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Molecular docking: a novel computational method for comprehending the pharmacokinetics of proteins related to Alzheimer's and Parkinson's disease

Abstract

Molecular docking is a computational technique widely used in modern drug discovery to predict the interaction between small molecules and biological targets such as proteins. In neurodegenerative disorders like Alzheimer's disease and Parkinson's disease, molecular docking plays a significant role in identifying potential therapeutic compounds and understanding disease mechanisms. These disorders are associated with abnormal protein behavior and aggregation. In Alzheimer's disease, proteins such as beta-amyloid and tau form plaques and tangles that disrupt neuronal communication and lead to cognitive decline. Molecular docking enables scientists to study how different molecules interact with these target proteins and potentially inhibit harmful aggregation or modify protein function. The technique uses three-dimensional structural information of proteins and ligands to simulate binding interactions through specialized software. By calculating binding affinity and interaction patterns, docking studies help prioritize compounds for laboratory testing, reducing time and cost in the early stages of drug development. Furthermore, molecular docking supports the design of more selective and effective drugs with fewer side effects. Overall, molecular docking serves as a valuable tool in comprehending protein-related mechanisms in Alzheimer's and Parkinson's diseases and contributes significantly to the advancement of targeted therapies for neurodegenerative disorders. The current article attempts to explore the pharmacokinetics of proteins and their clinical significance in Alzheimer's and Parkinson's diseases through computational methods.

Keywords: Alzheimer's and Parkinson's diseases, neurological disorders, molecular docking, ADMET.

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Introduction

Neurodegenerative disorders constitute one of the greatest biomedical and socioeconomic challenges of the twenty-first century. These disorders are characterized by progressive neuronal dysfunction, irreversible neuronal loss, synaptic degeneration, and deterioration of cognitive and motor functions. Among the major neurodegenerative diseases, Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and frontotemporal dementia collectively contribute toward increasing global morbidity and mortality (Figure 1).[1]

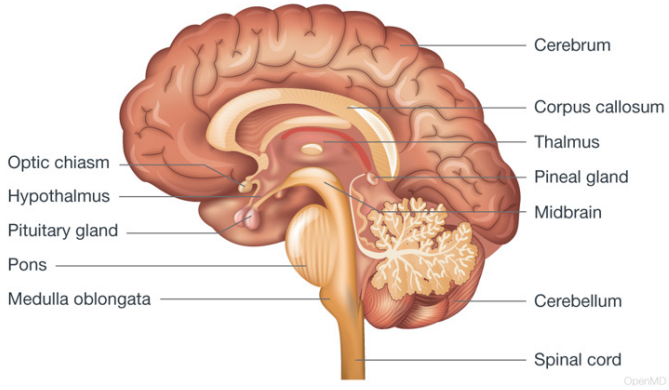

Figure 1 Neuronal organization.

Neurodegenerative diseases are a group of progressive disorders characterized by the gradual loss of structure and function of neurons in the brain and nervous system. Among these disorders, Parkinson's disease (PD) and Alzheimer's disease (AD) are the most common and extensively studied due to their increasing prevalence and significant impact on global health. Both diseases mainly affect older adults and lead to severe cognitive, behavioral, and motor impairments, thereby reducing the quality of life of patients and placing a major burden on caregivers and healthcare systems. Alzheimer's disease is the leading cause of dementia worldwide and is primarily associated with progressive memory loss, impaired thinking, confusion, and behavioral changes. The disease is characterized by the accumulation of beta-amyloid plaques outside neurons and neurofibrillary tangles formed by hyperphosphorylated tau proteins inside neurons.[2]

These abnormal protein aggregates disrupt neuronal communication, trigger inflammation, and eventually lead to neuronal death, particularly in regions of the brain associated with learning and memory such as the hippocampus and cerebral cortex. Although the exact cause of Alzheimer's disease remains unclear, genetic, environmental, and lifestyle factors are believed to contribute to its development and progression. Parkinson's disease is the second most common neurodegenerative disorder and primarily affects movement and motor coordination. It occurs due to the degeneration of dopamine-producing neurons in the substantia nigra region of the brain. The reduction in dopamine levels leads to symptoms such as tremors, muscle rigidity, bradykinesia (slowness of movement), and postural instability.[3] In addition to motor symptoms, patients may also experience cognitive decline, depression, sleep disturbances, and autonomic dysfunction. A major pathological hallmark of Parkinson's disease is the accumulation of alpha-synuclein protein aggregates known as Lewy bodies, which contribute to neuronal dysfunction and degeneration.Recent advances in molecular biology, bioinformatics,

and computational chemistry have improved the understanding of these diseases at the molecular level. Researchers are increasingly focusing on protein interactions, aggregation mechanisms, and therapeutic targets involved in AD and PD.

