M. Tech (Industrial Biotechnology)

[ABHISHEK SINGH]

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DECIPHERING CURCUMIN'S THERAPEUTIC POTENTIAL IN NEURODEGENERATION: IN SILICO ANALYSIS AND COMPARISON WITH GALANTAMINE AND PRAMIPEXOLE

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE AWARD OF THE DEGREE

OF

MASTER OF TECHNOLOGY

IN

INDUSTRIAL BIOTECHNOLOGY

Submitted By:

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2K21/IBT/01

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MAY, 2023

CANDIDATE'S DECLARATION

I, **Abhishek Singh**, Roll No. **2K21/IBT/01** student of M. Tech (Industrial Biotechnology), hereby declare that the Project Dissertation titled **"Deciphering Curcumin's Therapeutic Potential in Neurodegeneration: In Silico Analysis and Comparison with Galantamine and Pramipexole"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology is original and not copied from any source without proper citation. The work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

Place: Delhi

Date: 24 May 2023

(ABHISHEK SINGH)

DEPARTMENT OF BIOTECHNOLOGY

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CERTIFICATE

I hereby certify that the Project Dissertation titled **"Deciphering Curcumin's Therapeutic Potential in Neurodegeneration: In Silico Analysis and Comparison with Galantamine and Pramipexole"** which is submitted by **Abhishek Singh**, Roll No. **2K21/IBT/01** Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of requirement for the award of degree of Master of Technology, is a record of the project work carried out by the student under my supervision. To the best of my knowledge, this work has not been submitted in part or full for any Degree or diploma to this University or elsewhere.

08/06/2023

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Date: 30 May 2023

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ABHISHEK SINGH

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ABSTRACT

The worldwide healthcare system faces substantial problems from neurodegenerative diseases, including Alzheimer's and Parkinson's. Innovative therapeutic drugs that target certain neurotransmitter receptors are essential for treating these disorders. In contrast to two well-known medications, galantamine and pramipexole, this research focuses on the therapeutic potential of curcumin, a naturally occurring substance, for the treatment of neurodegenerative illnesses. A molecular docking study utilizing AutoDock Vina was conducted on five crucial receptors associated with neurodegeneration, including acetylcholinesterase and dopamine receptors. The visualization and analysis of protein-ligand interactions were then carried out in PyMOL using stick models for the ligands and surface representations for the proteins. In PyMOL, the polar contacts between ligands and protein atoms were identified, and the bond lengths of these interactions were measured to analyse the molecular interactions.

The findings demonstrated curcumin's potential as a medicinal agent by revealing particular binding affinities and interactions between it and the chosen receptors. Galantamine and pramipexole demonstrated varied degrees of binding affinity in a comparative investigation, indicating the unique modes of action for each ligand. This thesis offers important information about the molecular foundations of curcumin's ability to cure neurodegenerative disorders and lays the groundwork for future in vitro and in vivo studies. Curcumin has been identified as a viable therapeutic option, which might result in the creation of more efficient treatment plans and eventually enhance the lives of people suffering from neurodegenerative diseases.

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LIST OF ABBREVIATIONS AND SYMBOLS

SYMBOL/ABBREVIATION	MEANING
AD	Alzheimer's Disease
PD	Parkinson's Disease
ALS	Amyotrophic lateral sclerosis
AChE	Acetylcholinesterase
AChEIs	Acetylcholinesterase inhibitors
ACh	Acetylcholine
THC	Delta-9-tetrahydrocannabinol
NMDA	N-methyl-D-aspartate
RMSD	Root mean square deviation

CHAPTER 1

INTRODUCTION

Debilitating cognitive and motor deficits are hallmarks of neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), which are progressive disorders defined by the loss of structure and function of neurons [1,2]. Neurodegenerative diseases are predicted to become more common with the ageing global population, putting a heavy strain on healthcare and social services [3]. Greater knowledge of the molecular processes involved in neurodegeneration and the identification of possible therapeutic targets is required to develop successful treatment methods for these illnesses [4].

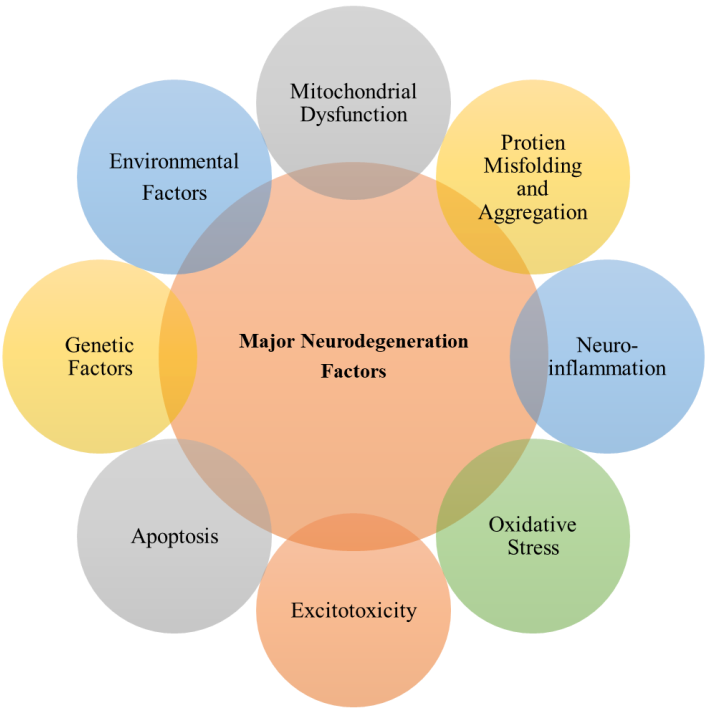

Fig 1.1: Major Factors Responsible for Neurodegeneration

The pathogenesis of neurodegenerative disorders is heavily influenced by neurotransmitter receptors [5, 6]. For example, the cholinesterase inhibitor galantamine and the dopamine receptor agonist pramipexole are both effective treatments for Alzheimer's disease and Parkinson's disease because they work by modulating these receptors [7,8]. Unfortunately, existing therapies aren't very effective and may have unwanted side effects [9]. Thus, novel treatment methods are required to address the complex pathophysiology of neurodegenerative disorders while minimizing associated side effects.

Natural compounds are being investigated as a possible route for the development of new therapies because they have the potential to provide various pharmacological activities with fewer adverse effects than synthesized medications [10]. A natural polyphenolic compound called curcumin has been isolated from the spice turmeric, and it's gotten a lot of interest for its possible neuroprotective qualities and low side-effect profile [11]. Multiple signalling pathways, including those involving neurotransmitter receptors, have been linked to neurodegeneration, and previous research has shown that curcumin may affect these pathways [12]. Curcumin has been shown to have therapeutic benefits, although the molecular interactions that produce these effects are still poorly understood.

This thesis aimed to examine curcumin's molecular interactions with major neurotransmitter receptors and determine whether it would be useful as a treatment agent for neurodegenerative diseases, similar to galantamine and pramipexole. Through the utilization of computational methodologies, specifically molecular docking and protein-ligand interaction analysis, the present study endeavours to offer innovative perspectives regarding the molecular basis of curcumin's therapeutic efficacy. This investigation aims to establish a fundamental framework for subsequent in vitro and in vivo research.

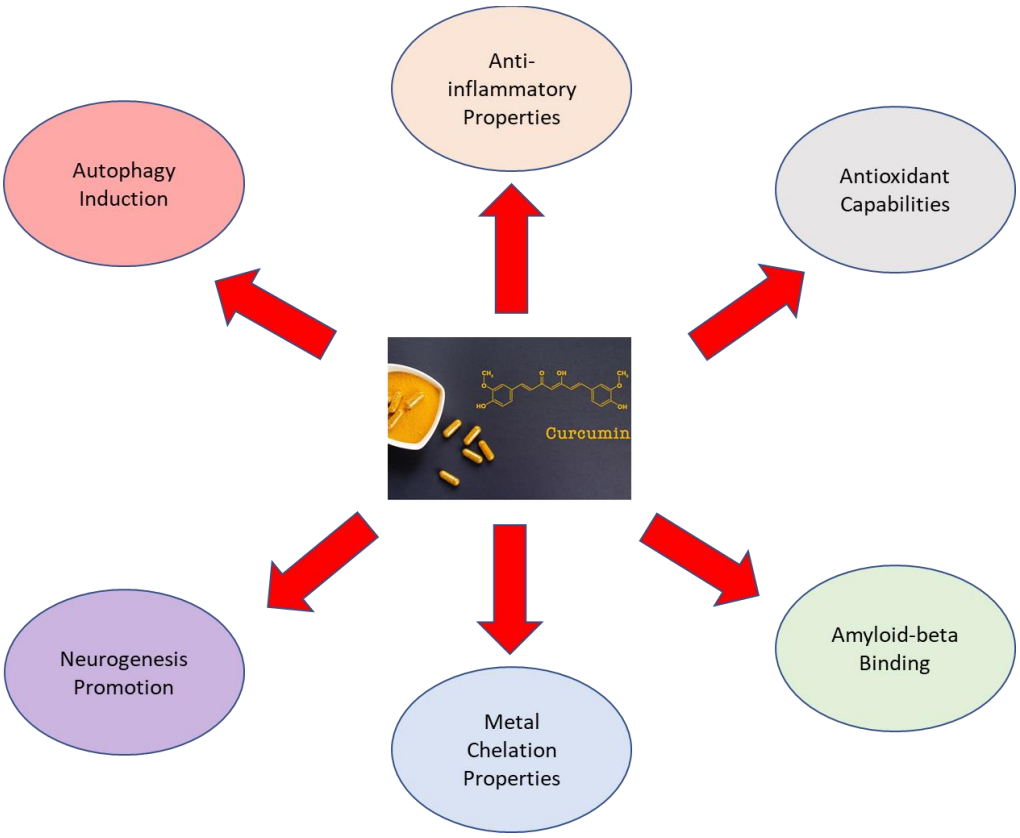

Figure 1.2: Multifaceted Neuroprotective Properties of Curcumin

Molecular docking is a popular computational approach in drug development that uses the complementary morphologies and physicochemical features of a ligand and a target protein to predict the binding position and affinity of the two [13]. This method has the potential to inform the rational development of novel therapeutic treatments [14] and shed light on the molecular recognition process. Successful applications of molecular docking to predict the binding modalities and affinities of different ligands to neurotransmitter receptors, such as serotonin and dopamine receptors, have been made in the setting of neurodegenerative disorders [15,16]. This work seeks to explain the molecular basis of curcumin's therapeutic potential for neurodegenerative illnesses by comparing its anticipated binding poses and affinities with those of galantamine and pramipexole.

