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Medicinal Plants

ANTI-PARKINSON POTENTIAL OF OCCIMUM SANTUM THROUGH IN-SILICO DOCKING STUDY

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ABSTRACT **Objective:** Parkinson's disease is affecting millions of people worldwide. The prevalence of Parkinson's disease is 0.3% globally, rising to 1% in more than 60 years of age and 4% in more than 80 years of age and the figures are thought to be doubled by 2030. Thus, there is a great need to identify novel therapeutic strategies or candidate drug molecule which can rescue neuronal degeneration. The aim of the present study was to assess bioactive compounds found in Tulsi as potential antiparkinson activity using molecular docking and to provide scientific justification in term of its active ingredient to target protein for prevention and symptomatic treatment of diabetics. **Methods:** The active compounds of Ocimum sanctum is to reveal its potentiality by molecular docking analysis to find out its potent compound against parkinsonism 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 Alpha-farnesene showed the highest negative value which is the best dock-score i.e., -6.2 followed by Cyclohexane-1,2,4- triethenyl (-5.9) followed by Benzene, 1, 2- dimethoxy-4-(1-propenyl) (-5.7) followed by Eugenol (-5.2). **Conclusion:** Alpha-farnesene and Cyclohexane-1,2,4- triethenyl are the best compounds for inhibiting of both, as it possessed best value in Molecular docking hence these are the potent antiparkinsonism agent.

KEYWORDS : Ocimum sanctum, Molecular docking, Parkinson's disease, Eugenol

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 trails.[1, 2] Parkinson's disease is the most common neurodegenerative movement disorder characterized by progressive loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) along with widespread intracellular aggregates of the protein α-synuclein.[3,4] Twenty genetic variants have been identified by human genetic studies, which are linked to PD pathogenesis. [5] Currently monogenetic PD accounts for 3–5% of total cases of PD . PARK genes are most commonly linked to pathogenesis of PD and the inheritance patterns may be autosomal dominant such as in case of PARK 1, 3, 5, and 8 or autosomal recessive as in case of PARK 2, 6, and 7. [6] The basic features of PD include tremors at rest, rigidity, bradykinesia, gait, and balance dysfunction. [7] It has been observed that PD is found in all ethnic groups but geographical differences exist is prevalence of disease. Approximately 1–2% of the population suffers from PD over the age of 65 years and this figure increases to 3–5% in people of 85 years and older.[8] The incidence rate of PD is 8–18 per 100,000 person-years. The rate of incidence is lower in Asian countries than in western countries. It is also documented that prevalence of PD will be almost double by 2030 and the burden of disease will also shift from developed western countries to developing eastern nations .[9]

Although no successful therapies are currently available that can modify the disease. However, dopaminergic medications are the mainstay of treatment for symptomatic relief of motor symptoms. The available medications that are currently in practice for management of PD include levodopa, dopamine agonists (ropinirole, bromocriptine, cabergoline), MAOIs (selegiline), amantadine, anticholinergics (trihexyphenidyl), carbidopa, and entacapone. [10] Levodopa is the most efficacious to control motor symptoms of the disease and is drug of choice to initiate first in course of treatment. Other medications indicated for control of non-motor symptoms are clozapine and quetiapine for psychotic symptoms, SSRIs, TCAs, and SNRIs for depression, rivastigmine for dementia, BZs and non-BZ hypnotics for insomnia, and fiber-rich diet for constipation . There are certain limitations to the use of anti-Parkinson's medications especially to efficacious classes of drugs. Dopaminergic medications including levodopa are most commonly associated with psychosis, motor complications, and impulsive compulsive disorder. Most of the patients with PD develop motor complications and dyskinesia within 5–10 years of levodopa treatment. Polyphenols are most abundant antioxidant phytochemicals present in human diet. They are secondary metabolites present in foods and beverages of plant origin including fruits, vegetables, cereals, herbs, spices, legumes, nuts, olives, chocolate, tea, coffee, and red wine. [11] Polyphenols possess antimicrobial, anti-inflammatory, antiviral, anticancer, and immunomodulatory activities. Polyphenols could be divided in different classes depending on chemical skeleton of compound including phenolic acids, flavonoids, stilbenes, and lignans . Polyphenols are capable of crossing blood–brain barrier and control neuronal disease pathogenesis at molecular and symptomatic level. The neuroprotective effects of polyphenols/natural compounds have been documented in various neurological disorders including cerebral ischemia, brain edema, PD, amyotrophic lateral sclerosis, brain tumors, and cognitive impairments. [12] Their neuroprotective activities are attributed to their antioxidant potential, anti-inflammatory actions, and alteration of signaling pathways. While managing neurodegenerative, novel therapeutic strategies support the application on antioxidant polyphenols as monotherapy or antioxidant cocktail formulation.