Techniques such as molecular docking, molecular dynamics simulations, and structure-based drug design are widely employed to identify potential drug candidates capable of interacting with disease-related proteins. These computational approaches accelerate the discovery of effective therapeutic agents and help in understanding the molecular mechanisms underlying neurodegeneration.[4] Despite extensive research, there is currently no complete cure for Alzheimer's or Parkinson's disease. Existing treatments mainly provide symptomatic relief rather than preventing disease progression. Therefore, continuous research aimed at identifying novel therapeutic targets and designing effective drugs is essential for combating these debilitating neurological disorders.

Causes and risk factors of Parkinson's disease and Alzheimer's disease

The exact causes of Parkinson's disease (PD) and Alzheimer's disease (AD) are not completely understood; however, researchers believe that these disorders develop through a complex interaction of genetic, environmental, biochemical, and lifestyle-related factors. Both diseases are characterized by progressive neuronal degeneration and abnormal protein accumulation in the brain, which ultimately disrupt normal brain function.[5]

Causes of Alzheimer's disease

Alzheimer's disease is mainly associated with the abnormal accumulation of beta-amyloid plaques and tau protein tangles in the brain. These protein aggregates interfere with neuronal communication, impair synaptic activity, and lead to neuronal death. Several factors contribute to the development of AD:

i. **Genetic factors:** Certain genes are strongly linked with Alzheimer's disease. Mutations in genes such as APP, PSEN1, and PSEN2 are associated with early-onset familial Alzheimer's disease. In late-onset AD, the APOE-e4 allele is considered a major genetic risk factor.

ii. **Aging:** Increasing age is the most significant risk factor. The risk of Alzheimer's disease rises substantially after the age of 65 due to gradual neuronal wear, oxidative stress, and reduced cellular repair mechanisms.

iii. **Oxidative stress and mitochondrial dysfunction:** Excessive production of reactive oxygen species (ROS) damages proteins, lipids, and DNA in neurons, contributing to neurodegeneration.

iv. **Neuroinflammation:** Chronic activation of microglial cells and inflammatory pathways in the brain may accelerate neuronal damage and disease progression.

v. **Lifestyle and environmental factors:** Poor diet, lack of physical activity, smoking, obesity, diabetes, hypertension, and cardiovascular diseases are associated with increased risk of AD.

Causes of Parkinson's disease

Parkinson's disease primarily results from the degeneration of dopamine-producing neurons in the substantia nigra region of the brain.[6] The exact trigger for neuronal loss remains unclear, but several contributing factors have been identified:

i. **Alpha-synuclein aggregation:** Misfolding and aggregation of alpha-synuclein proteins form Lewy bodies, which disrupt neuronal function and contribute to cell death.

ii. **Genetic mutations:** Mutations in genes such as SNCA, LRRK2, PARK2, PINK1, and DJ-1 have been linked to familial forms of Parkinson's disease.

iii. **Environmental toxins:** Exposure to pesticides, herbicides, heavy metals, and industrial chemicals may increase the risk of developing PD by inducing oxidative stress and mitochondrial damage.

iv. **Mitochondrial dysfunction:** Impaired mitochondrial activity reduces cellular energy production and increases oxidative damage in neurons.

v. **Aging and cellular stress:** Aging reduces the brain's ability to eliminate damaged proteins and maintain neuronal health, making older individuals more susceptible to Parkinson's disease.

Common mechanisms in both diseases

Both AD and PD share several pathological mechanisms, including protein misfolding, oxidative stress, mitochondrial dysfunction, neuroinflammation, and impaired protein clearance systems. These overlapping molecular pathways are important areas of research for developing targeted therapies and neuroprotective drugs. Understanding the underlying causes and risk factors of these diseases is essential for early diagnosis, prevention strategies, and the development of effective therapeutic approaches aimed at slowing or preventing neurodegeneration.