Understanding the molecular processes that underlie the biological activity of a ligand and its target protein requires an examination of the protein-ligand interaction [17]. Researchers may pinpoint important residues in the binding process and create novel compounds with enhanced binding capabilities by viewing and studying the interactions between the ligand and the protein, including hydrogen bonds, hydrophobic contacts, and salt bridges [18]. In this investigation, we will utilize the PyMOL molecular graphics system to display and evaluate the binding mechanisms and possible therapeutic effects of curcumin, galantamine, and pramipexole on the chosen neurotransmitter receptors.

Finally, using molecular docking and protein-ligand interaction analysis, this study aims to shed light on the potential of curcumin as a therapeutic agent for neurodegenerative diseases by comparing its molecular interactions with key neurotransmitter receptors to those of approved drugs like galantamine and pramipexole. Our goal is to aid in the discovery of new, more effective, and fewer harmful therapies for neurodegenerative diseases like Alzheimer's and Parkinson's by elucidating the molecular basis of curcumin's therapeutic potential. This research may pave the way for future in vitro and in vivo studies, which might lead to the development of novel treatment techniques to combat the increasing prevalence of neurodegenerative diseases in our ageing population.

Objectives of this study:

1. Perform a comprehensive computational analysis, including molecular docking, to understand the therapeutic potential of curcumin, galantamine, and pramipexole in neurodegeneration.
2. Compare the efficacy of curcumin with established drugs like galantamine and pramipexole to identify their strengths and weaknesses, guiding future drug development efforts.
3. Visualize and analyse the molecular interactions between these compounds and their receptors, uncovering the structural basis and key amino acid residues involved in binding and specificity. This knowledge will enhance our understanding of their therapeutic mechanisms in neurodegenerative diseases.

CHAPTER 2

REVIEW OF LITERATURE

Neurodegeneration involves the progressive loss of neuron structure or function, ultimately leading to neuron death [19]. Various neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), are associated with this process [20]. These conditions result in the gradual deterioration of cognitive and motor functions, causing significant disability and reduced quality of life [21].

Researchers have not yet fully understood the exact mechanisms underlying neurodegeneration, but they have implicated several factors, including protein aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation [22]. Specific types of neurons or neuronal populations often experience dysfunction in neurodegenerative diseases, leading to the characteristic clinical features of each disease [23]. For example, Alzheimer's disease primarily affects cholinergic neurons in the brain, while Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra [24].

Considering the growing global burden of neurodegenerative diseases and the limited efficacy of current treatments, researchers urgently need to develop novel therapeutic approaches targeting these conditions' underlying mechanisms [25]. Studying key receptors implicated in neurodegeneration, such as acetylcholinesterase, cannabinoid, dopamine, NMDA, and serotonin, presents a promising avenue for the development of new pharmacological interventions [26].

2.1 Neurodegenerative Receptors Focused on in This Study:

2.1.1 Dopamine Receptors:

Dopamine receptors are a class of G protein-coupled receptor that helps control movement, drive, reward, and the release of other neurotransmitters[27]. The two predominant families of dopamine receptors, namely D1-like (D1 and D5) and D2-like (D2, D3, and D4), manifest unique signalling pathways and physiological functions [28].

Several neurodegenerative diseases, including Parkinson's, Alzheimer's, and Huntington's, have been linked to dysfunctional dopamine receptors. Dopamine levels drop and dopamine receptors become dysfunctional in Parkinson's disease because of the death of neurons in the substantia nigra that produce dopamine [29].

The tremors, stiffness, and bradykinesia that are hallmarks of Parkinson's disease are all the outcomes of this dysfunction [30]. To alleviate the symptoms of Parkinson's disease, many doctors use drugs that either boost brain dopamine levels or act as agonists on dopamine receptors [31].

Dopamine receptors have been linked to Alzheimer's disease pathophysiology as well. Alzheimer's patients have been shown to have abnormal dopamine signalling, as well as changes in dopamine receptor expression and function [32]. Targeting dopamine receptors, especially the D1 and D2 subtypes, has been found in studies to enhance cognitive performance and reduce certain symptoms associated with Alzheimer's disease [33].

Abnormalities in dopamine receptor function have also been related to Huntington's disease [34], a neurodegenerative condition marked by the gradual loss of motor control and cognitive deterioration. Animal models of Huntington's disease have shown changes in dopamine signalling pathways and receptor expression, and pharmaceutical manipulation of dopamine receptors has shown some promise for alleviating symptoms [35].

2.1.2 Serotonin Receptors:

A wide variety of physiological activities, including mood, hunger, and sleep, are governed by serotonin (5-HT) receptors [36]. The bulk of these receptors belongs to the G protein-coupled receptor family (from 5-HT1 to 5-HT7), whereas the 5-HT3 receptor is a ligand-gated ion channel [37]. Depression and anxiety, among other neuropsychiatric illnesses, have been linked to serotonergic system dysregulation [38].

Serotonin receptors have been linked to the development of Alzheimer's disease. The density of some serotonin receptors, including 5-HT2A and 5-HT4, has been demonstrated to be lower in Alzheimer's patients [39]. Deficits in cognition and other symptoms of the disease may be triggered by this decline. In addition, preclinical models of Alzheimer's disease have indicated some hope for the pharmaceutical targeting of serotonin receptors, notably the 5-HT6 receptor, to improve cognitive performance [40].

Serotonin receptor abnormalities are also linked to Parkinson's disease. Dopaminergic neuron degeneration in the substantia nigra leads to decreased dopamine levels, which in turn causes motor symptoms in Parkinson's disease.

Non-motor symptoms such as anxiety and depression, on the other hand, are widespread in Parkinson's patients and may be linked to serotonin receptor malfunction [41]. The density of some serotonin receptors, such as 5-HT1A and 5-HT2A, has been observed to change in Parkinson's disease [42]. Non-motor symptoms in Parkinson's patients may be improved by treatments that target serotonin receptors [43].

Huntington's disease, a hereditary neurodegenerative condition with motor, cognitive, and behavioural symptoms, has also been related to changes in serotonin receptor function. Post-mortem investigations have shown decreased serotonin levels as well as changes in the density and location of serotonin receptors in the brains of Huntington's patients [44]. In animal models of Huntington's disease, pharmacological manipulation of serotonin receptors has shown some promise in easing symptoms and slowing disease development [45].

2.1.3 Acetylcholinesterase Receptors:

The function of the neurotransmitter acetylcholine at cholinergic synapses is blocked by the enzyme acetylcholinesterase (AChE) [46]. The cholinergic system, in which AChE plays an essential part, is involved in learning and memory, among other cognitive processes. As the cholinergic system is severely damaged in Alzheimer's disease [47], inhibiting AChE has been a prominent treatment method.

Alzheimer's disease is characterized by a notable decline in cholinergic neurons and an associated reduction in ACh levels, as per earlier studies [48]. The cognitive impairments that are commonly observed in Alzheimer's disease are thought to be linked to a deficiency in cholinergic activity. Acetylcholinesterase inhibitors (AChEIs) represent a key therapeutic approach for addressing Alzheimer's disease. These inhibitors function by blocking the activity of AChE, thereby elevating ACh levels within the brain [49]. AChEIs have been shown to provide modest improvements in cognitive function and global clinical outcomes in Alzheimer's patients [50].

Cholinergic dysfunction is a notable feature in Parkinson's disease, particularly in advanced stages and among patients with cognitive deficits. AChEIs have been investigated as a prospective therapeutic intervention for cognitive impairments in Parkinson's disease.

Several clinical trials have reported enhancements in attention, executive function, and memory following AChEI treatment [51]. Additionally, AChEIs may help alleviate some non-motor symptoms of Parkinson's disease, such as visual hallucinations and fluctuations in attention [52].

Cholinergic deficiencies have also been associated with Lewy body dementia [53], a neurodegenerative illness marked by gradual cognitive deterioration, parkinsonism, and visual hallucinations. Cognitive performance, overall clinical outcomes, and certain neuropsychiatric symptoms have all improved with the administration of AChEIs in Lewy body dementia [54].

2.1.4 Cannabinoid Receptors:

Another group of G protein-coupled receptors, cannabinoid receptors, are responsible for mediating the actions of endogenous and exogenous cannabinoids, such as the psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC) [55]. Cannabinoid receptors (CB1 and CB2) were shown to be mostly expressed in the brain and the immune system, respectively [56]. Multiple sclerosis, Parkinson's disease, and Alzheimer's disease are only some of the neurodegenerative conditions that have been linked to the endocannabinoid system [57].

CB1 and CB2 receptor expression and endocannabinoid levels are two areas of the endocannabinoid system that have been shown to fluctuate in Alzheimer's disease [58]. Targeting the endocannabinoid system has shown promise in preclinical research for its potential to have neuroprotective benefits in Alzheimer's disease [59]. These include lowering neuroinflammation, increasing amyloid-beta clearance, and enhancing synaptic plasticity.

Alterations in the endocannabinoid system, such as changes in endocannabinoid levels and the expression of cannabinoid receptors, have also been linked to Parkinson's disease [60]. Evidence from animal models of Parkinson's disease suggests that influencing the endocannabinoid system may reduce neuroinflammation and improve motor symptoms by influencing dopamine release [61].

The endocannabinoid system has been linked to the modulation of immunological responses and the management of neuroinflammation in demyelinating neurodegenerative diseases like multiple sclerosis [62]. Cannabinoids have shown potential for treating spasticity, pain, and other MS symptoms by acting on the endocannabinoid system [63].

2.1.5 NMDA Receptors:

The ionotropic glutamate receptors known as N-methyl-D-aspartate receptor (NMDA) receptors are essential for synaptic plasticity and memory [64]. Two GluN1 subunits and two GluN2 or GluN3 subunits make up these heterotetrameric complexes [65]. Alzheimer's disease, Parkinson's disease, and schizophrenia are only some of the neurodegenerative and neuropsychiatric diseases that have been linked to NMDA receptor dysregulation [66]. The therapeutic potential of NMDA receptor function modulation in various diseases has been extensively investigated [67].

