Exploring spearmint (*Mentha spicata*) and Exendin-4 as novel therapeutic approaches for Huntington's disease: a molecular insight

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Abstract

Huntington's Disease (HD) is an autosomal dominant neurodegenerative illness resulting from CAG trinucleotide repeat expansion in the Huntingtin (Htt) gene with a progressive course affecting motor, cognitive and affective domains. This disease has a progressive nature and the outcomes are fully serious motor disorders, psychotic symptoms and death. As for the disease, its spread is rated differently worldwide and the highest rates were identified in Europe and North America. As of now, there is really no cure, which is why investigators embark on the consideration of cure alternatives. Such approach includes use of plant extracts whereby the compounds used are from the members of mint family particularly Mentha spicata; scientifically proven to have medicinal value. This study looks at the prospect of spearmint in relation to therapy for those suffering from HD based on the plant's antibacterial and antioxidant characteristics. In addition, molecular docking analysis is employed examining the prospects of drug delivery by symptomatically acting peptides like Exendin-4 interacting with the Htt protein to address the issues of mutant protein aggregation.

Some of the neuroprotective properties of the peptide Exendin-4 have been demonstrated in an antic diabetes context for the enhancement of motor function to alleviate HD symptoms in animal models. We strongly argue for future studies exploring surviving phytochemical + peptide combinations in the context of Huntington's disease, as this work reveals important, hitherto uninvestigated aspects of the molecular pathology of this condition.

Keywords: Autosomal dominant neurodegenerative, Exendin-4, antibacterial, antioxidant and molecular docking.

Introduction

Huntington's disease (HD) is characterised by motor disorder, dementia and psychiatric state and the clinical onset is in middle age. Molecular changes in HD include mitochondrial dysfunction, increased oxidative stress, excitotoxicity, endoplasmic reticulum stress, myelin abnormalities and changes in gene expression that result in neuronal death in striatum and cortex. A great deal has been learnt about the genetic and molecular biology of HD; however, there are still no therapies that alter the course of the disease. Therefore, there is a clear niche to search for new interventions that can potentially mitigate the process of disease progression.[1]

Current research shows that plant-based compounds, along with peptide-based therapies are also useful in treating HD or can also act as an adjunct therapy. From a vast number of natural products, the appeal has been derived for *Mentha spicata*, also known as spearmint which is an edible herb. The present study has confirmed and supported previous findings that have attributed antioxidant, anti-inflammatory and anti-neurodegenerative properties to spearmint which has been known to be used as herbal medicine.

Among them, flavonoids, terpenoids and phenolic acid were identified to have neuroprotective potentials based on their effects on antioxidant activity, improvement of mitochondrial dysfunction and alteration of pro-survival signaling pathways[2]. Several of the newer and more recent investigations have posited that spearmint and the components of spearmint might have therapeutic use in patients with neurodegenerative diseases, such as HD.

Similarly, Exendin-4 a GLP-1 receptor agonist has been considered as promising molecule for the treatment of HD. The present study revealed that agonist for GLP-1 receptor contributes to the increase in the survival of neurons, the improvement of mitochondrial function, the synaptic plasticity and the decrease in neuroinflammation. The effect of Exendin-4 on neuronal survival and mHTT aggregation has been established based on earlier *in vivo* and *ex vivo* studies which have revealed that Exendin-4 reduces the neurodegeneration of models of HD by activating the neuroprotective factors and alters their transcriptional responses. Moreover, the impact of exendin-4 on insulin signaling and glucose metabolism may have additional therapeutic potential because metabolic disturbance is deemed to be involved in HD development.

The integration of plant medicines like spearmint with peptide therapy including exendin-4 may provide a strategy for the management of HD[3]. Presumably, by affecting several points linked to the disease's course, these compounds may have a beneficiary impact on the cell homeostasis, prevent neuronal stress and deteriorative effects on cognitive and motor spheres.

This combination strategy could possibly provide a broader therapeutic model for dealing with HD by directly targeting

the molecular initiators of the disease and also the symptomatic expressions associated with the affliction.