Alzheimer's disease

Alzheimer's disease (AD) is a chronic, progressive, irreversible, and multifactorial neurodegenerative disorder characterized by gradual deterioration of cognitive function, memory processing, language ability, executive reasoning, emotional regulation, behavioral responses, and social interaction. The disease represents the most common cause of dementia globally and accounts for approximately 60–70% of all dementia-associated cases. Alzheimer's disease primarily affects elderly populations; however, early-onset familial forms of the disease may also occur due to inherited genetic mutations involving amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes (Figure 2).[7]

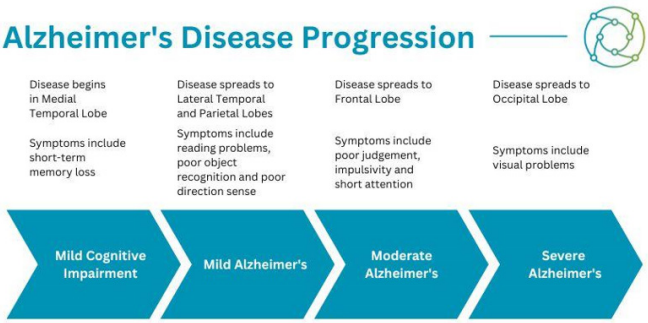

Figure 2 Pathological Progression of Alzheimer's Disease.[7]

Clinically, Alzheimer's disease progresses through multiple pathological stages beginning with mild cognitive impairment followed by progressive memory dysfunction, impaired judgment, reduced spatial orientation, language disturbances, personality

alterations, emotional instability, and severe neurological disability. Advanced disease stages result in complete dependence upon caregivers, profound neuronal degeneration, systemic physiological decline, and eventual mortality.

The disease exerts enormous socioeconomic and healthcare burdens worldwide. Increasing global life expectancy, demographic transition, urbanization, sedentary lifestyles, cardiovascular disorders, metabolic syndromes, and environmental stressors have collectively contributed toward the rapidly rising prevalence of Alzheimer's disease. Consequently, AD has evolved into a major public health crisis requiring multidisciplinary biomedical intervention and advanced therapeutic development.[8]

Histopathologically, Alzheimer's disease is characterized by extracellular amyloid-beta plaque deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, synaptic degeneration, neuronal apoptosis, and extensive cerebral atrophy. Progressive degeneration of the hippocampus, entorhinal cortex, temporal cortex, and cerebral cortex contributes directly toward cognitive decline and memory impairment.

Despite decades of extensive scientific investigation, currently available pharmacological interventions remain largely symptomatic and fail to completely prevent or reverse neurodegenerative progression. Existing therapeutic agents temporarily improve cognitive performance but possess limited disease-modifying capability. Therefore, identification of safer, multifunctional, and mechanistically advanced neurotherapeutic agents remains one of the most important priorities in modern neuropharmacology and computational medicinal chemistry.[9]

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Pathophysiology

Alzheimer's disease and Parkinson's disease are progressive neurodegenerative disorders characterized by the gradual loss of structure and function of neurons in the brain. These diseases develop through complex pathological mechanisms involving abnormal protein accumulation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and neuronal cell death. Although both conditions affect the nervous system, they differ in the regions of the brain involved and the clinical symptoms they produce (Figure 3).

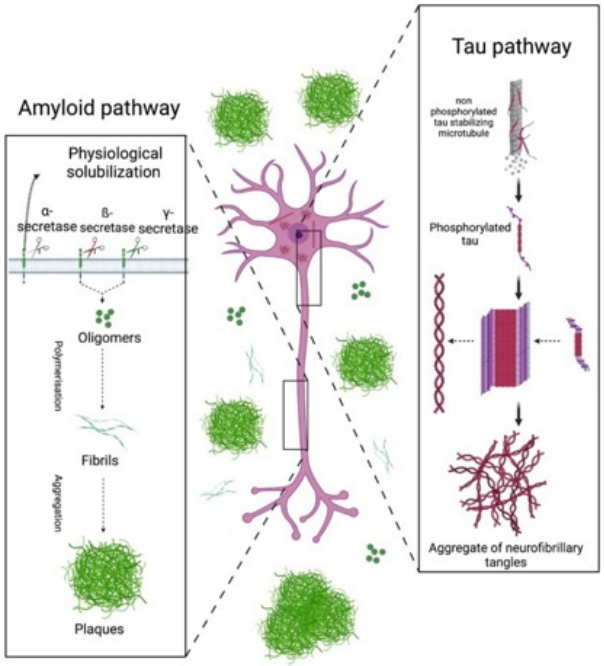

Figure 3 Amyloid Plaques and Neurofibrillary Tangle Formation.