Neuronal damage and loss are hallmarks of Alzheimer's disease, and there is mounting evidence that NMDA receptor-mediated excitotoxicity plays a role in this process [68]. Excessive NMDA receptor activation is hypothesized to cause excitotoxicity by raising intracellular calcium levels and setting off several cell death pathways [69]. Memantine, an NMDA receptor antagonist, has been shown to enhance cognitive function and overall clinical outcomes by a small amount, warranting its approval for the treatment of moderate to severe Alzheimer's disease [70].

Loss of dopaminergic neurons and the emergence of motor and non-motor symptoms in Parkinson's disease have both been linked to NMDA receptor dysfunction [71]. Animal models of Parkinson's disease have shown that NMDA receptor antagonists may have neuroprotective benefits and reduce motor symptoms [72].

Another progressive neurodegenerative ailment associated with NMDA receptor failure is Huntington's disease, which manifests in motor, cognitive, and psychiatric ways. Excessive activation of NMDA receptors has been linked to excitotoxicity and neuronal death in animal models of Huntington's disease [73]. More study is required to determine the therapeutic potential of NMDA receptor antagonists as a therapy for Huntington's disease, although clinical studies have not shown substantial improvements thus far [74].

2.2 Ligands investigated in this study for potential therapeutic effect:

2.2.1 Curcumin:

Chemical structure and properties: Curcumin, a natural polyphenol, is extracted from the turmeric (Curcuma longa) plant's rhizomes. It has a bright yellow hue and a characteristic smell. The pharmacological effects are attributed to its chemical structure, which consists of two aromatic rings linked by α,β-unsaturated carbonyl group [75].

Neurological effects: Curcumin has been demonstrated to have many neuroprotective benefits, particularly suppressing the pathogenesis-related processes of inflammation, oxidative stress, and beta-amyloid deposition [76].

Potential therapeutic effects on neurodegenerative diseases: Curcumin may have therapeutic benefits for neurodegenerative disorders, according to many studies. These include Alzheimer's, Parkinson's, and Huntington's diseases. Animal models of neurodegenerative disorders have shown that curcumin may enhance cognitive performance, decrease motor symptoms, and halt disease development [77].

Mode of action: It has yet to be discovered how curcumin really works in the brain and neurological system. It has been found to interact with a number of targets related to neurodegenerative diseases, including the NMDA receptor, the dopamine transporter, and acetylcholinesterase [78].

Interaction with selected receptors: Curcumin's interactions with the selected receptors have been established, and they include the serotonin receptor, the dopamine receptor, and the NMDA receptor. According to a recent study, curcumin may protect the NMDA receptor by decreasing its overactivation and resultant excitotoxicity [79].

Overall, curcumin's neuroprotective benefits and interactions with several nervous system targets make it a promising candidate as a therapeutic agent for neurodegenerative diseases. Its method of action and possible therapeutic uses need more study.

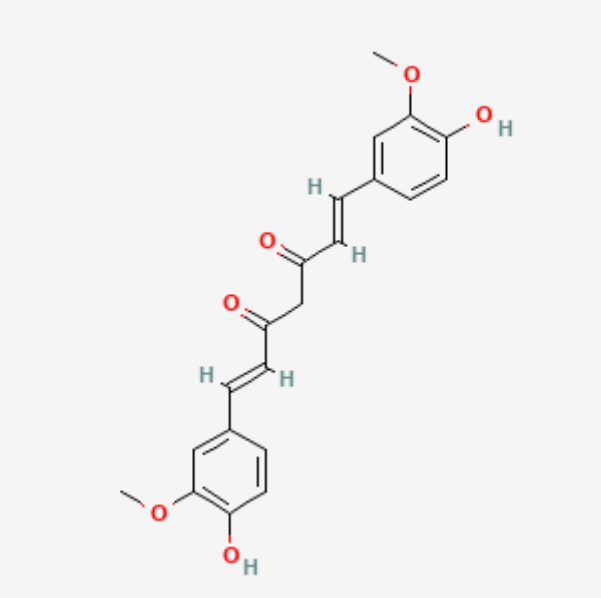

Figure 2.1: Curcumin Chemical Structure

2.2.2 Galantamine:

Chemical structure and properties: Galantamine, a chemical compound with unique characteristics, is extracted from the blooms and bulbs of the Galanthus Caucasus species [80]. Its tricyclic structure, which includes a nitrogen atom, is characteristic of alkaloids [81].

Neurological effects: Galantamine's ability to inhibit acetylcholinesterase, hence improving cholinergic function, has earned it recognition as a cognitive enhancer [82,83].

Potential therapeutic effects on neurodegenerative diseases: Galantamine has been licensed for the treatment of mild to moderate Alzheimer's disease, suggesting its therapeutic potential for other neurodegenerative diseases. Improved cognition and function are only two of the many treatment effects that have been shown in clinical studies [84].

Mode of action: Galantamine works by blocking an enzyme called acetylcholinesterase, which keeps acetylcholine in the synaptic cleft for a longer period of time. Its unique therapeutic benefits may be attributed in part to its ability to alter nicotinic acetylcholine receptors [85].

Interaction with selected receptors: Galantamine's interactions with the selected receptors have been thoroughly investigated. The enzyme acetylcholinesterase breaks down acetylcholine, a neurotransmitter that is crucial for memory and cognition [86].

In conclusion, galantamine is a significant contributor in the area of neurodegenerative diseases due to its dual mode of action and established therapeutic advantages in Alzheimer's disease. However, further study is needed to determine whether or not it can be used as a treatment for other forms of neurodegeneration.

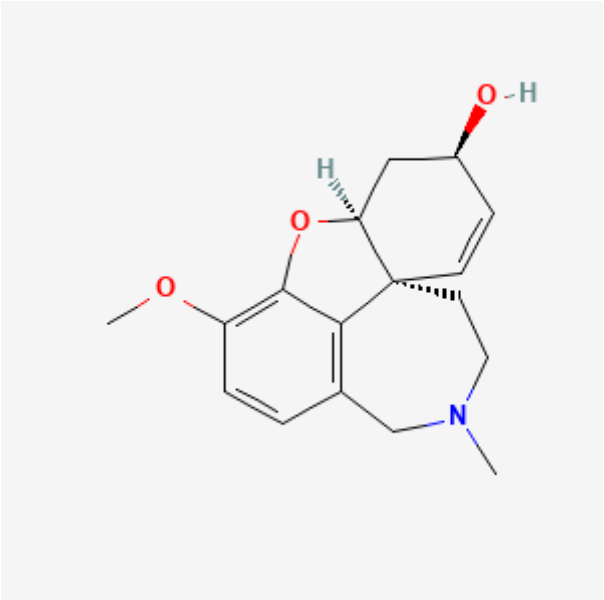

Figure 2.2 : Galantamine Chemical Structure

2.2.3 Pramipexole:

Chemical structure and properties: Pramipexole, a non-ergoline dopamine agonist, uniquely belongs to the benzothiazole class of compounds. Its structure comprises a six-membered thiazole ring fused with a benzene ring [87].

Neurological effects: Studies have shown that Pramipexole exerts potent effects on the dopaminergic system, specifically activating D2 and D3 dopamine receptors in the striatum and substantia nigra, areas of the brain that control motor functions [88].

Potential therapeutic effects on neurodegenerative diseases: Physicians primarily prescribe Pramipexole for the treatment of Parkinson's disease and Restless Legs Syndrome, conditions that stem from dopamine deficiency. Recent studies are starting to explore its potential neuroprotective properties and its effects on depressive symptoms [89,90].

Mode of action: Pramipexole primarily works by activating dopamine receptors, thereby mimicking the effects of dopamine, a neurotransmitter deficient in patients with Parkinson's disease. Besides, Pramipexole may also inhibit the release of glutamate, which in turn protects neurons from excitotoxic damage [89].

Interaction with selected receptors: Pramipexole exhibits a high affinity for the D2, D3, and D4 dopamine receptors, but it mainly acts on the D2 and D3 subtypes [27].

In conclusion, the dopaminergic activity of Pramipexole and its potential neuroprotective properties make it a crucial drug in treating neurodegenerative diseases. Further research is needed to fully understand its therapeutic potential and safety profile.

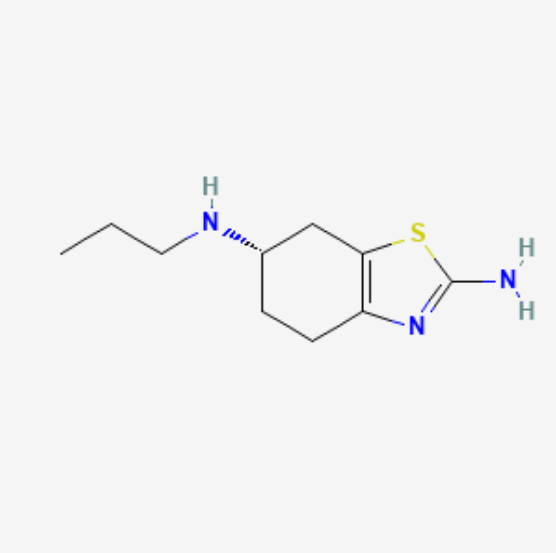

Figure 2.3: Pramipexole Chemical Structure

2.3 Bioinformatics Tools Used in This Study

2.3.1 AutoDock Vina:

AutoDock Vina is a highly known and often used molecular docking program created by the Scripps Research Institute [91]. It is notable for its accuracy in predicting binding affinities and poses, computational efficiency, and user-friendly interface. Trott and Olson (2010) made substantial enhancements to the original AutoDock, which increased its speed and made its search method more effective. Drug discovery, protein engineering, and structure-based drug design are just some of the many areas of study that have recently made use of AutoDock Vina to investigate molecular interactions between ligands and protein targets [92].