Therefore, the goal of this study is to discover the possibility of Spearmint and Exendin-4 for treatment of HD and to study molecular action, neuroprotection and the possibility of combining them. By critically reviewing the potential publications about HD and conducting a preliminary abstraction of preclinical findings, this study aims at offering practical inputs to formulate the new treatments of HD, laying the foundation for coming clinical trials and clinical uses.

Applying active natural ingredients in conjunction with innovative peptide technologies may provide an unprecedented chance of a better life for Huntington's disease patients.

Material and Methods

Collection of plant material and extraction of plant sample: The plant samples were collected in January 2024 from grown plants of *M.spicata* (Spearmint), Latitude (10.730186^{O}), Longitude (78.544462^{O}) located at ICAR – KVK, Pulutheri Village, Kulithalai, Karur District, Tamil Nadu. The experimental plant was further authenticated and identified (voucher No. 3263) by taxonomist. The dried plant material was then crushed into a fine powder and utilised with a Soxhlet equipment to make an extraction. Separately, 50 g of leaf powder was immersed for 24 hours in 50 mL of organic solvent methanol. After that, the plant extract was subjected to extraction for 4 hours using Soxhlet apparatus containing 250 mL of methanol. Thereafter, until solid residues were formed, the extract was concentrated in a rotating vacuum evaporator under reduced pressure at 40 °C. The dried extracts were then gathered and kept at -4°C for use in further research.

Agar Well diffusion assay: In this method, 1 mL of each bacterial inoculum is evenly distributed over the agar surface using the spread plate technique. Subsequently, a volume of the *M. spicata* extract solution (2–6 µL) is introduced into a well created by aseptically drilling a hole in pipette tip. An ampicillin disc (10 µg/mL) is placed on the agar plate as a positive control. [4] The test microorganism is then incubated on the agar plate at 37°C for 24 hours[5]. The positive control diffuses its antimicrobial agent into the agar medium, inhibiting the growth of the tested microbial strain, forming a clear zone of inhibition.

Similarly, if the plant extract exhibits antimicrobial activity, a zone of inhibition will form around the well containing the extract, indicating its efficacy in hindering microbial growth[6].

Antioxidant activity by DPPH assay: The DPPH test, which gauges antioxidant activity by scavenging the stable free radical DPPH was used to evaluate *Mentha spicata's* radical scavenging capacity. When DPPH is scavenged, it changes color from purple to yellow, signifying that it has been reduced to DPPH-H, demonstrating the antioxidants' ability to donate hydrogen[8-10].

Gas Chromatography-Mass Spectrometry (GC-MS) analysis: The phytochemical composition of *Mentha spicata* was analyzed using Gas Chromatography-Mass Spectrometry (GC-MS). The analysis was performed with a Shimadzu (AOC-20i) mass spectrometer equipped with a capillary column (30 meters in length, SH-Rxi-5Sil-MS non-polar coating, 0.25 mm inner diameter and 0.25 µm thick polydimethylsiloxane film)[11-13].

Compound Identification: The phytocompounds were identified by comparing their retention indices (RI), calculated relative to a (C9–C24), with those reported in the literature or with authentic standards. Further identification and authentication were performed by analyzing the complete mass fragmentation patterns of the compounds and matching them with entries in the National Institute of Standards and Technology (NIST) library.

Molecular docking: The structure of the Exendin-4 receptor protein was obtained from the Protein Data Bank (PDB), specifically using the entries PDB: 3C59 and PDB: 3C5T. The structures were downloaded in .pdb format. The active site of the Exendin-4 receptor was predicted using Biovia's Discovery Studio 2021. A sphere based description (SBD) was generated around the receptor protein and the active site was selected based on the XYZ coordinates. Protein docking was performed using Biovia Discovery Studio Visualizer and AutoDock Tools 1.5. During this process, solvent water molecules were removed, Kollman charges were assigned to all atoms, polar hydrogens were added and atom types were determined. The receptor structure was then converted into .pdbqt format for further docking studies and stored for subsequent use[15].

