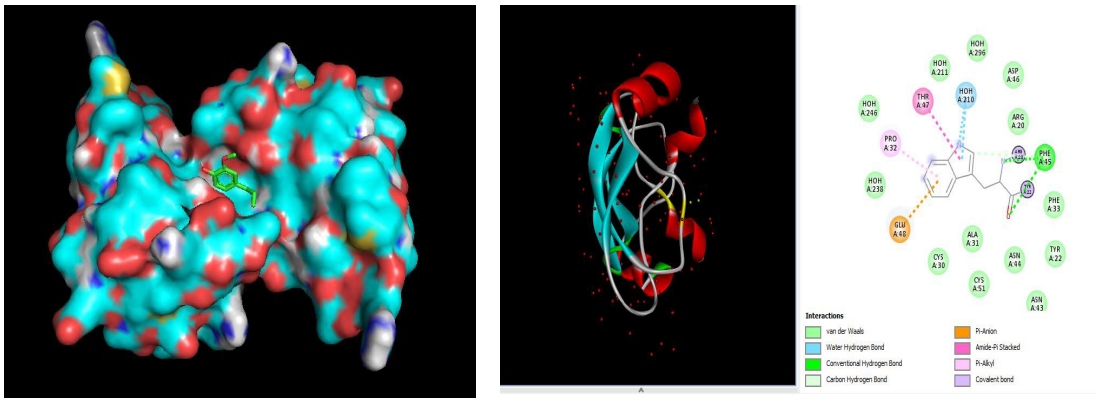

Figure 6 Eugenol with 1AAP Pymol Visualization; Eugenol with 1AAPBioviaVisualization

1, it is observed that based on lipophilicity of Alpha-farnesene showed highest that is 5.01 followed by Cyclohexane-1,2,4-triethenyl showed 3.63 followed by Benzene,1,2-dimethoxy-4-(1-propenyl) showed 2.72 followed by Eugenol 2.25. On basis of Table-2,it is obsereved that on the basis of the binding energy or docking energy of Cyclohexane-1,2,4-triethenyl shows the highest negative value which is the best dock-score i.e. -5.8 followed by Alpha-farnesene -5.6 , followed by Benzene,1,2-dimethoxy-4-(1-propenyl) -5.2 and Eugenol -5.2.

Conclusion

Plants are the richest resource of drugs molecules for modern medicines, nutraceuticals, traditional medicine and even chemical entities for synthetic drugs. Ocimum species (Tulsi) is a well-known medicinal plant which has used in the six Indian systems of medicine from ancient times. The latest review on the Ocimum species revealed that the species holds a very good antiviral activity [17]. Based on Insilico Docking, the ligand with the name Eugenol, α – Farnesene, Benzene, 1, 2- dimethoxy-4-(1-propenyl) and Cyclohexane,1,2,4-triethenyl is found to be good inhibitor of 4 well-known drug targets. However, Cyclohexane-1,2,4-triethenyl has highest binding affinity score with targets.

The *in silico* findings on Tulsi indicated that it has potential neuroprotective properties due to its ability to bind to specific protein targets for AD. Tulsi exhibited comparatively higher than standard drugs used against both AD. The information on thermodynamic and dynamic properties of Tulsi was clarified by molecular dynamics simulations, which were connected with the docking findings. Our study can serve as a basis for the development of a novel drug from a natural product which is cost effective for the treatment of neurodegenerative diseases. Moreover, the mechanism(s) of action of Tulsi in preventing AD progression can yield new knowledge in drug development for neurodegenerative disorders [18,19].

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