Silymarin is the polyphenolic flavonoid extracted from dried fruit of Silybum marianum and is most commonly used for hepatoprotective activities since ancient times. Among phytochemicals it is one of the most widely used flavonoid because of its extensive therapeutic properties . Silymarin has been indicated in pathological conditions of various origins such as prostate, lungs, CNS, pancreas, and skin. It is considered safe at therapeutic doses but improper administration of dosages may lead to cause adverse drug reactions (ADRs) where gastrointestinal effects are more common among them . Neuroprotective effects of silymarin have been studied in various models of neurological disorders such as Alzheimer's disease, PD, and cerebral ischemia.

Reducing oxidative stress, inflammatory cytokines, altering cellular apoptosis machinery, and estrogen receptor machinery are mechanisms that are responsible for neuroprotection by silymarin . Additionally because of poor aqueous solubility the bioavailability of silymarin is low and only 23–47% of silymarin reaches systemic circulation after oral administration. The aim of the present study is to provide comprehensive review of the recent literature exploring the effects of silymarin administration on progression of PD. Our primary focus is on the chemical basis of pharmacology of silymarin and its anti-Parkinson's mechanisms. [13]

MATERIALS AND METHODS [16]

In Silico Analysis Molecular Docking Analysis Of Isolated Compounds

Parkinson's disease (PD) are both associated with elevated levels of MAO-B (PDB ID: 1GOS); Human Monoamine Oxidase B in complex with Farnesol in the brain. The normal activity of MAO-B creates reactive oxygen species, which directly damage cells. Over-expression and increased levels of MAO-B in the brain have also been linked to the accumulation of amyloid β-peptides (Aβ), through mechanisms of the amyloid precursor protein secretase, γ-secretase, responsible for the development of plaques, observed in Parkinson's patients. Evidence suggests that siRNA silencing of MAO-B, or inhibition of MAO-B through -B (Selegiline, Rasagiline), slows the progression, improves and reverses the symptoms, associated with PD, including the reduction of Aβ plaques in the brain. Monoamine oxidase B (MAO B) is a mitochondrial outer-membrane flavoenzyme that is a well-known target for antidepressant and neuroprotective drugs. We determined the structure of the human enzyme to 3 A resolution. The enzyme binds to the membrane through a C-terminal transmembrane helix and a polar loop located at various positions in the sequence. The electron density shows that pargyline, an analog of the clinically used MAO B inhibitor, deprenyl, binds covalently to the flavin N5 atom. The active site of MAO B consists of a 420 A(3)-hydrophobic substrate cavity interconnected to an entrance cavity of 290 A(3). The recognition site for the substrate amino group is an aromatic cage formed by Tyr 398 and Tyr 435. The structure provides a framework for probing the catalytic mechanism, understanding the differences between the B- and A-monoamine oxidase isoforms and designing specific inhibitors.

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[17].

Protein Preparation[17]

Three-dimensional crystal Structure of MonoAmine Oxidase (PDB ID: 1GOS) was downloaded in pdb format from the protein data bank. After that, the structure was prepared and refined using the AutoDockTools-1.5.6. The extra water-molecules were removed, charges(Kollman-charges) and bond orders were assigned, hydrogens were added to the heavy atoms.

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.

RESULTS AND DISCUSSIONS :

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.

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

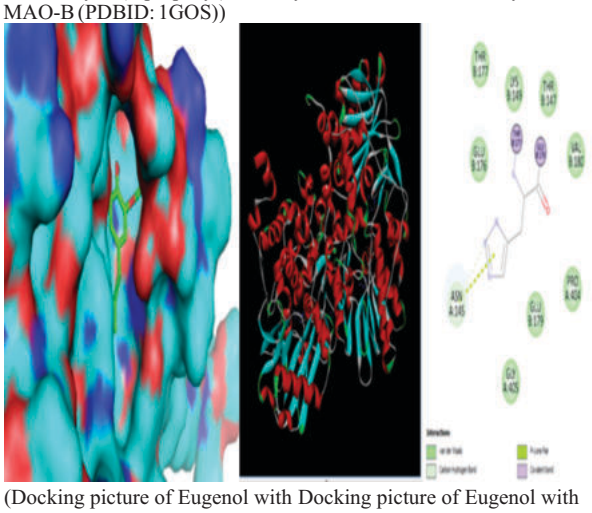
In Table-1, it is observed that basing on lipophilicity of Alpha-farnesene showed highest i.e., 5.01 followed by Cyclohexane-1,2,4-triethenyl showed 3.63 followed by Benzene, 1, 2- dimethoxy-4-(1-propenyl) showed 2.72 followed by Eugenol showed 2.25. Also, on the basis of Molar Refractivity of Alpha-farnesene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

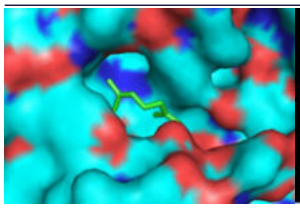
In this study, the binding mode of MAO-B was investigated by doing computational analysis, Rigid Docking. The results of docking analysis were described in Table 1 and the docking figures showed in Figure 1-4. Among all the compounds, α – Farnesene showed well docking score MAO-B.