The ligands used in this research were sourced from the GC-MS analysis of *Mentha spicata* plant and downloaded from PubChem in .sdf format. These ligand structures were then optimized and transformed to 3D structures using an online tool, Convert SMILES to 3D structure found at www.novoprolabs.com and saved as .pdb format. Ligand preparation was done using AutoDock 1.5.7, the Kollman charges were assigned, non-protoned hydrogen atoms were clustered and bond flexibility was established. The last prepared ligands were stored in the .pdbqt structure.

Structural analysis was done with AutoDock 1.5.7 software for the receptor and ligand files. Ligand interaction with the protein was initiated at the X, Y and Z coordinates of 20Å, 20Å and 20Å respectively. Polar hydrogen of AutoDock was generalized, Kollman charges were assigned, solvation parameters were also assigned for the protein. Structure prediction and docking were carried out by Autogrid for generation of grid maps and Lamarckian genetic algorithm with 9 iterations and RMSD of <1.0. The obtained results

were compared by free energy, hydrogen bonding, hydrophobic interactions as well as electrostatic interactions. The best ligand was selected and using its 3D structure I was able to visualize and save the surface interactions as an image. Also 2D interaction diagram was saved in .png format to be used later on a further analysis[16].

***In silico* pharmacokinetics studies of active ligands:** The pharmacokinetics studies are done with the help of software Swiss ADME at the URL www.swissadme.ch. This software gives all the details. The toxicity prediction of selected lead ligand molecules was assessed using the pkCSM server and checked for the presence of main effects such as skin sensitisation, AMES toxicity, maximum tolerated dose for humans, hepatotoxicity and minnow toxicity[17].

Results

The plant species was identified as *Mentha spicata* (Voucher No. 3263) by taxonomist. The extraction of phytochemicals from *M.spicata* was carried out by Soxhlet extraction method (Figure 1) using organic solvent methanol. Five cycles were completed for the extraction of phytochemicals. Around 25 ml of concentrated plant extract was obtained and was diluted with methanol in the ratio of 1:3 which is used for further studies i.e. antibacterial activity by agar well diffusion assay, antioxidant assay by DPPH and *in silico* pharmacokinetics study.

Antibacterial activity: The antibacterial activity of *Mentha spicata* extract was evaluated against various bacterial species. The results indicated that the mint extract exhibited a strong inhibitory effect against *S. aureus*, *Pseudomonas fluorescens* and *E. coli* (Table 1), forming distinct zones of clearance. The inhibition zones ranged from 1.5 to 2.5 mm. In contrast, no zones of inhibition were observed for *S. typhi*, *E. faecalis*, or *S. pyogenes*. Among the tested bacteria, the extract displayed the strongest antibacterial activity against *S. aureus*, followed by *E. coli* and *Pseudomonas fluorescens* (*S. aureus* > *E. coli* > *Pseudomonas fluorescens*).

Antioxidant activity: The antioxidant activity of *Mentha spicata* was evaluated using various concentrations with ascorbic acid as the standard at corresponding concentrations. When DPPH (1,1-diphenyl-2-picrylhydrazyl) was added to the samples, the formation of a yellow color after the incubation period confirmed the scavenging activity. The absorbance of the reaction mixture was measured at 517 nm using a Systronics UV-Visible spectrophotometer (Model 119). The percentage of Radical Scavenging Activity (% RSA) for both *M. spicata* and ascorbic acid was determined and recorded (Table 2).

The DPPH radical, which has maximum absorption at 517 nm, is reduced by antioxidants to yellow-colored diphenyl-picrylhydrazine. The results revealed that the free radical scavenging capacity of *M. spicata* extract increased with increasing concentrations, demonstrating its potential as a natural antioxidant. Results show that ascorbic acid has the highest antioxidant activity. In the same time, spearmint extract has very good antioxidant activity ranges from 79% to 89%. The comparative was shown in the graph (Figure 2).

Figure 1: Soxhlet extraction of *M.spicata*

GC/MS analysis: The GC-MS analysis of the methanolic extract of *Mentha spicata* revealed the presence of 14 chemical constituents, characterized by their molecular weight, retention time and peak area.

