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MOLECULAR DOCKING OF STIGMASTEROL AND CAMPESTEROL AS INHIBITORS OF ALZHEIMER'S DISEASE

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ABSTRACT

Millions of people worldwide, mostly older individuals have been diagnosed with Alzheimer's disease (AD), a progressive and irreversible neurological disorder. A steady deterioration in cognitive function, including memory loss, language impairment, and challenges with abstract thought and problem solving, is an indication of AD. Acetylcholinesterase inhibitors, which raise acetylcholine levels in the brain, and memantine, which inhibits glutamate neurotransmitter action, are the most often prescribed medications for Alzheimer's disease because there is presently no known cure and the effectiveness of current treatments is limited. In this research, we explore the possibility of using the medicinal herb Cocciniaindica to treat Alzheimer's disease. In particular, we emphasized on the potential of stigmasterol and campesterol, two substances present in Cocciniaindica, to interact with target proteins linked to Alzheimer's disease.

KEYWORDS: *Alzheimer, Campestrol, Stigmasterol, Disorder, Targeted Proteins.*

Article History

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INTRODUCTION

Alzheimer's Disease

Alzheimer's disease is a neurological disorder that mainly affects older adults and has a significant impact on millions of people worldwide. It is a progressive and irreversible condition that accounts for 60-70% of all dementia cases, making it the most common cause of dementia. AD is defined by a gradual decline in cognitive abilities, such as memory loss, difficulty with language, and challenges with abstract thinking and problem-solving. The illness is also associated with behavioral and emotional changes, including apathy, agitation, and depression. AD is characterized at the molecular level by the buildup of beta-amyloid peptides in the brain, which causes plaques that obstruct neuronal function and ultimately lead to cell death.

The development of neurofibrillary tangles, which are tau protein aggregates that impair neurons' ability to function normally, is another hallmark of AD. The exact processes that cause the build-up of tau protein and beta-amyloid peptides in the brain, ultimately leading to Alzheimer's disease, remain unclear. However, it is believed that a complex interaction between environmental and hereditary factors plays a role in the development of the disease. Unfortunately, there is currently no known cure for Alzheimer's, and current therapies only offer minimal relief from symptoms. However, research into the underlying mechanisms of the disease is ongoing, and new treatment strategies are being considered. For example, enzymes involved in the synthesis and removal of beta-amyloid peptides may be targeted, and immunotherapy may be used to boost the immune system's ability to remove beta-amyloid from the brain. Analytical chemistry is currently focused on using modern, high-tech instruments. Nonetheless, the concepts that underpin the creation of these instruments have roots in earlier techniques.

Role of Enzymes in Alzheimer's Disease

There are two types of enzymes that have been associated with Alzheimer's disease: acetylcholinesterase (AChE) and beta-secretase (BACE1), in addition to gamma-secretase. Beta-amyloid peptides are crucial to the development of the condition and are produced when BACE1 cleaves the amyloid precursor protein (APP). Researchers are exploring BACE1 inhibitors as potential treatment options. Gamma-secretase cleaves APP at different locations, producing beta-amyloid 1-40 and amyloid-beta 1-42 peptides. These peptides build up in the brain, causing plaques. Therapeutic approaches that involve inhibiting gamma-secretase activity have been investigated. Cognitive impairment in Alzheimer's disease has been linked to reduced levels of acetylcholine.

Acetylcholinesterase (AChE) breaks down acetylcholine in the brain. While enzymes like neprilysin, insulin-degrading enzyme, and endothelin-converting enzyme can break down beta-amyloid peptides, their activity may be reduced in Alzheimer's disease, which could lead to an increase in beta-amyloid accumulation. Understanding the onset and course of Alzheimer's disease requires an understanding of enzymes and current research is concentrated on creating novel treatment strategies.