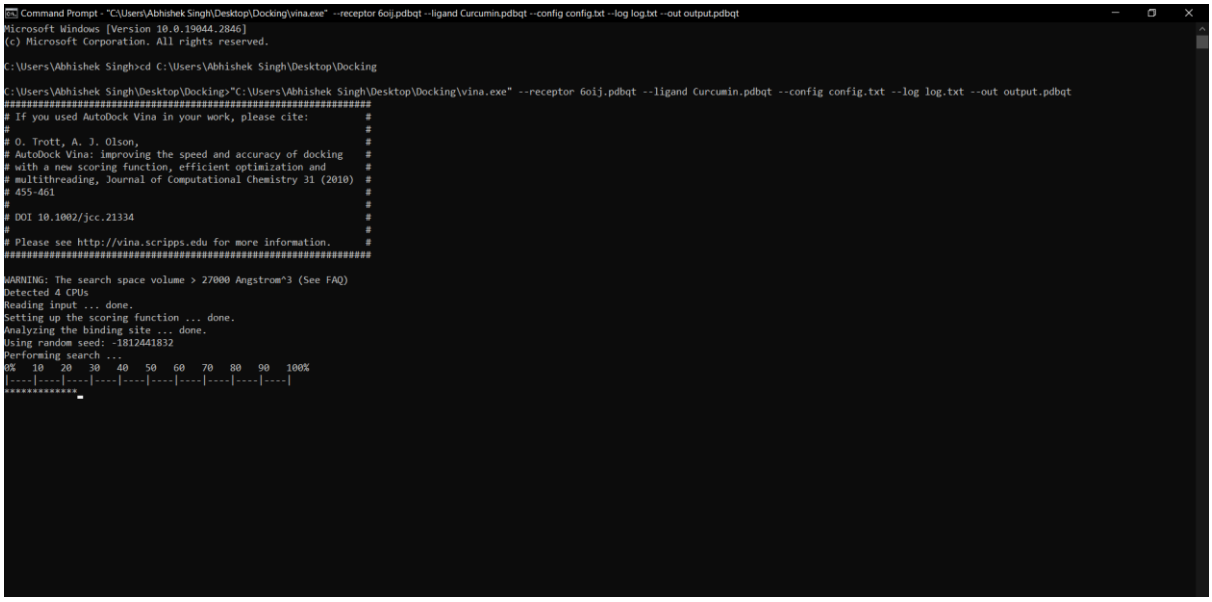

Figure 2.4: A Typical AutoDock Vina Running Window

2.3.2 PyMOL:

PyMOL is a versatile and popular molecular visualization tool developed by Warren L. DeLano and currently maintained by Schrödinger. The program enables researchers to examine and study three-dimensional molecular structures, including proteins, nucleic acids, and tiny compounds. PyMOL's powerful features allow the development of high-quality pictures and animations of protein-ligand complexes, offering vital insights into binding sites and crucial interactions that contribute to ligand binding and specificity [93]. Lill and Danielson (2011) explored the implementation of PyMOL as a platform for computer-aided drug design, stressing its promise in structure-based drug discovery efforts. PyMOL has been used in various studies to examine and show the results of molecular docking simulations, validating the validity of computational models and helping researchers understand the structural basis of ligand-protein interactions [94].

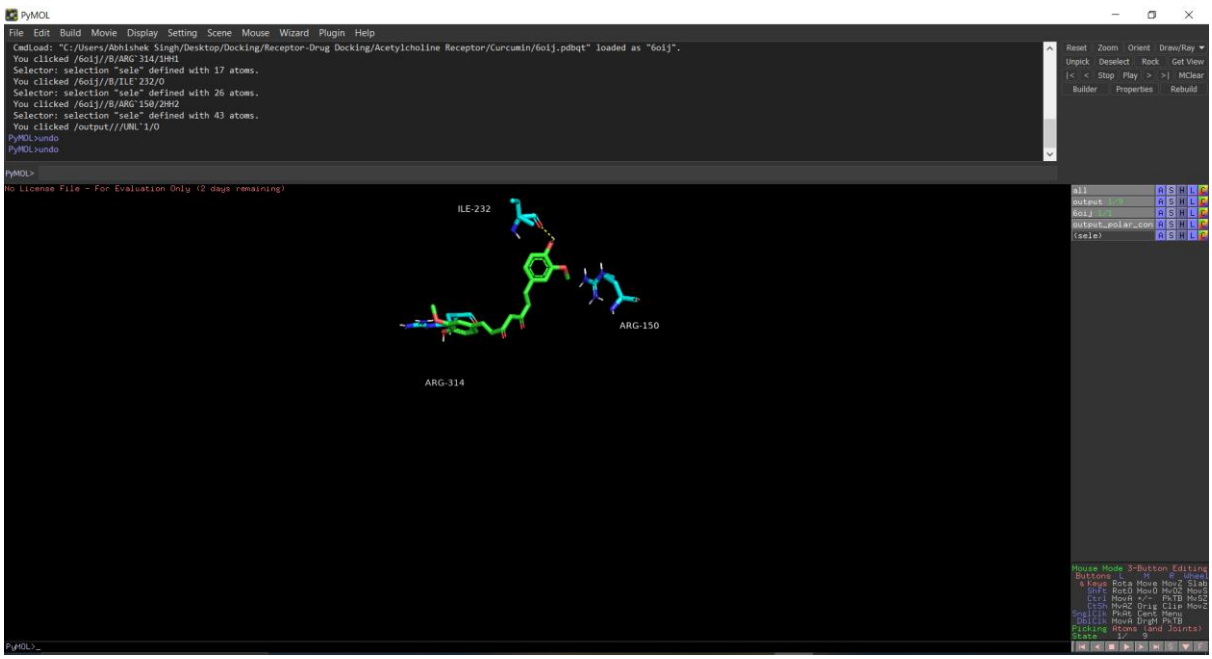

Figure 4.5: A PyMol Window during Visualisation

CHAPTER 3

METHODOLOGY

3.1 Acetylcholinesterase Receptor

3.1.1 Acetylcholinesterase Receptor-Curcumin Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of curcumin from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of acetylcholinesterase receptor (PDB ID: 6oij) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 118.192, 101.959, and 113.034, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked curcumin) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked curcumin as sticks

c. Identified polar contacts between the docked curcumin and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and curcumin-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.1.2 Acetylcholinesterase Receptor-Galantamine Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of galantamine from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of acetylcholinesterase receptor (PDB ID: 6oij) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 118.192, 101.959, and 113.034, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked galantamine) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked galantamine as sticks

c. Identified polar contacts between the docked galantamine and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and galantamine-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.1.3 Acetylcholinesterase Receptor-Pramipexole Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of pramipexole from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of acetylcholinesterase receptor (PDB ID: 6oij) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 118.192, 101.959, and 113.034, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked pramipexole) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked pramipexole as sticks

c. Identified polar contacts between the docked pramipexole and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and pramipexole-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.2 Cannabinoid Receptor

3.2.1 Cannabinoid Receptor-Curcumin Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of curcumin from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the cannabinoid receptor (PDB ID: 5zty) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 5.902, -4.854, and -26.652, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked curcumin) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked curcumin as sticks

c. Identified polar contacts between the docked curcumin and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and curcumin-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.2.2 Cannabinoid Receptor-Galantamine Docking and Visualisation

I. Data preparation for cannabinoid receptor-curcumin interaction:

a. Downloaded the 3D structure of galantamine from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the cannabinoid receptor (PDB ID: 5zty) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 5.902, -4.854, and -26.652, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked galantamine) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked galantamine as sticks

c. Identified polar contacts between the docked galantamine and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and galantamine-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.2.3 Cannabinoid Receptor-Pramipexole Docking and Visualisation

I. Data preparation for cannabinoid receptor-curcumin interaction:

a. Downloaded the 3D structure of pramipexole from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the cannabinoid receptor (PDB ID: 5zty) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 5.902, -4.854, and -26.652, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked pramipexole) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked pramipexole as sticks

c. Identified polar contacts between the docked pramipexole and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and pramipexole-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.3 Dopamine Receptor

3.3.1 Dopamine Receptor-Curcumin Molecular Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of curcumin from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the dopamine receptor (PDB ID: 6cm4) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 17.684, 1.438, and 14.969, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked curcumin) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked curcumin as sticks

c. Identified polar contacts between the docked curcumin and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and curcumin-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.3.2 Dopamine Receptor-Galantamine Molecular Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of galantamine from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the dopamine receptor (PDB ID: 6cm4) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 17.684, 1.438, and 14.969, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked galantamine) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked galantamine as sticks

c. Identified polar contacts between the docked galantamine and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and galantamine-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.3.3 Dopamine Receptor-Pramipexole Molecular Docking and Visualisation

I. Data preparation:

a. Downloaded the 3D structure of pramipexole from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the dopamine receptor (PDB ID: 6cm4) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 17.684, 1.438, and 14.969, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked pramipexole) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked pramipexole as sticks

c. Identified polar contacts between the docked pramipexole and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and pramipexole-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.4 N-methyl-D-aspartate (NMDA) Receptor

3.4.1 NMDA Receptor-Curcumin Molecular Docking and Visualisation

I. Data preparation for N-methyl-D-aspartate (NMDA) receptor-curcumin interaction:

a. Downloaded the 3D structure of curcumin from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the NMDA receptor (PDB ID: 6dwq) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 32.313, -21.122, and 5.097, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked curcumin) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked curcumin as sticks

c. Identified polar contacts between the docked curcumin and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and curcumin-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.4.2 NMDA Receptor-Galantamine Molecular Docking and Visualisation

I. Data preparation for N-methyl-D-aspartate (NMDA) receptor-Galantamine interaction:

a. Downloaded the 3D structure of galantamine from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the NMDA receptor (PDB ID: 6dwq) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 32.313, -21.122, and 5.097, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked Galantamine) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked galantamine as sticks

c. Identified polar contacts between the docked galantamine and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and Galantamine-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.4.3 NMDA Receptor-Pramipexole Molecular Docking and Visualisation

I. Data preparation for N-methyl-D-aspartate (NMDA) receptor-Pramipexole interaction:

a. Downloaded the 3D structure of pramipexole from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the NMDA receptor (PDB ID: 6dwq) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 32.313, -21.122, and 5.097, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked Pramipexole) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked pramipexole as sticks

c. Identified polar contacts between the docked pramipexole and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and Pramipexole-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.5 Serotonin Receptor

3.5.1 Serotonin Receptor-Curcumin Molecular Docking and Visualization

I. Data preparation for serotonin receptor-curcumin interaction:

a. Downloaded the 3D structure of curcumin from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the serotonin receptor (PDB ID: 6bqh) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 40.188, 33.467, and 40.750, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked curcumin) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked curcumin as sticks

c. Identified polar contacts between the docked curcumin and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labelled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the color, transparency, and resolution of the protein surface and curcumin-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.5.2 Serotonin Receptor-Galantamine Molecular Docking and Visualization

I. Data preparation for serotonin receptor-galantamine interaction:

a. Downloaded the 3D structure of galantamine from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the serotonin receptor (PDB ID: 6bqh) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 40.188, 33.467, and 40.750, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked galantamine) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked galantamine as sticks

c. Identified polar contacts between the docked galantamine and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labeled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the colour, transparency, and resolution of the protein surface and galantamine-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