Table 1
Antimicrobial activity of different microbial species using mint extract at different concentration by Agar well diffusion method

Microorganisms	Positive control	2µL	4µL	6µL
S.aureus	1.8	1.6	2.1	2.6
S.pyogenes	0.3	0	0.1	0.1
E.faecalis	0.1	0	0	0.1
S.typhi	0.5	0	0.1	0.2
Pseudomonas fluorescencs	1.5	1.1	1.7	1.9
E.coli	1.7	1.2	1.7	2.1

Table 2
Antioxidant activity of ascorbic acid and *M.spicata* extract at different concentration using DPPH assay

Amount of extract taken	10 µL	20 µL	30 µL	40 µL	50 µL
% RSA for Standard (Ascorbic acid)	95.97	96.98	97.48	98.49	98.99
% RSA for Sample (*M.spicata*)	79	81.31	83.51	86	89

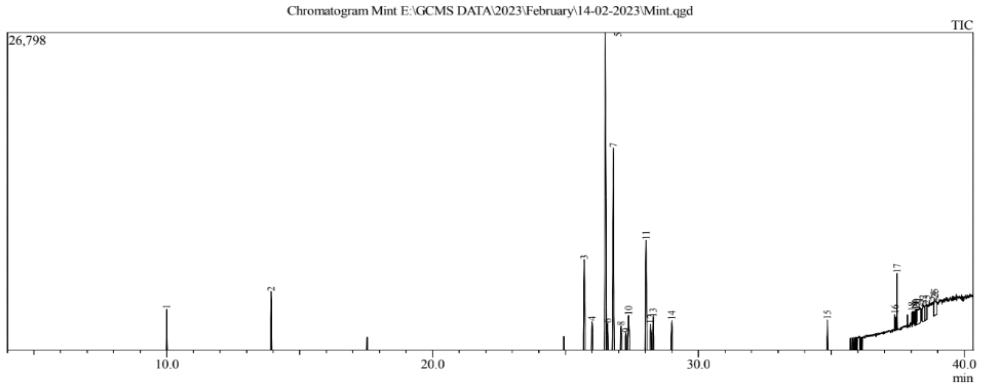


Figure 2: GC/MS Chromatogram of methonolic *Mentha spicata* extract

The chromatogram (Figure 2) displayed six prominent peaks, highlighting key compounds with significant peak areas. These include furo[2,3-c]pyridine, 2,3-dihydro-2,7-dimethyl- (retention time: 25.706, peak area: 6.9%), 1,2-Benzene dicarboxylic acid, dibutyl ester (retention time: 25.502, peak area: 25.75%), 1,2-Benzene dicarboxylic acid, Bis(2-Methyl Propyl) Ester (retention time: 26.696, peak area: 16.06%), 2-((TrimethylSilyl)Ethnyl) Heptamethyltrisilane (retention time: 37.389, peak area: 0.92%), indolizine, 2-(4-methylphenyl)- (retention time: 38.852, peak area: 0.86%) and (SS)- or (RR)-2,3-Hexanediol (retention time: 38.043, peak area: 0.38%).

The high peak area of compounds such as 1,2-Benzene dicarboxylic acid, dibutyl ester and bis(2-Methyl Propyl) ester suggests their abundance in the extract, indicating potential bioactivity. This analysis underscores the phytochemical diversity of *M. spicata*, which may contribute to its pharmacological properties. The GC-MS chromatogram of the methanolic extract of *Mentha spicata* displayed six major peaks alongside numerous smaller peaks, indicating the presence of significant compounds as well as minor constituents. The structural assignment of the compounds was performed by matching their GC retention data and spectral profiles with the NIST library (National Institute of Standards and Technology). The smaller peaks are likely due to compounds present in trace amounts or the disintegration of major compounds during analysis. Additionally, peaks with lower retention times correspond to low-polarity plant compounds, reflecting the chemical diversity of the extract.

