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In silico Molecular docking of Herbal plant extract for Antioxidant activity

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ABSTRACT:

The metabotropic glutamate receptors (mGluR1) are key receptors in the modulation of excitatory synaptic transmission in the central nervous system. The main objective of this research was to in silico screen the Leonotis nepetifolia to develop the antioxidant activity. Docking studies on Leonotis nepetifolia have been carried out using V Life MDS 4.3 software. The molecular docking analysis was carried out to better understand the interactions between Leonotis nepetifolia and metabotropic glutamate receptors. Hydrophobic and hydrogen bond interactions lead to the identification of active binding sites. The mint family has enormous economic value; it is a source of fragment plants like lavender and rosemary and flavourful ingredients like menthe and thyme that are used for a variety of therapeutic purposes, including the relief of stomach aches, gas, and loose stools. Additionally, mint contains antiviral and antibacterial properties. The Vander walls, hydrophobic, and hydrogen interaction are responsible for forming the stable compound of the ligand with the receptor. The molecular docking studies resulted in highlighting the ligand and their conformations which efficiently fit into the cavity of the target protein. The above studies are useful in understanding the structural requirements for the design of novel, potent and selective compounds with specific antioxidant activity. Docking is an important tool in understanding the structural requirements for the design of novel, potent and selective inhibitors and can be employed to design new drug discoveries and can be used for antioxidant activity.

KEYWORDS: Leonotis nepetifolia; metabotropic glutamate receptors; Docking study; Antioxidant; drug discovery;

INTRODUCTION:

A library of extremely numerous random compounds has been whittled down into a more manageable list of potentially useful inhibitors using the molecular modelling study method[1].

To better understand how ligands and receptors interact, the molecular docking study is a crucial tool in the drug discovery process. Additionally, a crucial model that is frequently utilised in the drug discovery process is used to link the chemical structures of various compounds to the biological activities that have been discovered for a group of them. A query of this type could be used to search chemical databases for fresh chemical entities.

The structural underpinnings of a dimeric metabotropic glutamate receptor's detection of glutamate. The central nervous system's excitatory synaptic transmission is mostly regulated by the metabotropic glutamate receptors (mGluR1) which are important. In this study, the extracellular ligand-binding region of mGluR1 was crystallized three times, once in a complex with glutamate and twice in two unliganded states. They all displayed disulphide-linked homodimers, whose "active" and "resting" conformations are controlled by a packed alpha-helical structure across the dimeric interface. The domain configurations of the bi-lobed protomer designs can be changed to provide either “open" or "closed" conformation[2]. According to the structures,

glutamate binding maintains dynamic equilibrium between the "active" dimer and the "closed" protomer. The spacing of the transmembrane and intracellular areas may be affected by the motions of the dimer's four domains, activating the receptor. This method of early receptor activation could be used by all G-protein-coupled neurotransmitter receptors with extracellular ligand-binding sites, according to the research[2].

It is the most investigated member of the family and has been widely considered as an antioxidant activity[3-5]. A few phytochemicals are recognized to have antimicrobial, immune-modulating, anti-cancer, and nutrient-rich qualities that support normal cell health and function[6]. The less studied plants have a long history of being used as food additives and even by the food industry to slow or stop the growth of pathogenic germs[7]. In the treatment of various bacterial contaminations, such as staphylococcal infections, anti-toxin mixtures are frequently crucial. To prevent the development of antimicrobial resistance, these mixtures—which include antitoxins like rifampicin among others are used[8].

Plants against bacteria are synergistic enhancers, meaning that even while they may not have many antimicrobial capabilities on their own when taken along with conventional pharmaceuticals, they may boost the effects of those drugs. There are significant advantages to combining well-known anti-contamination agents with plant separation in phytotherapy [9,10]. The Lamiaceae family (the family of mints) typically contains 3500 species distributed among 200 genera, with the majority of them being herbaceous, less frequently shrubs, and infrequently trees[11].

The mint family has enormous economic value; it is a source of fragrant plants like lavender and rosemary and flavourful ingredients like menthe and thyme that are used for a variety of therapeutic purposes, including the relief of stomach aches, gas, and loose stools. Additionally, mint contains antiviral and antibacterial properties. The flavonoid-rich Lamiaceae family is thought to contain flavanones, flavone-C-glycosides, flavonols, and flavanols [12]. Twelve species of the genus Leonotis, which is extensively dispersed throughout Pantropic, are represented in India by Leonotis nepetifolia[13]. Several well-known Indian traditional medical systems, including Ayurveda, Unani, and Siddha, use the medicinal herb Leonotis nepetifolia. This plant displayed a variety of biological behaviours, which have been linked to several physiological impacts. Cancer has been treated with Labiatae in traditional medicine. Therefore, every part of this plant has beneficial medicinal qualities[14].