3.5.3 Serotonin Receptor-Pramipexole Molecular Docking and Visualization

I. Data preparation for serotonin receptor-pramipexole interaction:

a. Downloaded the 3D structure of pramipexole from PubChem in SDF format and converted it to PDB format using PyMOL

b. Obtained the PDB file of the serotonin receptor (PDB ID: 6bqh) from the Protein Data Bank

II. Ligand and protein preparation using AutoDock Tools:

a. Prepared the ligand and protein by removing water molecules, adding polar hydrogens, and assigning Kollman charges

b. Created .pdbqt files for both the ligand and the protein

III. Grid box and configuration file preparation:

a. Defined the grid box using AutoDock Tools with size_x, size_y, and size_z set to 40 and center_x, center_y, and center_z set to 40.188, 33.467, and 40.750, respectively

b. Prepared the configuration file for AutoDock Vina

IV. Molecular docking with AutoDock Vina:

a. Changed the directory in the command prompt to the folder containing the vina.exe file

b. Executed the docking simulation using the command template: "--receptor receptor.pdbqt --ligand ligand.pdbqt --config config.txt --log log.txt --out output.pdbqt"

V. Visualization and analysis of docking results using PyMOL:

a. Opened the output.pdbqt file (containing the docked pramipexole) and the receptor protein pdbqt file in PyMOL

b. Displayed the receptor as lines and the docked pramipexole as sticks

c. Identified polar contacts between the docked pramipexole and amino acid residues in the receptor

d. Created a selection for the identified polar binding residues and renamed it to "binding residues"

e. Displayed binding residues as sticks and labeled them with amino acid names and residue numbers using the label function

f. Measured the distances between interacting atoms using the "Measurement" option in the "Wizard" menu

g. Displayed the receptor protein as a surface model

h. Adjusted the color, transparency, and resolution of the protein surface and pramipexole-receptor interaction for better visualization

i. Saved the customized image of the protein-ligand complex for further analysis and documentation

Figure 3.1: Research Methodology Flowchart

CHAPTER 4

RESULT AND DISCUSSION

4.1 RESULT

4.1.1 Acetylcholinesterase Receptor Interactions

The molecular docking simulations for acetylcholinesterase (AChE) with curcumin, galantamine, and pramipexole were performed using AutoDock Vina. The top 2 hits of each docking were selected for further analysis and presentation based on their binding affinities and RMSD values. The binding affinities and RMSD values for the selected hits are presented in Table 4.1.

Table 4.1: Binding affinities and RMSD values for the top 2 hits of Acetylcholinesterase Receptor interactions.

Interaction	Mode	Affinity (kcal/mol)	RMSD l.b.	RMSD u.b.
Acetylcholinesterase-Curcumin	1	-7.8	0.000	0.000
Acetylcholinesterase-Curcumin	2	-7.7	2.188	3.933
Acetylcholinesterase-Galantamine	1	-7.9	0.000	0.000
Acetylcholinesterase-Galantamine	2	-7.3	27.969	30.083
Acetylcholinesterase-Pramipexole	1	-5.9	0.000	0.000
Acetylcholinesterase-Pramipexole	2	-5.8	4.596	7.571

The molecular interactions between AChE and the ligands were visualized using PyMOL. The top-scoring binding mode for each ligand showed the following interactions:

1. Acetylcholinesterase-Curcumin: Curcumin interacted with key residues in the active site of AChE, forming hydrogen bonds and hydrophobic interactions with ARG 150, ARG 314, and ILE 232 (Figure 4.1).
2. Acetylcholinesterase-Galantamine: Galantamine established several hydrogen bonds and hydrophobic interactions with AChE, occupying the enzyme's active site, and making polar contacts with MET 61 and ARG 150 (Figure 4.2).
3. Acetylcholinesterase-Pramipexole: Pramipexole interacted with AChE through hydrogen bonding and hydrophobic interactions, binding to the enzyme's active site, and making polar contacts with ARG 150, LEU 190, ILE 232, SER 275, and SER 316 (Figure 4.3).

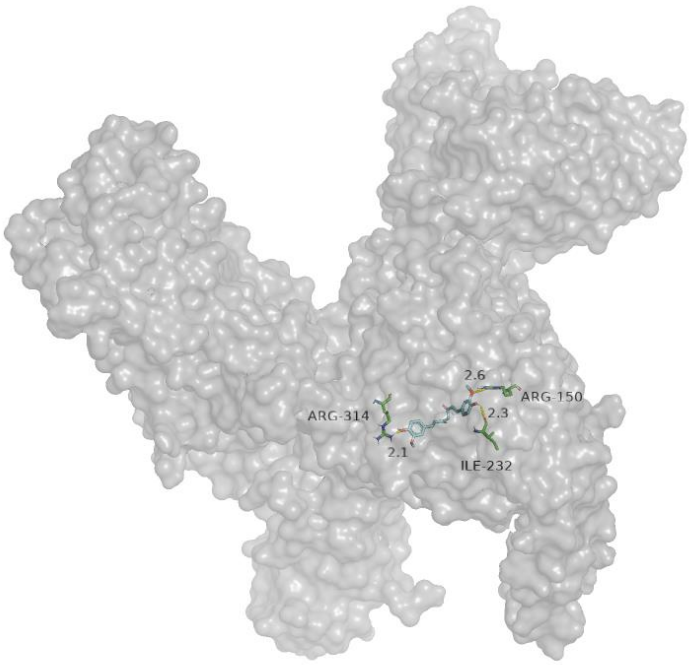

Figure 4.1: Acetylcholinesterase Receptor-Curcumin interaction

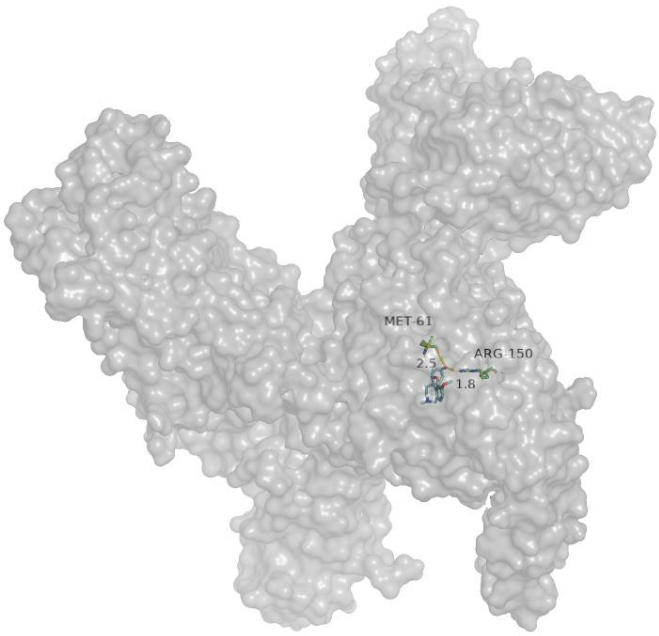

Figure 4.2: Acetylcholinesterase Receptor-Galantamine interaction

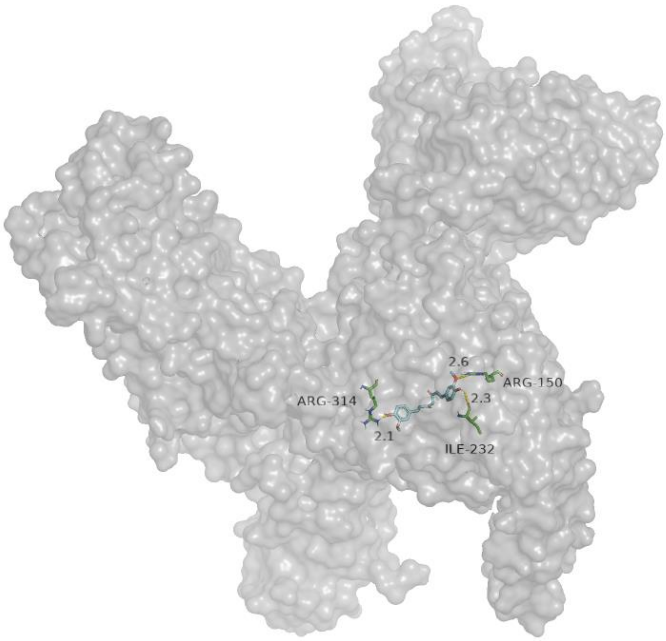

Figure 4.3: Acetylcholinesterase Receptor-Pramipexole interaction.

In summary, the molecular docking results suggest that curcumin, galantamine, and pramipexole can interact with acetylcholinesterase, with curcumin and galantamine showing higher binding affinities than pramipexole. The visualization of these interactions provides insights into the potential binding modes and key residues involved in ligand-receptor interactions.

4.1.2 Cannabinoid Receptor Interactions

The molecular docking simulations for the cannabinoid receptor with curcumin, galantamine, and pramipexole were performed using AutoDock Vina. The top 2 hits of each docking were selected for further analysis and presentation based on their binding affinities and RMSD values. The binding affinities and RMSD values for the selected hits are presented in Table 4.2.

Table 4.2: Binding affinities and RMSD values for the top 2 hits of Cannabinoid Receptor interactions

Interaction	Mode	Affinity (kcal/mol)	RMSD l.b.	RMSD u.b.
Cannabinoid Receptor-Curcumin	1	-7.1	0.000	0.000
Cannabinoid Receptor-Curcumin	2	-6.6	1.346	9.562
Cannabinoid Receptor-Galantamine	1	-6.5	0.000	0.000
Cannabinoid Receptor-Galantamine	2	-5.9	31.420	33.532
Cannabinoid Receptor-Pramipexole	1	-5.3	0.000	0.000
Cannabinoid Receptor-Pramipexole	2	-4.8	3.054	6.064

The molecular interactions between the cannabinoid receptor and the ligands were visualized using PyMOL. The top-scoring binding mode for each ligand showed the following interactions:

1. Cannabinoid Receptor-Curcumin: Curcumin interacted with key residues in the active site of the cannabinoid receptor, forming polar contacts with 2 amino acids: ARG 1007 and ARG 1147 (Figure 4.4).
2. Cannabinoid Receptor-Galantamine: Galantamine established a polar contact with 1 amino acid of the receptor: MET 147 (Figure 4.5).
3. Cannabinoid Receptor-Pramipexole: Pramipexole interacted with the cannabinoid receptor through polar contacts with 2 amino acids: GLN 218 and VAL 220 (Figure 4.6).