Cocciniaindica

The ivy gourd, also known as Cocciniaindica, is a climbing plant that belongs to the Curcurbitaceae family. It can be found in India, Southeast Asia, and China, and is originally from tropical regions of Africa and Asia. It is a fast-growing shrub that can be easily grown through stem cuttings or seeds. The leaves, stems, and fruits of Cocciniaindica are commonly used as a vegetable and in traditional medicine to treat various ailments like fever, coughing, skin conditions, and diabetes. Besides its medicinal properties, Cocciniaindica contains bioactive substances like alkaloids, flavonoids, and terpenoids that have antibacterial, antioxidant, and anti-inflammatory properties.These compounds have been studied for their potential in treating various diseases, including cancer, diabetes and neurodegenerative disorders.

AIM AND OBJECTIVE

Aim

The current interest in natural products as a source of therapeutic compounds is certainly expected, to give predication of the ligand-receptor complex structure by using computation method.

Objectives

- The main objective of the present study is to isolate the potent anti-Alzheimer activity compounds from the Cocciniaindica belonging to Curcurbitaceae
- To identify the most active chemical compounds are effective as anti-Alzheimer are performing docking software.
- Binding energy of ligand with macromolecule was find out by Auto dock software.
- To visualize the protein with ligand, discovery studio and chimera were used.

MATERIALS AND METHODS

Molecular Docking

Molecular docking is a technique used to predict the binding mechanism and binding affinity of a protein-ligand complex. It has become an important part of the drug discovery process. Insilico docking investigations are conducted or produced using computer modeling or computer simulation. Based on a literature survey, the enzyme Transferase for Anti-Alzheimer activity has been chosen for insilico docking research. The protein will be obtained from the protein database, and the required research will be carried out in an organized and logical manner.

Key stages in docking

- Target/ receptor selection and preparation
- Ligand selection and preparation
- Docking
- Evaluating docking result

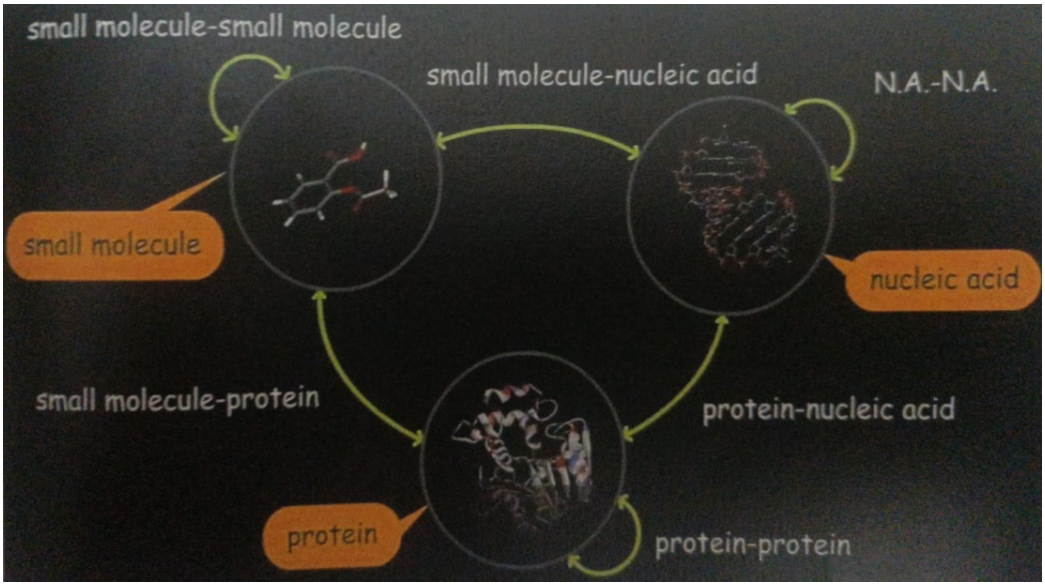

Figure 1: Process of Docking Studies.