MATERIALS AND METHODS:

Data sets and biological activity

The molecular modelling programme V-Life Molecular Design Suite (V-Life MDS) version 4.3[15] was used to conduct molecular modelling experiments (molecular docking) on an HP-PC (PAVILION) running Windows 11 with an AMD Ryzen processor. The current investigation used a dataset of Leonotis nepetifolia with reported activity.

Ligand preparation

Leonotis nepetifolia's 2D structure was depicted using the VLife2 Draw tool. Clean-up and 3D optimization were performed on the building. Utilizing the Merck molecular force field (MMFF)[16] with a distance-dependent dielectric function and an energy gradient of 0.01 kcal/mol over 10000 cycles, the 3D structure was optimised. MMFF can be used to determine a conformation's total energy using the relation;

Etotal = EB+ EA+ EBA+ EOOP+ ET+ Evdw + Elec

Were,

EB = energy of bond stretching
EA = energy of bond binding
EBA = energy of bond stretching and angle bending
EOOP = out-of-plane bending energy
ET = torsion energy term
Evdw = van der Waals energy;
Elec = electrostatic energy.

All of the conformers were produced, and the low-energy conformer of each compound was chosen and used for further research.

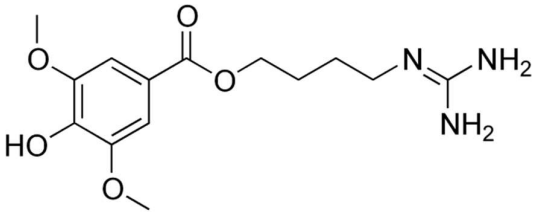

Figure 1. Leonotis nepetifolia structure.

Molecular docking study

Leonotis nepetifolia's binding free energy to the 3KS9 receptor was assessed using the VLifeMDS 4.3 BioPredicta tool to shed light on the plant's binding mechanisms.

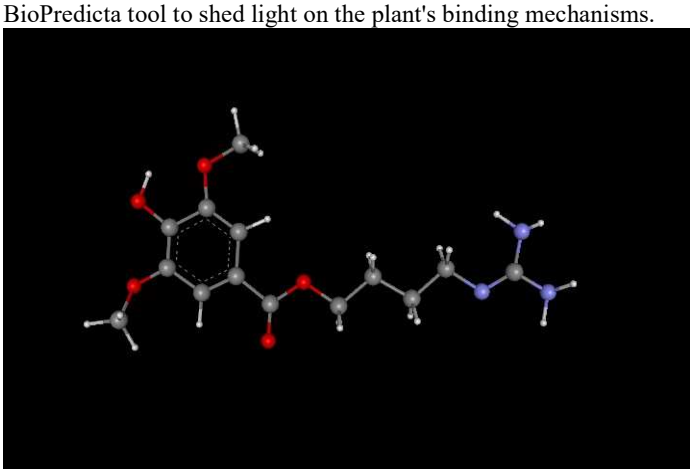

Figure 2. Leonotis nepetifolia structure in 3D formate.

Figure 3. Optimized structure of Leonotis nepetifolia.

Selection and preparation of ligands and target protein crystal structures

The ligands' binding activities were investigated. Leonotis nepetifolia's 2D structures were created using V-Life to Draw 1.0 and then transformed into 3D conformations. The resulting conformers were MMFF optimised until they had an RMS gradient energy of 0.001 kcal/mol. The RCSB Protein Data Bank was used to obtain the crystal structure of Leonotis nepetifolia in combination with LY341495 antagonist (3SK9; resolution:1.90 Å). Polar hydrogens were added after all bound water molecules and ligands were taken out of the proteins. Using the Merck molecular force field (MMFF) and a distance-dependent dielectric function with an energy gradient of 0.01 kcal/mol over 10000 cycles, the protein structure was energy minimised[16].

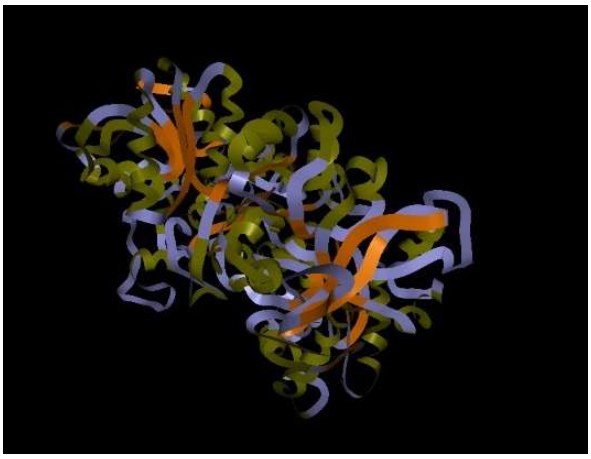

Figure 4. Protein metabotropic glutamate receptor mGluR1.