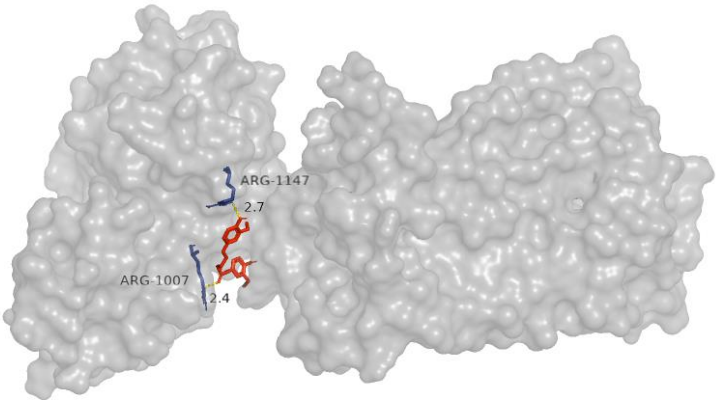

Figure 4.4: Cannabinoid Receptor-Curcumin interaction

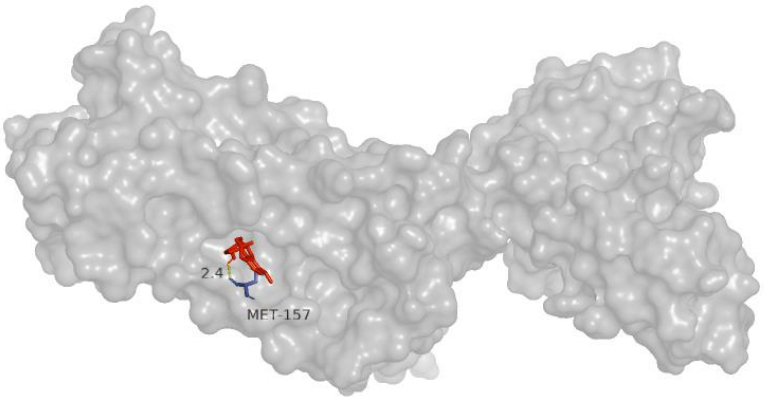

Figure 4.5: Cannabinoid Receptor-Galantamine interaction

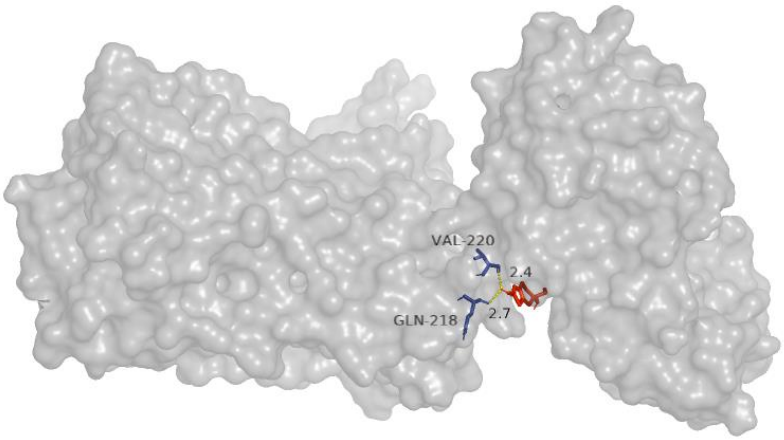

Figure 4.6: Cannabinoid Receptor-Pramipexole interaction

In summary, the molecular docking results suggest that curcumin, galantamine, and pramipexole can interact with the cannabinoid receptor, with curcumin showing the highest binding affinity followed by galantamine and pramipexole. The visualization of these interactions provides insights into the potential binding modes and key residues involved in ligand-receptor interactions.

4.1.3 Dopamine Receptor Interactions

The molecular docking simulations for the dopamine receptor with curcumin, galantamine, and pramipexole were performed using AutoDock Vina. The top 2 hits of each docking were selected for further analysis and presentation based on their binding affinities and RMSD values. The binding affinities and RMSD values for the selected hits are presented in Table 4.3.

Table 4.3: Binding affinities and RMSD values for the top 2 hits of dopamine receptor interactions.

Interaction	Mode	Affinity (kcal/mol)	RMSD l.b.	RMSD u.b.
Dopamine-Curcumin	1	-6.7	0.000	0.000
Dopamine-Curcumin	2	-6.3	3.175	6.340
Dopamine-Galantamine	1	-7.2	0.000	0.000
Dopamine-Galantamine	2	-6.7	2.944	4.902
Dopamine-Pramipexole	1	-5.1	0.000	0.000
Dopamine-Pramipexole	2	-5.0	1.315	2.044

The molecular interactions between the dopamine receptor and the ligands were visualized using PyMOL. The top-scoring binding mode for each ligand showed the following interactions:

1. Dopamine-Curcumin: Curcumin interacted with one key residue in the active site of the dopamine receptor, forming polar contact with ASN 1068 (Figure 4.7).
2. Dopamine-Galantamine: Galantamine established polar contact with one amino acid, TYR 1088, in the active site of the dopamine receptor (Figure 4.8).
3. Dopamine-Pramipexole: Pramipexole interacted with the dopamine receptor through polar contacts with two amino acids, LEU 216 and ARG 220 (Figure 4.9).

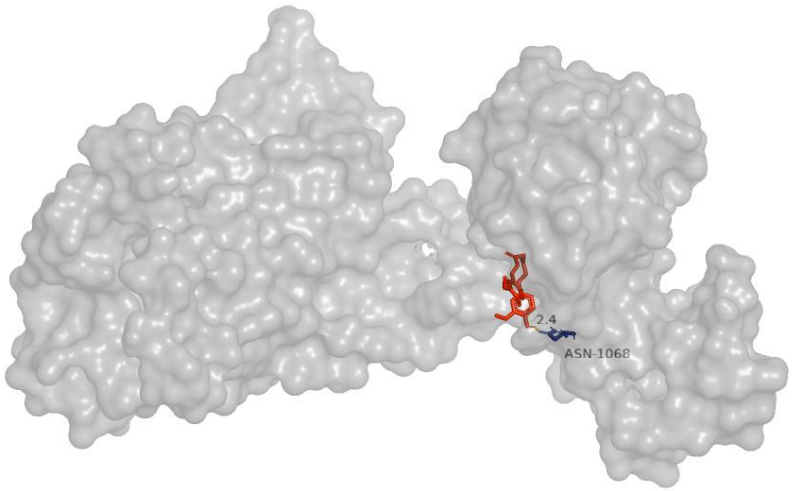

Figure 4.7: Dopamine Receptor-Curcumin interaction

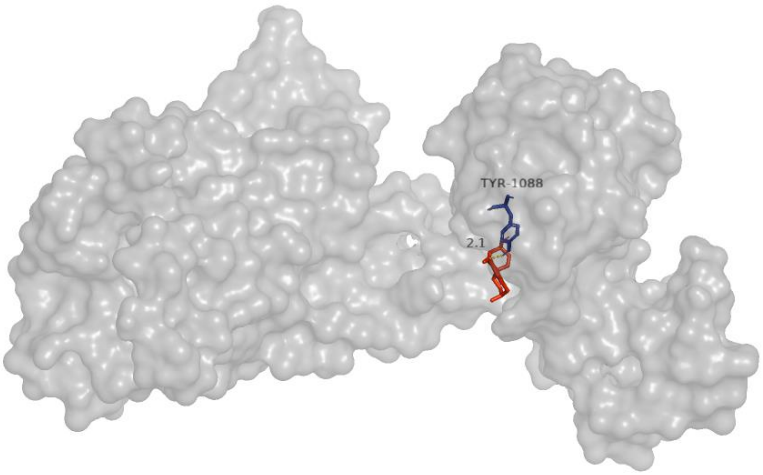

Figure 4.8: Dopamine Receptor-Galantamine interaction

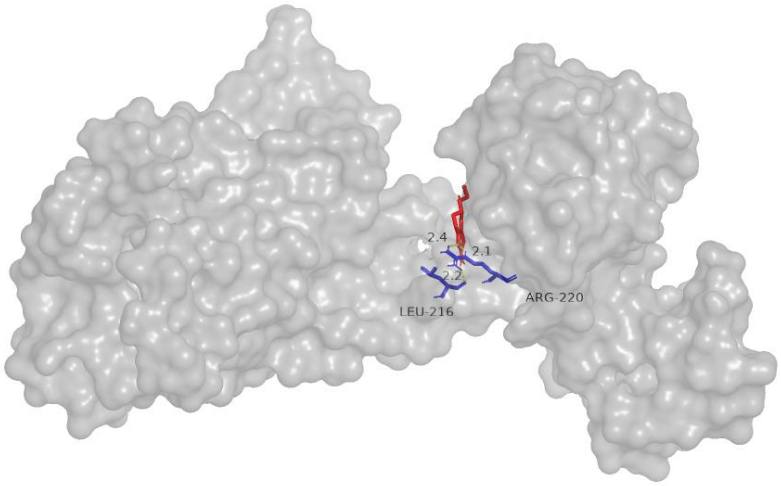

Figure 4.9: Dopamine Receptor-Pramipexole interaction

In summary, the molecular docking results suggest that curcumin, galantamine, and pramipexole can interact with the dopamine receptor, with galantamine showing the highest binding affinity followed by curcumin and pramipexole. The visualization of these interactions provides insights into the potential binding modes and key residues involved in ligand-receptor interactions.

4.1.4 NMDA Receptor Interactions

Molecular docking simulations for the NMDA receptor with curcumin, galantamine, and pramipexole were performed using AutoDock Vina. The top 2 hits of each docking were selected for further analysis and presentation based on their binding affinities and RMSD values. The binding affinities and RMSD values for the selected hits are presented in Table 4.4.

Table 4.4: Binding affinities and RMSD values for the top 2 hits of NMDA Receptor interactions.

Interaction	Mode	Affinity (kcal/mol)	RMSD l.b.	RMSD u.b.
NMDA-Curcumin	1	-7.9	0.000	0.000
NMDA-Curcumin	2	-7.6	1.996	6.658
NMDA-Galantamine	1	-7.1	0.000	0.000
NMDA-Galantamine	2	-6.9	1.542	2.039
NMDA-Pramipexole	1	-4.8	0.000	0.000
NMDA-Pramipexole	2	-4.6	2.268	5.750

The molecular interactions between the NMDA receptor and the ligands were visualized using PyMOL. The top-scoring binding mode for each ligand showed the following interactions:

1. NMDA-Curcumin: Curcumin interacted with four key residues in the active site of the NMDA receptor, forming polar contacts with GLY 126, ASN 154, SER 155, and EDO 301 (Figure 4.10).
2. NMDA-Galantamine: Galantamine established polar contact with one amino acid, GLY 126, in the active site of the NMDA receptor (Figure 4.11).
3. NMDA-Pramipexole: Pramipexole interacted with the NMDA receptor through polar contacts with two amino acids, ASN 25 and EDO 307 (Figure 4.12).