The pathophysiology of Alzheimer's disease is primarily associated with the accumulation of amyloid-beta peptides and tau proteins in the brain. Amyloid precursor protein (APP) undergoes abnormal cleavage by beta-secretase and gamma-secretase enzymes, resulting in the formation of amyloid-beta plaques that accumulate extracellularly between neurons. These plaques disrupt neuronal communication and trigger inflammatory responses in the brain. At the same time, tau proteins become hyperphosphorylated and form intracellular neurofibrillary tangles, which impair the stability of microtubules necessary for intracellular transport.[11] The combined effect of amyloid plaques and tau tangles leads to synaptic dysfunction, neuronal degeneration, and progressive brain atrophy, particularly in regions responsible for memory and cognition such as the hippocampus and cerebral cortex.

In addition to protein aggregation, oxidative stress and mitochondrial dysfunction play major roles in Alzheimer's disease progression. Increased production of reactive oxygen species damages cellular components including lipids, proteins, and DNA, ultimately contributing to neuronal death. Neuroinflammation caused by activated microglial cells and astrocytes further accelerates neuronal injury. Deficiency of neurotransmitters, especially acetylcholine, also contributes to impaired memory and cognitive decline observed in affected individuals.

The pathophysiology of Parkinson's disease mainly involves the degeneration of dopaminergic neurons in the substantia nigra pars compacta, a region of the midbrain responsible for motor control. The loss of these neurons leads to reduced dopamine levels in the basal ganglia, disrupting the balance of excitatory and inhibitory signaling pathways that regulate movement.[12]

As dopamine deficiency progresses, patients develop characteristic symptoms such as resting tremors, muscle rigidity, bradykinesia, and postural instability. A major pathological hallmark of Parkinson's disease is the formation of Lewy bodies, which are intracellular aggregates primarily composed of misfolded alpha-synuclein

proteins. Abnormal accumulation of alpha-synuclein interferes with neuronal function, synaptic transmission, and mitochondrial activity, ultimately leading to neuronal apoptosis. Oxidative stress, impaired protein degradation pathways, mitochondrial dysfunction, and chronic neuroinflammation further contribute to the progression of neuronal damage in Parkinson's disease. Environmental toxins, genetic mutations, and aging are also considered important factors influencing disease development.[13]

Overall, the pathophysiology of Alzheimer's and Parkinson's diseases involves multiple interconnected molecular and cellular mechanisms that progressively damage neurons and impair brain function. Understanding these pathological processes is essential for identifying therapeutic targets and developing effective treatment strategies aimed at slowing disease progression and improving the quality of life of affected individuals.

Results

Retrieval, Validation, and Preparation of 4EY7 Human Acetylcholinesteras (Table 1) (Figures 4-8).

Table 1 Key Differences Between Alzheimer's and Parkinson's

Feature	Alzheimer's Disease	Parkinson's Disease
Main symptom	Memory/cognitive decline	Motor dysfunction
Main protein	Amyloid-beta & Tau	α-synuclein
Main pathology	Cortical neuron degeneration	Dopaminergic neuron loss
Key brain region	Hippocampus/cortex	Substantia nigra
Main neurotransmitter affected	Acetylcholine	Dopamine
Hallmark lesion	Plaques & tangles	Lewy bodies

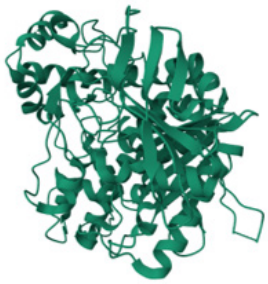

Figure 4 Ribbon representation of 4EY7 human acetylcholinesterase visualized using molecular graphics software showing secondary structural organization.