Identification of cavities

To identify the proper active site, the cavities in the receptor were mapped. Surface mapping of the receptor, locating geometric voids, and scaling the void for its hydrophobic properties using the V Life MDS analysis tool were the fundamental features employed to map the cavities. As a result, the size and hydrophobic surface area of each cavity found in the 3KS9 receptor are determined. Cavity-1 was discovered to be the ideal void as active site residues, taking into account its size and hydrophobic surface area. (LYSA, ASPA, ARGA, ASPA, SERA, LEUA, PROA, PROA, GLYA, ARGA, THRA, ARG36A, ILE46A, ILE47A, GLY48A, ALA49A, GLU60A, LYS61A, VAL62A, PRO63A, GLU64A, ARG65A, TYR74A, ARG78A, MET82A, GLU104A, ARG106A, ASP107A, SER108A, CYS109A, TRP110A, HIS111A, SER112A, SER113A, VAL114A, ALA115A, LEU116A, GLU117A, GLN118A, SER119A, ILE120A, GLU121A, PHE122A, ILE123A, ARG124A, ASP125A, SER126A, LEU127A, GLY163A SER164A, SER165A, SER166A, VAL167A, ALA168A, ILE169, GLN170, VAL171, GLN172A, ARG213A, ALA214A, MET215A, LEU216A, ASP217A, ILE218A, VAL219A, LYS220A, VAL227A, SER228A, ALA229A, VAL230A, HIS231A, THR232A, GLU233A, GLY234A, ASN235A, TYR236A, GLY237A, GLU238A, SER239A, GLY240A, MET241A, ASP242A, ALA243A,PHE244A, LYS245A, GLU246A,LEU247A,ALA248A, ALA249A, GLN250A, GLU251A,GLY252A, LEU253A, SER254A, ILE255A, ALA256A, HIS257A, SER258A, ASP259A, LYS260A, ILE261A, TYR262A, SER263A, ASN264A, ALA265A, GLY266A, GLU267A, LYS268A, SER269A, PHE270A, ASP271A, ARG272A, LEU273A, LEU274A, ARG275A, LYS276A, LEU277, GLU279, ARG280, VAL286, VAL287, VAL288A, CYS289A, PHE290A, CYS291A, GLU292A, GLY293A, MET294A, THR295A, VAL296A, ARG297A, GLY298A, LEU299A, LEU300A, SER301A ALA302A, MET303A, ARG304A, ARG305A, LEU306A, LEU314A, ILE315A, GLY316A, SER317A, ASP318A, GLY319A, TRP320A, ALA321A, ASP322A, ARG323A, VAL326A, ILE327A, TYR330A, GLU333A, ALA334A, GLY337A, ILE338A, THR339A, ILE340A, LYS341A, LEU342A, GLN343A, SER344A,, LYS409A, PHE5412A, VAL413A, ASN415A, ALA416A, ILE417A, MET420A, LEU451A, ILE455A, GLU456A etc.)

Run of docking study

By aligning with cavity-1's active site and utilising the V Life MDS 4.3 software by best practices, the conformers of Leonotis nepetifolia were docked using a genetic algorithm (GA) [15]. The MMFF approach was used to minimise the energy of the complexes until they had an RMS gradient of 0.1 kcal/mol. Following ligand docking into the enzyme active site, the binding energy (measured in kcal/mol) or ligand-receptor interaction energy can be described as:

E = InterEq + InterEvdW + IntraEq + IntravdW + IntraEtor

Were,

InterEq= Intermolecular electrostatic energy of complex;
InterEvdW = intermolecular vdW energy of complex
IntraWq = Intramolecular electrostatic energy of ligand
IntraEvdW = Intramolecular vdW energy of ligand
IntraEtor= Intramolecular torsion energy of ligand

RESULTS AND DISCUSSION:

Molecular docking study

To determine the molecular basis of Leonotis nepetifolia's antioxidant properties, molecular docking was carried out. The substance was docked with the glutamate receptor 3KS9. Hydrogen bond interactions and docking calculations are carried out. The docking results showed that these substances were retained in the protein's active pocket by a mix of hydrophobic and van der Waals interactions.

Table 1. Scorning function values for the studied substances.

Substance	Scorning function values of Metabotropic glutamate receptor mGluR1 (PDB code 3KS9)
Leonotis nepetifolia	-52.241562
1EWK	-49.624803

CONCLUSION:

The stepwise method is applied for optimization using V-Life MDS 4.3 drug design software. The docking simulation suggested that the modifications in the series result in better binding potential. Leonotis nepetifolia shows better binding with glutamate receptors (PDB code 3KS9). The Vander walls, hydrophobic, and hydrogen interaction are responsible for forming the stable compound of the ligands with the receptor. The molecular docking studies resulted in highlighting the ligand and their conformations which efficiently fit into the cavity of the target protein. The above studies are useful in understanding the structural requirements for the design of novel, potent and selective compounds with specific antioxidant activity.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

The Project was designed, and all the data collected during the study were analyzed by Dr Pallavi M. Patil, All the data obtained during the study and alignment of data and presentation of data is completed by Miss. Dnyaneshwari Chopade.

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