Molecular Docking

Processing of receptors: The three dimensional crystal structures of different Exendin-4 receptors EX-4 [PDB: 3C59] were retrieved from RCSB protein data bank as **.pdb* format. Then the receptors were pre-processed by the deletion of water molecule. The Inbuild ligands were removed which are attached in the receptor protein of the active site. The SBD sphere covers the entire receptor and the active sites were predicted for Exendin-4 receptor. The coordinates of the Ex-4 receptor [PDB: 3C59] and [PDB: 3C5t] were calculated using Bio-via Discovery Studio. The XYZ coordinates for [PDB: 3C59] were calculated as follows: X= 4.524939, Y= 53.811636 and Z= -5.267364 respectively. The size of XYZ was provided as 20:20:20.

Now, the polar hydrogen bonds were added. After preparing the protein structure, the next step is to predict its active site. Although the receptor may contain multiple potential active sites, only the most relevant one should be selected for further analysis. Any water molecules and heteroatoms present in the receptor structure are typically removed during this step. The processed receptor can then be visualized using BIOVIA Discovery Studio. Finally, the processed protein structure is saved in **.pdbqt* format for subsequent docking studies or further analysis.

Retrieval of 3D structure and Processing of Ligands: The ligands were retrieved from the phytochemical extract of *M.spicata* by GC/MS analysis. The three dimensional structure of ligands were obtained by Convert Smiles to Structure (https://www.novoprolabs.com/tools/smiles2pdb). The ligands were saved in **.pdb* format.

Once the summary of ligand shows no non bonded atoms and rotatable bonds were defined, the structure of the ligand was saved in **.pdbqt* format and used as input ligand file for Auto Dock in docking.

Screening of Ligands using Auto Dock Vina: The ligands were screened using auto dock vina by binding energy and affinity with Ex-4 receptor [PDB: 3C59]. Based on this screening process, top six ligands were selected for the further active site-specific docking with protein [PDB: 3C59]. As a result of docking process, the ligands were collected with lowest binding energy while interacting with protein [PDB: 3C59] which are Furo[2,3-c]pyridine, 2,3-dihydro-2,7-dimethyl, 1,2-Benzene dicarboxylic acid, Dibutyl ester, 1,2-Benzene dicarboxylic acid, Bis(2-Methyl Propyl) Ester, (SS)- or (RR)-2,3-hexanediol, 3,4-Dihydro-4-(1,3-Dioxolan-2-yl)-5,7-Dimethoxy-1(2H)-Benzopyran-2-ONE and Indolizine, 2-(4-methylphenyl) and for the ligands with low binding energy with protein.

Docking of Ligand with Ex-4: The selected ligands were evaluated for binding affinity with the EX-4 receptor [PDB: 3C59]. For each ligand, Auto Dock Vina created 9 different conformations with different binding energies (Table 3) showing variable RMSD. The interaction pattern of these selected ligands with the Ex-4 receptor was studied using Bio via Discovery studio 2021 client. Various ligands were analyzed for their interactions with the EX-4 protein [PDB: 3C59] through non-bonded interactions, with results visualized in both 2D and 3D structures.

The result was shown in figure 3, (SS)- or (RR)-2,3-hexanediol exhibiting interactions involving alkyl bonds, Van der Waals forces and hydrogen bonds, with a binding energy of -3.3 kcal/mol.

The ligand 1,2-benzene dicarboxylic acid, dibutyl ester displayed Van der Waals and hydrogen bonding interactions, achieving a binding energy of -4.2 kcal/mol, while 1,2-benzene dicarboxylic acid, bis(2-methylpropyl) ester showed similar bonds with a binding energy of -4.6 kcal/mol. The ligand 3,4-dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one exhibited Van der Waals and pi-alkyl interactions, with a binding energy of -4.6 kcal/mol. Indolizine, 2-(4-methylphenyl), demonstrated unique pi-sulfur, pi-alkyl and Van der Waals interactions, resulting in a binding energy of -5.7 kcal/mol.

Lastly, furo[2,3-c]pyridine, 2,3-dihydro-2,7-dimethyl showed alkyl, hydrogen bond and Van der Waals interactions, with a binding energy of -4.6 kcal/mol. These findings indicate diverse binding mechanisms and varying ligand efficiencies with EX-4.