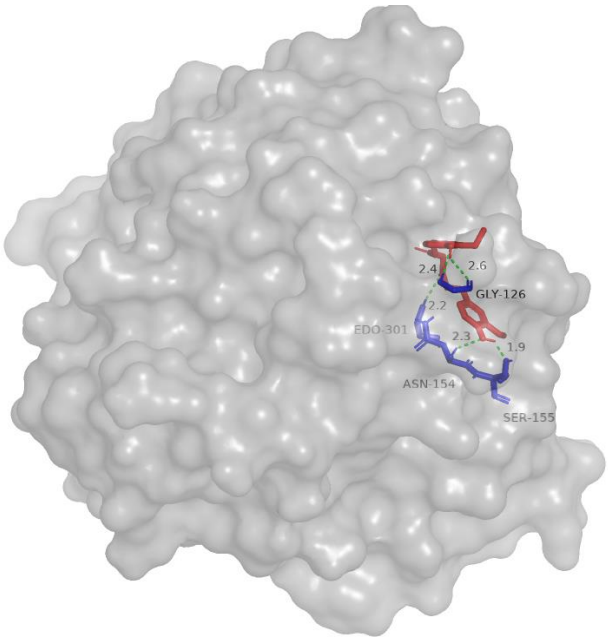

Figure 4.10: NMDA Receptor-Curcumin interaction

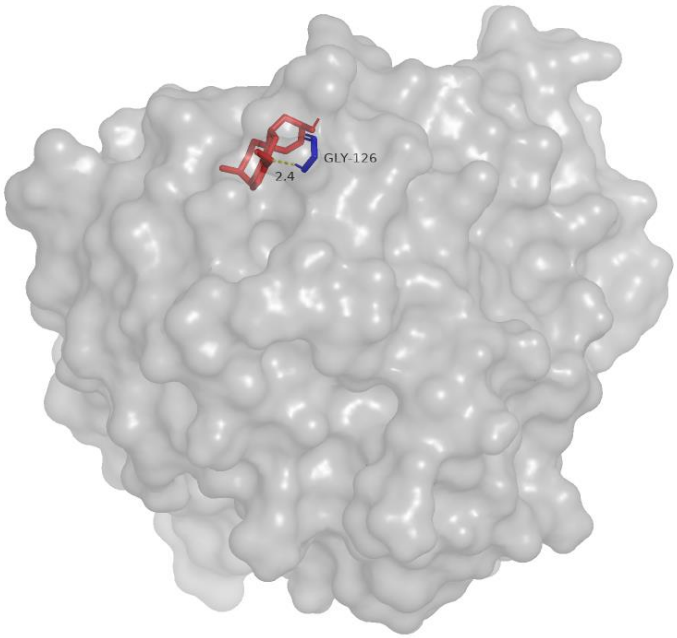

Figure 4.11: NMDA Receptor-Galantamine interaction

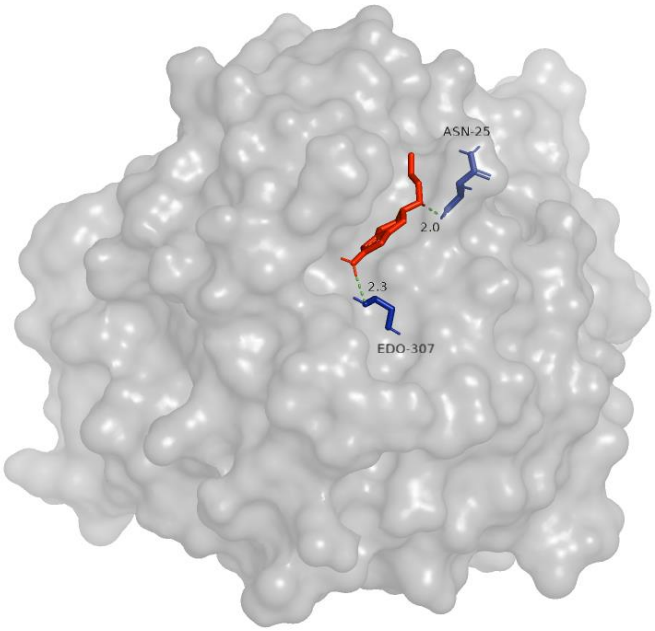

Figure 4.12: NMDA Receptor-Pramipexole interaction.

In summary, the molecular docking results suggest that curcumin, galantamine, and pramipexole can interact with the NMDA receptor, with curcumin showing the highest binding affinity followed by galantamine and pramipexole. The visualization of these interactions provides insights into the potential binding modes and key residues involved in ligand-receptor interactions.

4.1.5 Serotonin Receptor Interactions

Molecular docking simulations for the serotonin receptor with curcumin, galantamine, and pramipexole were performed using AutoDock Vina. The top 2 hits of each docking were selected for further analysis and presentation based on their binding affinities and RMSD values. The binding affinities and RMSD values for the selected hits are presented in Table 4.5.

Table 4.5: Binding affinities and RMSD values for the top 2 hits of Serotonin Receptor interactions.

Interaction	Mode	Affinity (kcal/mol)	RMSD l.b.	RMSD u.b.
Serotonin-Curcumin	1	-6.6	0.000	0.000
Serotonin-Curcumin	2	-6.6	17.594	21.350
Serotonin-Galantamine	1	-7.3	0.000	0.000
Serotonin-Galantamine	2	-7.1	2.441	4.408
Serotonin-Pramipexole	1	-5.4	0.000	0.000
Serotonin-Pramipexole	2	-5.4	15.952	17.964

The molecular interactions between the serotonin receptor and the ligands were visualized using PyMOL. The top-scoring binding mode for each ligand showed the following interactions:

1. Serotonin-Curcumin: Curcumin interacted with two key residues in the active site of the serotonin receptor, forming polar contacts with ARG 152 and ASN 372 (Figure 4.13).
2. Serotonin-Galantamine: Galantamine established polar contact with one amino acid, ARG 152, in the active site of the serotonin receptor (Figure 4.14).
3. Serotonin-Pramipexole: Pramipexole interacted with the serotonin receptor through polar contacts with two amino acids, GLY 362 and THR 369 (Figure 4.15).

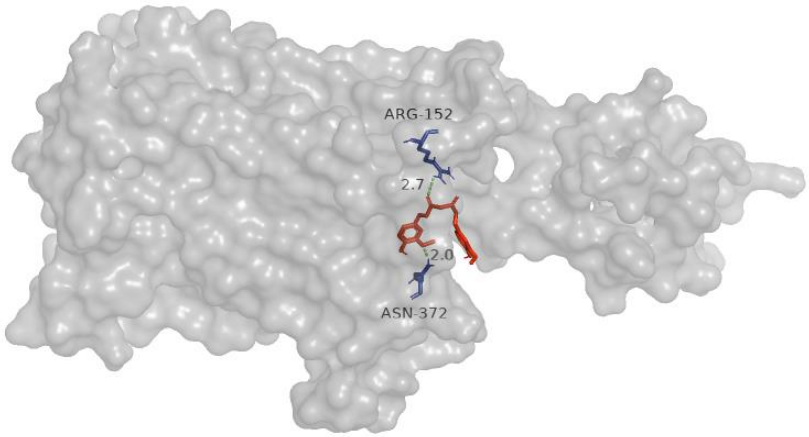

Figure 4.13: Serotonin Receptor-Curcumin interaction

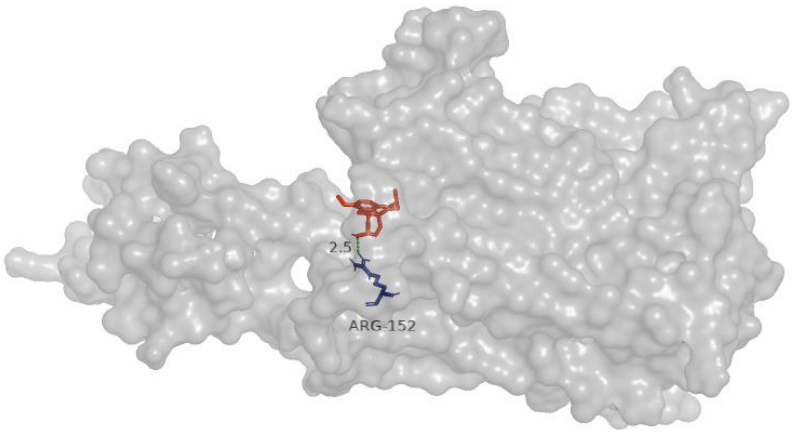

Figure 4.14: Serotonin Receptor-Galantamine interaction

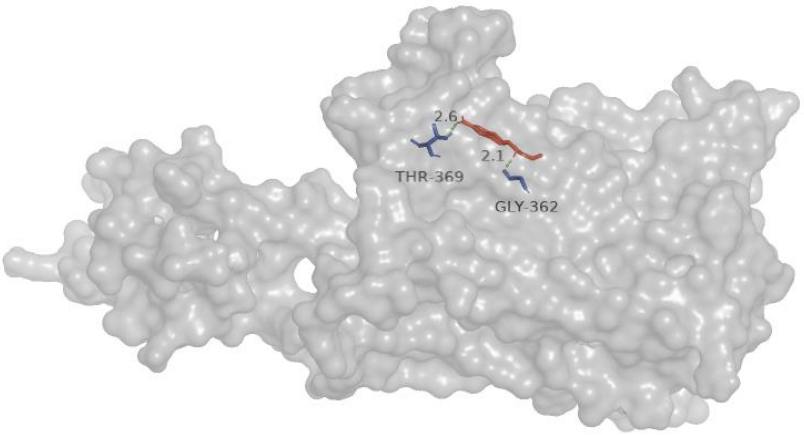

Figure 4.15: Serotonin Receptor-Pramipexole interaction

In summary, the molecular docking results suggest that curcumin, galantamine, and pramipexole can interact with the serotonin receptor, with galantamine showing the highest binding affinity followed by curcumin and pramipexole. The visualization of these interactions provides insights into the potential binding modes and key residues involved in ligand-receptor interactions.