Docking Studies

- Molecular docking analysis preparation of protein structure: The protein data bank (PDB) web contains a collection of 3D structure of large biological molecules including proteins and nucleic acids.
- The structure of transferase proteins having PDB ID 4XZ7 with resolution 2.10 A^{O} was retrieved from the protein bank data http://www.resb.org/pdb/.
- All the interacting heavy atoms, water molecules, metal ions are removed and added with hydrogen atoms, stabilized with minimized energy using "Add Energy", Kollman Charge, Gasteiger Charge were added in the Autodock MGL Tool.
- Ligand preparation drug compound resveratrol was drawn using the ACD/Chemsketch software as MOL format and then converted to pdb format using "OpenBabel" of MGL Tool.
- Docking the compounds prepared as ligands were docked against each of the prepared protein receptors using "AutoDock" of MGL Tool.
- In Autodock MGL Input the PDB format of ligand from the OpenBabel software, and save the output as .PDBQT format. Now add the grid by input the macromolecule and select the ligand. In grid box set the x,y,z dimension as 60X60X60 and pick the atom from Atom toolbar, Save the atom grid as .TXT config file and output was saved as GPF (Grid Parameter File). Run the Autogrid, and do the docking manual select macromolecule and ligand, In search parameter set the genetic algorithm RA run as 25. Save the output as Lamarckian GA (4.2) DPF. Run Autodock, In docking save the output as Vina Config (config.txt). Vina and save as outpdbqt file after and analyse it and save the result data.

INSILICO DOCKING STUDIES

Anti-Alzheimer Activity

The binding affinity score given by atomic contact energy (ACE) value for Stigmasterol at transferase enzyme is -6.1 and the hydrogen bond interaction formed by Stigmasterol on transferase enzyme is shown in figure a&b along with their polarity view and visualization figure c&d.

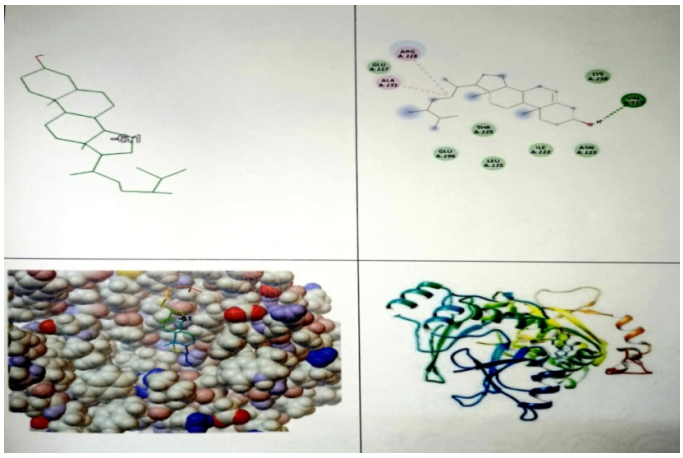

Figure 2: Docking Image of Stigmasterol at Transferase Enzyme.

The binding affinity score given by atomic contact energy (ACE) value for Campesterol at Transferase enzyme is -6.2 and the hydrogen bond interaction formed by Campesterol on transferase enzyme is shown in figure a&b along with their polarity view and visualization c&d.

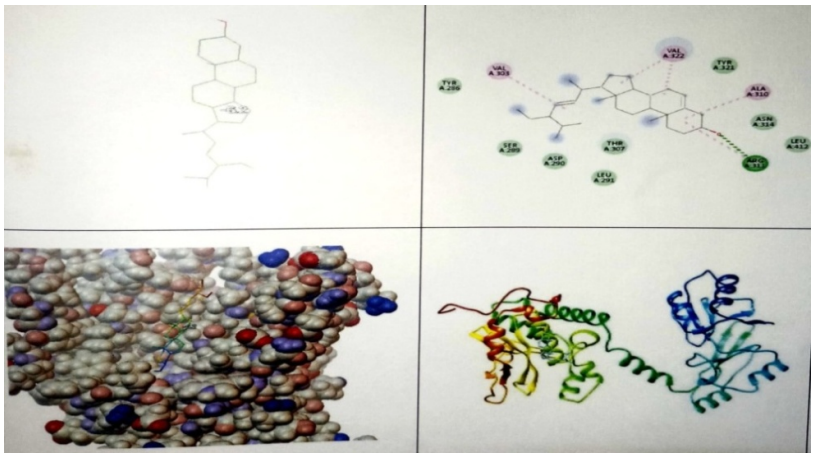

Figure 3: Docking Image of Campesterol at Transferase Enzyme.