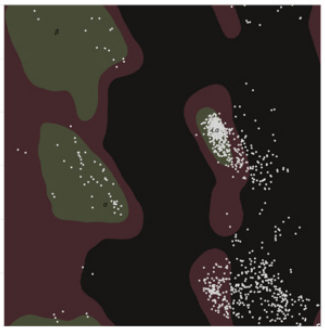

Figure 5 Ramachandran plot analysis of the 4EY7 receptor structure demonstrating acceptable stereochemical quality and structural stability.

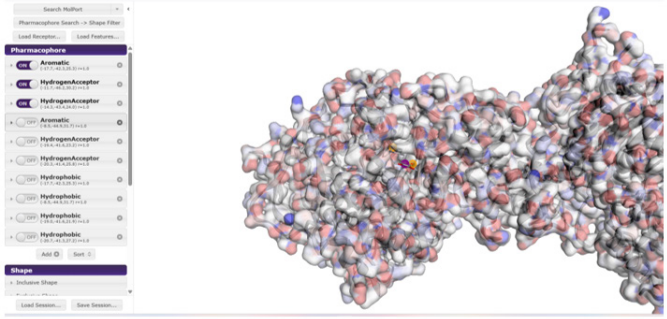

Figure 6 Pharmacophore mapping of the 4EY7 acetylcholinesterase active site showing aromatic, hydrophobic, and hydrogen bond acceptor interaction regions

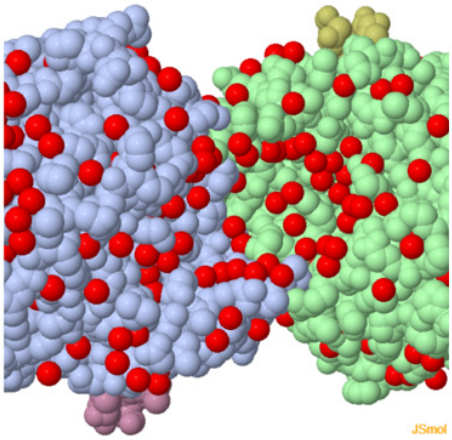

Figure 7 Surface topology analysis of human acetylcholinesterase demonstrating catalytic cavity accessibility and protein surface organization.

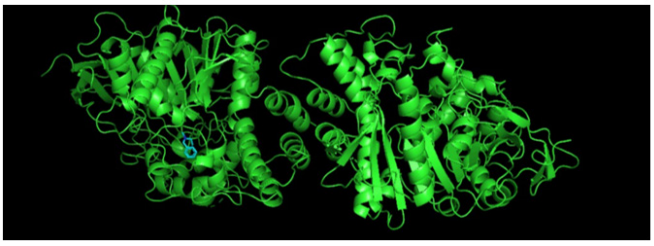

Figure 8 Three-dimensional receptor-ligand complex of Donepezil docked within the catalytic cavity of 4EY7 human acetylcholinesterase.

Discussion

Both Alzheimer's disease (AD) and Parkinson's disease (PD) are **progressive neurodegenerative disorders** associated with abnormal protein aggregation, neuronal dysfunction, neuroinflammation, mitochondrial injury, and selective neuronal death. Progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons and accumulation of alpha-synuclein aggregates within neuronal cells. Alpha-synuclein plays a central role in Parkinson's disease pathology through its abnormal misfolding, aggregation, and formation of Lewy bodies, which contribute to neuronal dysfunction, oxidative stress, mitochondrial damage, and neuroinflammation. Due to its major involvement in disease progression, alpha-synuclein has emerged as an important therapeutic target for computational drug discovery studies.[14,15]

In the present investigation, molecular docking and pharmacokinetic analysis were performed to evaluate the interaction between alpha-synuclein protein (8BQV) and 2-Methylbutanoic acid as a potential inhibitory compound. Human acetylcholinesterase therefore continues to serve as an important molecular target for symptomatic management of cognitive decline associated with Alzheimer's disease. In the present investigation, the crystal structure 4EY7 of human acetylcholinesterase was selected because of its high structural resolution, catalytic relevance, and suitability for structure-based computational drug discovery investigations. Structural validation studies demonstrated acceptable stereochemical quality and receptor stability, thereby supporting the suitability of the receptor model for docking analysis.[16] The Ramachandran plot confirmed that the majority of amino acid residues occupied favorable conformational regions, indicating reliable backbone geometry and minimal structural distortion. Pharmacophore mapping and active-site analysis demonstrated that the catalytic gorge of acetylcholinesterase possesses a highly organized aromatic cavity enriched with hydrophobic and electrostatic interaction regions. These structural features are critically important for stabilization of aromatic inhibitor molecules within the active-site tunnel. Molecular docking analysis demonstrated that Donepezil exhibited strong binding affinity toward the 4EY7 receptor with a docking score of -8.438308 kcal/mol. The obtained binding-energy value indicates favorable thermodynamic interaction stability and efficient receptor accommodation within the catalytic cavity.[17] Comparable docking studies reported in previous anti-Alzheimer computational investigations similarly demonstrated strong inhibitory interaction of Donepezil with acetylcholinesterase catalytic residues.