4.2 DISCUSSION

4.2.1 Acetylcholinesterase Receptor

The aim of the molecular docking study of acetylcholinesterase (AChE) with curcumin, galantamine, and pramipexole was to find out if they could potentially be used as AChE inhibitors and to learn more about how the enzyme and these ligands interact at the molecular level. Acetylcholinesterase is a very important target for developing treatments for Alzheimer's disease and other neurodegenerative diseases because it breaks down the neurotransmitter acetylcholine, which is essential for cognitive functions such as learning and memory.

Our docking results revealed that curcumin and galantamine exhibited higher binding affinities to AChE compared to pramipexole, suggesting their potential as AChE inhibitors. In both in vitro and in vivo studies [95,96], curcumin and galantamine have slowed the activity of AChE. These results are in line with those studies. The visualization of the interactions showed that curcumin and galantamine formed hydrogen bonds and hydrophobic interactions with key residues in the active site of AChE, such as ARG 150 and ILE 232, which are known to be essential to the enzyme's catalytic activity. When pramipexole was docked, the results showed that it binds to AChE less strongly than curcumin and galantamine. Still, pramipexole made polar bonds with ARG 150, LEU 190, ILE 232, SER 275, and SER 316, which are all important residues in the enzyme's active site. These findings suggest that pramipexole might still possess some inhibitory effects on AChE, although it is likely to be less potent than curcumin and galantamine. Further experimental studies are needed to evaluate the potential inhibitory effects of pramipexole on AChE and its potential role in the treatment of neurodegenerative disorders.

In conclusion, the molecular docking analysis of AChE interactions with curcumin, galantamine, and pramipexole provided valuable insights into their potential as AChE inhibitors and the molecular basis of their interactions. Our study showcases that curcumin and galantamine are more effective AChE inhibitors as compared to pramipexole. In addition, the potential therapeutic applications of these ligands in the context of neurological disorders require further exploration.

4.2.2 Cannabinoid Receptor

The cannabinoid receptor is involved in a wide variety of physiological processes, such as pain regulation, appetite control, and immune system regulation. The molecular docking study aimed to learn how curcumin, galantamine, and pramipexole could interact with this receptor. Multiple neurological and psychological disorders, including Alzheimer's, Parkinson's, and schizophrenia, have been associated with the cannabinoid receptor. Knowing how these ligands interact with the cannabinoid receptor on a molecular level might shed light on their therapeutic potential.

According to our docking data, curcumin binds to the cannabinoid receptor with the greatest affinity, followed by galantamine and pramipexole. These results show that curcumin, in comparison to galantamine and pramipexole, may have a greater capacity to regulate cannabinoid receptor function. Curcumin's interaction with the cannabinoid receptor may be responsible for some of its various biological benefits, including its anti-inflammatory, antioxidant, and neuroprotective properties [97-99].

Curcumin was shown to make polar interactions with ARG 1007 and ARG 1147, two essential amino acids in the cannabinoid receptor's active site. These amino acids may be pivotal for ligand-receptor interaction and may contribute to curcumin's known biological effects. On the other hand, galantamine and pramipexole had fewer polar contacts with the receptor. This may indicate that their binding affinities are lower and that they have weaker interactions with the receptor.

Cannabinoid receptor interactions with curcumin, galantamine, and pramipexole were analysed using molecular docking, yielding important insights into the binding affinities of these compounds and the critical residues involved in ligand-receptor interactions. Based on our results, curcumin may have a greater ability than galantamine and pramipexole to alter cannabinoid receptor function. Further experimental research is required to corroborate these discoveries and study the functional effects of these interactions on cannabinoid receptor signalling and associated physiological processes. Additionally, these ligands' therapeutic potential for neurological and neurological disorders needs further investigation.

4.2.3 Dopamine Receptor

In this molecular docking study, we sought to explore the dopamine receptor's possible interactions with curcumin, galantamine, and pramipexole. Dopamine receptors have significance in the pathophysiology of multiple neurological and psychiatric illnesses such as Parkinson's disease, schizophrenia, and addiction because of their roles in cognition, motor control, and reward. Learning how these ligands interact with the dopamine receptor on a molecular level might shed light on their therapeutic potential.

According to our docking analysis, pramipexole and curcumin have the next-highest affinities for the dopamine receptor after galantamine. This indicates that galantamine, in comparison to curcumin and pramipexole, may have a greater capacity to alter dopamine receptor function. The pharmacological effects of galantamine in Alzheimer's disease may be attributable to its many biological functions, such as the inhibition of acetylcholinesterase and the allosteric regulation of nicotinic acetylcholine receptors [100-102]. Interacting with the dopamine receptor might broaden its potential therapeutic uses.

Galantamine was discovered to interact with TYR 1088, a critical amino acid in the dopamine receptor's active site, through polar interactions. The biological effects of galantamine may be related to the importance of this residue in the ligand-receptor interaction. Curcumin and pramipexole, in contrast, made less polar contact with the receptor, which may have led to fewer polar interactions and lower binding affinities.

Our molecular docking investigation of curcumin, galantamine, and pramipexole with the dopamine receptor elucidates various binding mechanisms and critical residues involved in ligand-receptor interactions. Based on our results, galantamine may have a higher ability than curcumin and pramipexole to alter dopamine receptor activation. However, more experimental research is required to corroborate these discoveries and investigate the functional effects of these interactions on dopamine receptor signalling and associated physiological processes. More research is required to determine whether or not these ligands have any therapeutic use in the treatment of neurological and psychological disorders.

4.2.4 NMDA Receptor

The purpose of the molecular docking study of the NMDA receptor with curcumin, galantamine, and pramipexole was to determine how they may interact with this important receptor, which plays a significant role in the central nervous system by influencing synaptic plasticity and excitatory neurotransmission. Alzheimer's disease, Parkinson's disease, and schizophrenia, among other neurological disorders, have been linked to NMDA receptors. Understanding the molecular interactions between these ligands and the NMDA receptor may therefore shed light on their possible therapeutic applications.

After curcumin, galantamine and pramipexole were the NMDA receptor ligands with the second-highest binding affinity, according to our docking results. These results indicate that curcumin may have a greater capacity to modulate NMDA receptor activity than galantamine and pramipexole. It has been said to have different biological qualities, such as anti-inflammatory, antioxidant, and neuroprotective effects [103–105]. The interaction with the NMDA receptor could further expand its potential therapeutic applications.

The visualisation of the interactions showed that curcumin made polar connections with GLY 126, ASN 154, SER 155, and EDO 301, which are all important residues in the active site of the NMDA receptor. These residues might be crucial for the ligand-receptor interaction and could play a role in the observed biological effects of curcumin. Galantamine and pramipexole, on the other hand, made fewer polar contacts with the receptor. This could mean their interactions with the receptor are weaker and their binding affinities are lower.

The molecular docking analysis of how the NMDA receptor interacts with curcumin, galantamine, and pramipexole gives important information about how they might bind and which key residues are involved in how ligands interact with receptors. Our findings suggest that curcumin might have a stronger potential to modulate NMDA receptor activity compared to galantamine and pramipexole. However, further experimental studies are needed to validate these observations and investigate the functional consequences of these interactions on NMDA receptor signalling and related physiological processes. In addition, the potential therapeutic applications of these ligands in the context of neurological disorders require further exploration.

4.2.5 Serotonin Receptor

The molecular docking study of the serotonin receptor with curcumin, galantamine, and pramipexole aimed to discover how they might interact with this important receptor, which is involved in many physiological processes like regulating mood, controlling hunger, and sleep. Several psychological disorders, such as sadness, anxiety, and obsessive-compulsive disorder, have been linked to the serotonin receptor in the way they work. So, knowing how these ligands interact with the serotonin receptor at the molecular level could help us figure out how they could be used as therapeutics.

According to our docking results, pramipexole and curcumin had the next highest binding affinities for the serotonin receptor after galantamine. These findings suggest that galantamine might have a stronger potential to modulate serotonin receptor activity compared to curcumin and pramipexole. Galantamine is primarily known for its effects on Alzheimer's disease through acetylcholinesterase inhibition and allosteric modulation of nicotinic acetylcholine receptors [106,107]. The interaction with the serotonin receptor could further expand its potential therapeutic applications.

When the interactions were visualised, it was seen that galantamine made polar contacts with ARG 152, a key amino acid in the active site of the serotonin receptor. This residue could be vital to the contact between the drug and the receptor, and it could also play a part in the metabolic effects of galantamine. Curcumin and pramipexole, on the other hand, made fewer polar contacts with the receptor, which could make their interactions weaker and their binding affinities lower.

The molecular docking analysis of serotonin receptor interactions with curcumin, galantamine, and pramipexole provides valuable insights into their potential binding modes and key residues involved in ligand-receptor interactions. Our findings suggest that galantamine might have a stronger potential to modulate serotonin receptor activity compared to curcumin and pramipexole. However, further experimental studies are needed to validate these observations and investigate the functional consequences of these interactions on serotonin receptor signalling and related physiological processes. In addition, the potential therapeutic applications of these ligands in the context of neurological disorders require further exploration.

CHAPTER 5

CONCLUSION

In conclusion, molecular docking simulations showed that curcumin interacts with a wide variety of neurotransmitter receptors, highlighting its potential as a versatile therapeutic agent. These receptors include acetylcholinesterase, cannabinoid, dopamine, serotonin, and NMDA receptors. Curcumin's high binding affinities for several receptors, especially the NMDA receptor, indicate that it may alter many features of neuronal activity. This might be the reason why curcumin has a wide range of pharmacological actions, including anti-inflammatory, antioxidant, and neuroprotective characteristics.

On the other hand, galantamine and pramipexole exhibit more selective receptor interactions, with galantamine demonstrating the highest binding affinity for the serotonin receptor, suggesting that it may also be able to modulate serotonin receptor activity in addition to its well-established effects on Alzheimer's disease. However, pramipexole has lower binding affinities for all of the receptors tested.

Experimental validation and optimization of curcumin against proven drugs such as galantamine and pramipexole as potential therapeutic agents for various neurological and psychiatric disorders can now proceed with this newfound knowledge of the molecular interactions and mechanisms underlying their therapeutic effects. Future research needs to devote effort to understanding the specific molecular mechanisms and verifying the in vivo effectiveness of curcumin. Researchers should also investigate potential synergistic effects and combination treatments involving curcumin.

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