Discussion

This study examines the phytochemical constituents, pharmacological properties and *in silico* molecular docking studies of *Mentha spicata* (spearmint) for potential drug development in Huntington's disease, specifically targeting the Exendin-4 receptor. Numerous studies have highlighted the widespread use of *M. spicata* in ethnomedicine and pharmacological investigations have illuminated its broad biological activities. The research indicates that *M. spicata* possesses significant pharmacological effects such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, cytotoxic and gastrointestinal protective properties. The essential oils (EOs) from *Mentha* plants are commonly used in herbal cosmetics, foods and skin care products. Furthermore, plant-based antimicrobials are gaining attention due to their natural origins and comparatively safer profiles than synthetic alternatives[18].

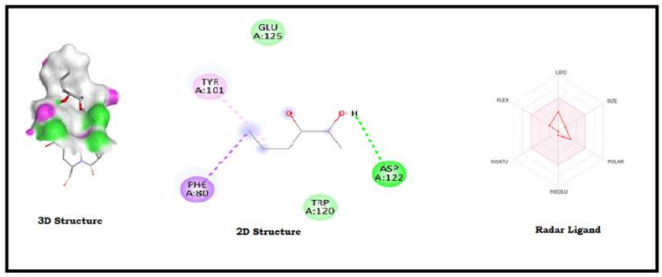
In terms of antimicrobial activity, the methanolic extract of *M. spicata* demonstrated a strong inhibitory effect against *Staphylococcus aureus*, followed by *Escherichia coli* and *Pseudomonas fluorescens*. However, it was ineffective against *Enterococcus faecalis* and *Streptococcus pyogenes*. The antioxidant potential of *M. spicata* was evaluated using the DPPH method, showing a Radical Scavenging Activity (RSA) of nearly 89%, indicating its capacity to scavenge free radicals effectively.

Phytochemical analysis using Gas Chromatography-Mass Spectrometry (GC-MS) identified 13 bioactive compounds in the methanolic extract, with 1,2-benzene dicarboxylic acid, dibutyl ester emerging as the most abundant compound[19]. *In silico* molecular docking studies were conducted to explore the binding affinity of the compounds with the Exendin-4 receptor (PDB: 3C59).

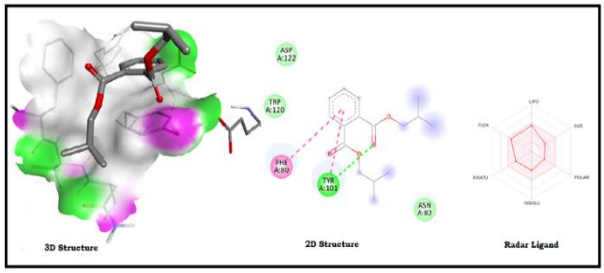
Among the compounds tested, indolizine, 2-(4-methylphenyl) exhibited the lowest binding energy of -5.7 kcal/mol, indicating a strong affinity for the receptor. Other compounds, such as 1,2-Benzene dicarboxylic acid, dibutyl ester and 1,2-Benzene dicarboxylic acid, Bis(2-Methyl Propyl) Ester, also showed favorable binding energies of -4.8 kcal/mol.

Table 3
Molecular docking score for the selected ligands with Ex-4 receptor [PDB: 3C59]

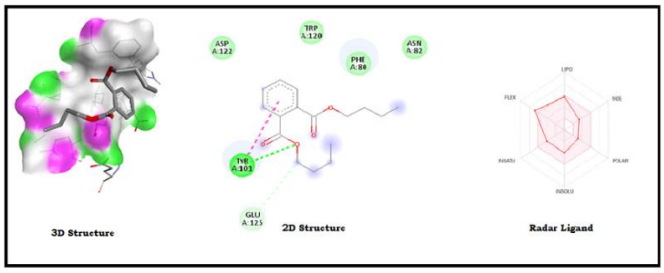
S.N.	Ligand	Docking score	No. of hydrogen bonds
1	(SS) - or (RR)-2,3-hexanediol	-3.3 kCal/mol	1
2	1,2-Benzene dicarboxylic acid, Dibutyl ester	-4.2 kCal/mol	2
3	1,2-Benzene dicarboxylic acid, Bis(2-Methyl Propyl) Ester	-4.6 kCal/mol	2
4	3,4-Dihydro-4-(1,3-Dioxolan-2-yl)-5,7-Dimethoxy-1(2H)-Benzopyran-2-ONE	-4.6 kCal/mol	1
5	Indolizine, 2-(4-methylphenyl)	-5.7 kCal/mol	0
6	Furo[2,3-c]pyridine, 2,3-dihydro-2,7-dimethyl-	-4.6 kCal/mol	1