Protein-ligand interaction analysis revealed that Donepezil interacted with several important aromatic and catalytic residues including Tyr337, Phe338, Tyr124, Tyr341, and His447. Interaction with His447 is particularly important because this residue forms part of the catalytic triad responsible for acetylcholine hydrolysis. Such interactions suggest that Donepezil effectively occupies the catalytic gorge and interferes with enzymatic activity.[18,19] Aromatic residues Tyr337 and Phe338 contributed toward hydrophobic and π-associated stabilization of the ligand inside the aromatic gorge architecture. These interactions are highly significant because aromatic gorge stabilization represents one of the major mechanisms underlying acetylcholinesterase inhibition. ADMET analysis demonstrated favorable pharmacokinetic behavior of Donepezil including excellent intestinal absorption, favorable membrane permeability, and lipophilicity compatible with blood-brain barrier penetration. Efficient CNS penetration is critically important for anti-Alzheimer therapeutics because target receptors are localized within neuronal tissues of the brain.[20]

The three-dimensional structure of alpha-synuclein retrieved from the Protein Data Bank exhibited characteristic fibrillar β-sheet-rich architecture commonly associated with amyloidogenic neurodegenerative proteins. Structural validation through Ramachandran plot analysis demonstrated that most amino acid residues were located within energetically favorable conformational regions, confirming acceptable stereochemical quality and structural reliability of the receptor model. The predominance of β-sheet conformations observed in the Ramachandran plot strongly supports the pathological fibrillar organization of alpha-synuclein reported in Parkinson's disease. Similar observations have been reported in previous structural studies where alpha-synuclein fibrils exhibited extensive β-sheet stacking responsible for protein aggregation and neuronal toxicity.[21,22]

Molecular docking analysis performed using SwissDock and CB-Dock platforms demonstrated measurable interaction between alpha-synuclein and 2-Methylbutanoic acid. The docking affinity score obtained during the study was approximately −2.547 kcal/mol in SwissDock and −2.8 kcal/mol in CB-Dock analysis. These docking scores indicate relatively weak to moderate binding affinity between the ligand and the target protein. The comparatively lower binding energy may be attributed to the small molecular size, limited functional groups, and reduced intermolecular interaction capacity of 2-Methylbutanoic acid. Nevertheless, the ligand demonstrated the ability to occupy accessible binding regions present on the alpha-synuclein fibrillar surface, indicating preliminary interaction potential with aggregation-associated regions of the protein.[23,24]

The docking analysis further revealed that the ligand formed weak polar and hydrophobic interactions within the protein structure. Although strong hydrogen bonding interactions were not extensively observed, the ligand demonstrated surface accessibility toward aggregation-prone regions of alpha-synuclein. This observation is important because even weak molecular interactions may influence fibrillar stability and aggregation kinetics in amyloidogenic proteins.[25] Previous computational studies targeting alpha-synuclein have similarly reported that small molecules with moderate binding affinity may interfere with oligomer formation, fibrillization, or aggregate propagation. Therefore, the present findings suggest that 2-Methylbutanoic acid may serve as a preliminary scaffold molecule for further structural optimization and lead compound development.[26]

The ADMET and pharmacokinetic analysis performed during the study provided additional insights into the drug-likeness and pharmacological suitability of the ligand. The ligand demonstrated high intestinal absorption with a predicted absorption value of 92.454%, indicating favorable oral bioavailability. The moderate LogP value and acceptable water solubility suggest balanced hydrophilic and lipophilic properties, which are important for membrane permeability and systemic distribution.[27,28]