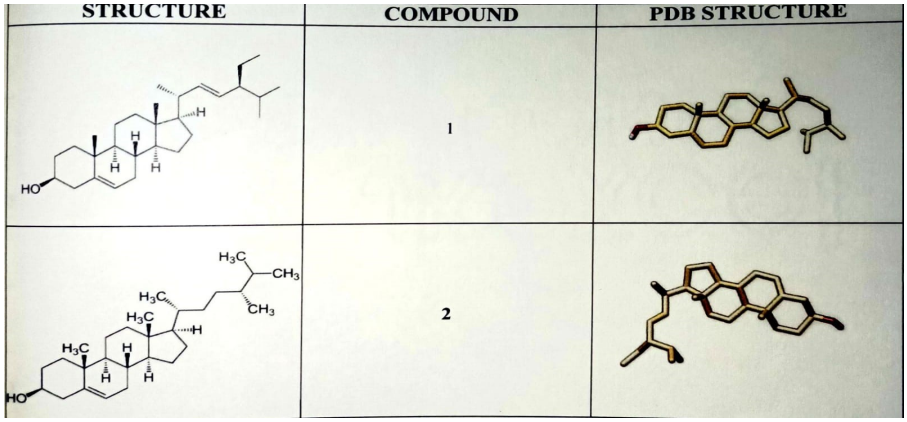

Figure 4: Structure of Ligands.

3.5 Binding Energy of the Molecular Docking Study of Compound Ligands with the Protein 4XZ7

Table 5: Binding Energy

S. No	Compound	Conformation	Binding Energy	No. of Hydrogen Bonds	Hydrogen Contacts
1	Stigmasterol	1	-6.1	3	VAL 219, ARG 228, ALA 231
2	Campesterol	1	-6.2	4	VAL 322, ARG 311, ALA 310, VAL 303

RESULTS AND DISCUSSION

The objective of our research was to investigate the potential of Cocciniaindica, a medicinal plant, in the treatment of Alzheimer's disease. Specifically, we focused on two compounds found in Cocciniaindica, namely stigmasterol and campesterol, and their ability to interact with target proteins implicated in Alzheimer's disease.

To accomplish this, we employed molecular docking techniques using Autodock software. Molecular Docking is a computational method that predict the binding affinity between a ligand (in this case, stigmasterol and campesterol) and a

target protein (associated with Alzheimer's disease). It allows you to explore the potential interactions and binding modes of the compounds within the protein's active site. We began by obtaining the 3D structures of the target proteins involved in Alzheimer's disease. These proteins include amyloid beta plaques, tau protein, or other relevant targets.

Next, we prepared the ligands (stigmasterol and campesterol) by obtaining their 3D structures and optimizing their conformations. Using Autodock software, we performed molecular docking simulations. The software utilizes various algorithms to explore the binding interactions between the ligands and the target proteins. It calculates binding energies and generates docking scores, which provides insights into the strength and stability of the ligand- protein complexes. After the docking simulations, we analysed the results to identify the most favourable binding poses of stigmasterol and campesterol within the target proteins.

And assessed the docking scores and binding energies to rank the compounds based on their predicted binding affinity and potential therapeutic efficacy. In this research paper, we presented the results and discussed the implications of the molecular docking findings. And also highlighted the specific interactions between stigmasterol/campesterol and the target proteins, emphasizing their potential to modulate key pathways involved in Alzheimer's disease.

Additionally, we have compared the docking results of stigmasterol and campesterol to determine which compound exhibited stronger binding or unique interactions. Overall, this research paper aimed to explore the therapeutic potential of Cocciniaindica compounds, stigmasterol and campesterol, in Alzheimer's disease by employing molecular docking techniques using Autodock software. The findings from this study contribute to the understanding of how these natural compounds could interact with target proteins associated with Alzheimer's disease, offering insights into their potential as therapeutic agents for the treatment of this neurodegenerative disorder.

CONCLUSION

The recent study has highlighted that the main area of focus in emerging research is the exploration of natural sources of medication for their anti-Alzheimer's activity. Additionally, this research can be employed to identify a lead molecule against a protein target or alternatively, to locate a protein target against a query ligand.

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