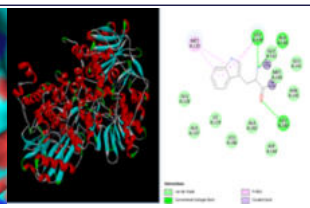
Compound Name	PubChem CID	Docking Energy(Kcal/mol)
Eugenol	3314	-5.2
α – Farnesene	5281516	-6.2
Benzene, 1, 2- dimethoxy-4-(1-propenyl)	637776	-5.7
Cyclohexane,1,2,4-triethenyl	96529	-5.9

(Table 5: Docking results with Eugenol, α – Farnesene, Benzene, 1, 2-dimethoxy-4-(1-propenyl) and Cyclohexane,1,2,4-triethenyl in the MAO-B (PDBID: 1GOS))



(Docking picture of Eugenol with MAO-B in Pymol Viewer) Docking picture of Eugenol with MAO-B in DS Visualizer


Docking picture of α – Farnesene with MAO-B in Pymol Viewer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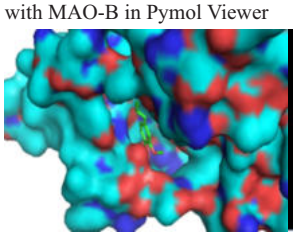
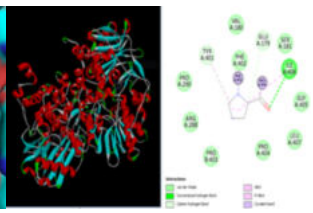

Docking picture of Benzene, 1, 2- dimethoxy-4-(1-propenyl) with MAO-B in Pymol Viewer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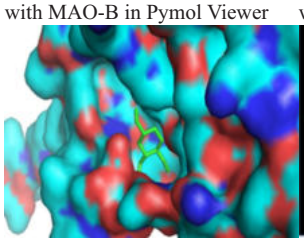
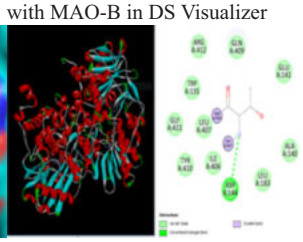
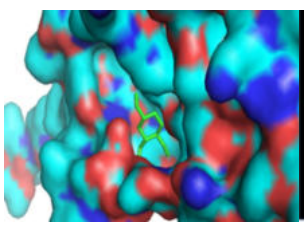
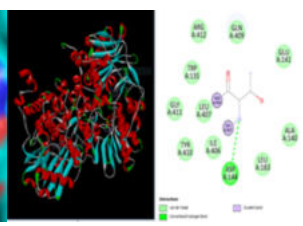

Docking picture of Cyclohexane,1,2,4- triethenyl with MAO-B in Pymol Viewer


Docking picture of Cyclohexane,1,2,4- triethenyl with MAO-B in DS Visualizer


Docking picture of Cyclohexane,1,2,4- triethenyl with MAO-B in Pymol


ViewerDocking picture of Cyclohexane,1,2,4- triethenyl with MAO-B in DS Visualizer

DISCUSSION

it is observed that on the basis of the binding energy or docking energy of Alpha-farnesene shows the highest negative value which is the best dock-score i.e., -6.2 followed by Cyclohexane-1,2,4-triethenyl (-5.9) followed by Benzene, 1, 2- dimethoxy-4-(1-propenyl) (-5.7) followed by Eugenol (-5.2).

In dopaminergic neurons of the substantia nigra, oxidative stress is one of the foremost factors leading to neurodegenerative PD disorder. Some medicinal plants embody appreciative quantities of flavonoids, glycophorins, alkaloids, and polyphenolic compounds that are considered to be effective against oxidative stress-induced neurotoxicity. Tulsi is enriched with alkaloids, flavonoids, and steroidal saponins, which are helpful against neurodegeneration and mental disorders. Compounds which have low bioavailability are less effective against disease. [18] 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 score express the strong binding of constituents with the selected receptor.[19]

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. Parkinson's disease (PD) is a neurodegenerative disorder that have emerged as among the serious health problems of the 21st century. The medications currently available to treat PD have limited efficacy and are associated with side effects. The main purpose of this study was to analyse the inhibitory action of phytochemical compounds were identified from the plant species Ocimum through literature survey by computational docking studies. Thus, docking result revealed that only one compound Alpha¬-farnesene exhibited the best binding interaction with in the active site of the MAO-B protein through hydrogen bonding interaction. Further in vitro studies on MAO-B compounds from the Ocimum species can lead to the discovery of novel drug for PD. So, Alpha-farnesene is the best compounds for inhibiting of both, as it possessed best value in Molecular docking. Further in vitro and in vivo investigation need to identify MAO-B inhibitory activity of isolated compounds from Ocimum sanctum.

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