Conclusion

Neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease continue to be major concerns in biomedical research because of their complex pathology and progressive impact on the nervous system. Alzheimer's disease is primarily associated with memory loss and cognitive decline caused by the accumulation of amyloid-beta plaques and tau protein tangles, whereas Parkinson's disease is characterized by motor dysfunction linked to the degeneration of dopaminergic neurons and the aggregation of alpha-synuclein proteins. Understanding the molecular mechanisms involved in these disorders is essential for developing effective therapeutic strategies and improving patient outcomes. In recent years, molecular docking has emerged as a valuable computational tool in studying the proteins involved in Alzheimer's and Parkinson's diseases.[29]

Molecular docking helps researchers predict the interaction between drug molecules and target proteins by analyzing binding affinity, stability, and molecular orientation at the active site. This approach plays a significant role in identifying potential drug candidates that can inhibit abnormal protein aggregation or modulate disease-related pathways. By simulating ligand–protein interactions, molecular docking accelerates the drug discovery process while reducing the time and cost associated with experimental screening methods.[29]

Furthermore, molecular docking contributes significantly to understanding the pharmacokinetic behavior of therapeutic

compounds, including their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Through computational modeling, researchers can evaluate how effectively a drug molecule interacts with proteins associated with neurodegenerative diseases and predict its biological activity and safety profile. In Alzheimer's disease, docking studies often focus on proteins such as beta-secretase (BACE1), acetylcholinesterase, and tau proteins, while in Parkinson's disease, targets commonly include monoamine oxidase-B (MAO-B), alpha-synuclein, and dopamine receptors. These studies provide valuable insights into the molecular basis of drug action and help optimize compounds with improved efficacy and reduced side effects.[30]

In conclusion, the integration of molecular docking techniques into neurodegenerative disease research has greatly enhanced the understanding of protein–ligand interactions and pharmacokinetic properties in Alzheimer's and Parkinson's diseases. By enabling the rapid screening and optimization of therapeutic compounds, molecular docking supports the development of more targeted and effective treatments. As advancements in computational biology and artificial intelligence continue to evolve, molecular docking is expected to play an increasingly important role in personalized medicine and the discovery of novel therapies for neurodegenerative disorders.

Future scope

Molecular docking has emerged as one of the most influential computational techniques in modern drug discovery, offering valuable insights into protein–ligand interactions associated with complex neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). As these diseases continue to impose a significant global healthcare burden due to increasing life expectancy and aging populations, the future scope of molecular docking in understanding the pharmacokinetics and therapeutic targeting of disease-associated proteins is exceptionally promising.[31] Advances in computational biology, artificial intelligence, structural bioinformatics, and high-performance computing are expected to further enhance the accuracy and applicability of molecular docking approaches, enabling researchers to identify novel drug candidates and optimize existing therapeutic interventions with unprecedented efficiency. One of the major future directions of molecular docking lies in the integration of dynamic protein behavior into docking simulations. Traditional docking methods often rely on static protein structures, which may not accurately represent the conformational flexibility exhibited by proteins involved in Alzheimer's and Parkinson's diseases.[32]

Future developments are expected to incorporate enhanced molecular dynamics simulations and ensemble docking techniques, allowing researchers to capture multiple protein conformations and better understand ligand-binding mechanisms. This advancement will improve the prediction of binding affinities and facilitate the discovery of compounds capable of interacting with transient or cryptic binding sites that are often overlooked in conventional studies. Such capabilities are particularly relevant for proteins such as amyloid-beta, tau, alpha-synuclein, and leucine-rich repeat kinase 2 (LRRK2), which undergo significant structural alterations during disease progression. The growing availability of experimentally resolved protein structures and the emergence of highly accurate protein structure prediction tools have opened new avenues for molecular docking applications.[33] Future research is expected to leverage these structural databases to investigate previously unexplored therapeutic targets implicated in neurodegeneration. Computational docking can be employed to screen vast libraries of natural products, synthetic compounds, and repurposed drugs against newly identified protein targets, significantly accelerating the drug discovery process. Furthermore, advances in cryo-electron microscopy and machine-learning-based structural prediction methods will provide increasingly reliable protein models, enabling docking studies even when experimental structures are unavailable. This expanded structural knowledge will contribute to a deeper understanding of the pharmacokinetic and pharmacodynamic behavior of candidate molecules within the central nervous system.[34] Another promising area involves the integration of molecular docking with pharmacokinetic prediction platforms. Future drug development strategies will increasingly combine docking studies with absorption, distribution, metabolism, excretion, and toxicity (ADMET) analyses to evaluate both target affinity and pharmacological suitability simultaneously. Such integrated approaches can identify compounds that not only bind effectively to disease-related proteins but also possess favorable blood–brain barrier permeability, metabolic stability, and reduced toxicity. This is particularly critical in neurodegenerative diseases, where successful therapeutics must reach adequate concentrations within the brain while minimizing systemic side effects. The combination of docking and pharmacokinetic modeling is expected to reduce drug attrition rates during clinical development and improve the success of translational research.[35]