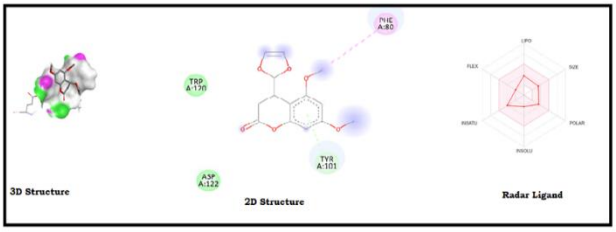
a) Interaction of (SS) - or (RR)-2,3-hexanediol with EX-4 [PDB: 3C59] protein



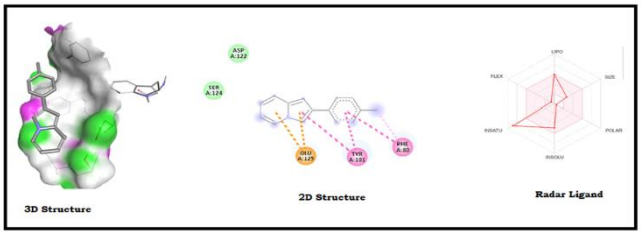
C) Interaction of1,2-Benzene dicarboxylic acid, Bis(2-Methyl Propyl) Ester with EX-4 [PDB: 3C59] protein



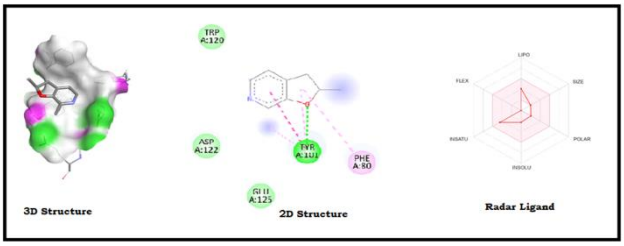
b) Interaction of1,2-Benzene dicarboxylic acid, Dibutyl ester with EX-4 [PDB: 3C59] protein



d) Interaction of 3,4-Dihydro-4-(1,3-Dioxolan-2-yl)-5,7-Dimethoxy-1(2H)-Benzopyran-2-ONE with EX-4 [PDB: 3C59] protein



e) Interaction of Indolizine, 2-(4-methylphenyl) with EX-4 [PDB: 3C59] protein



f) Interaction of Furo[2,3-c]pyridine, 2,3-dihydro-2,7-dimethyl with EX-4 receptor [PDB: 3C59]

Figure 3: Docking of Ligand with Ex-4

Furthermore, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) predictions using the Pre-ADMET server indicated that indolizine, 2-(4-methylphenyl) complies with all druglikeness rules, demonstrating high gastrointestinal absorption and permeability to the blood-brain barrier (BBB). The compound was found to be non-mutagenic and non-toxic to the liver, making it a promising candidate for further drug development[20]. The study underscores the potential of *M. spicata* as a source of bioactive compounds for the treatment of Huntington's disease and other pharmacological applications, combining traditional ethnomedicinal knowledge with modern computational methods for drug discovery[21].

Conclusion

The antibiogram of *M.spicata* was studied by using the methanolic extract through Soxhlet method. The result showed antibacterial activity against certain microbial species. *S.aureus* has good antibacterial activity. The phytochemicals extracted from the *M.spicata* were further analysed for Huntington's disease through molecular docking analysis. This species has some mind refreshing compounds and boosts the brain cells to active fast. The binding energy showed that indolizine, 2-(4-methylphenyl) (binding energy -5.7 kCal/mol) has the lowest binding energy for PDB: 3C59.

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