Artificial intelligence and machine learning are likely to revolutionize the future landscape of molecular docking. AI-driven algorithms can rapidly analyze massive datasets of protein structures, ligand libraries, and binding interactions to predict highly probable drug candidates. Deep learning models are already demonstrating the ability to improve scoring functions, binding affinity predictions, and virtual screening accuracy. In the coming years, the integration of AI with molecular docking will facilitate automated drug design pipelines capable of generating novel compounds specifically tailored for Alzheimer's and Parkinson's disease targets. These intelligent systems may significantly reduce the time and cost associated with traditional drug discovery while increasing the likelihood of identifying effective therapeutic molecules.[36] Personalized medicine represents another significant future application of molecular docking technologies. Genetic variations among patients can influence protein structure, drug metabolism, and therapeutic response. As genomic sequencing becomes more accessible, molecular docking can be adapted to evaluate patient-specific protein variants and predict individualized drug responses. Such personalized computational analyses may support precision medicine strategies, enabling clinicians to select the most effective treatment for individual patients based on their molecular profiles.[37]

In Alzheimer's and Parkinson's diseases, where therapeutic outcomes often vary considerably among patients, personalized docking approaches could contribute to improved clinical efficacy and reduced adverse effects. The future scope of molecular docking also extends to multi-target drug discovery. Neurodegenerative diseases are multifactorial disorders involving numerous interconnected biological pathways. Rather than focusing on a single protein target, future research is expected to emphasize the design of compounds capable of modulating multiple disease-associated proteins simultaneously. Molecular docking can facilitate the identification of such multi-target ligands by evaluating interactions across diverse protein networks. This strategy may prove particularly beneficial in addressing the complex pathological mechanisms underlying amyloid aggregation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and alpha-synuclein accumulation.[38] Multi-target therapeutics developed through advanced docking methodologies could potentially offer greater clinical benefits than conventional single-target drugs. Cloud

computing and high-performance computational infrastructures are expected to further expand the capabilities of molecular docking. The increasing availability of powerful computing resources will enable researchers to perform large-scale virtual screening campaigns involving millions of compounds within relatively short timeframes. These technological advancements will support collaborative research initiatives across academic institutions, pharmaceutical companies, and healthcare organizations worldwide. Additionally, cloud-based platforms can democratize access to sophisticated docking tools, allowing researchers from resource-limited settings to participate in neurodegenerative disease research and contribute to global drug discovery efforts.[39] Another important future direction involves the incorporation of systems biology and network pharmacology into molecular docking workflows. By integrating docking results with biological pathway analyses, gene expression data, and protein interaction networks, researchers can develop a more comprehensive understanding of disease mechanisms. Such holistic approaches may reveal novel therapeutic targets and uncover synergistic drug combinations capable of modifying disease progression.

In Alzheimer's and Parkinson's diseases, where multiple molecular processes contribute to neuronal degeneration, combining docking with systems-level analyses could facilitate the development of more effective and sustainable treatment strategies. The application of molecular docking in natural product research also holds considerable promise. Many plant-derived compounds possess neuroprotective, antioxidant, anti-inflammatory, and anti-aggregation properties that may be beneficial in treating neurodegenerative disorders.[40] Future studies are likely to employ molecular docking extensively for the screening and optimization of phytochemicals targeting Alzheimer's and Parkinson's disease proteins. This approach may lead to the identification of safer and more affordable therapeutic alternatives while expanding the repertoire of bioactive compounds available for drug development. The future of molecular docking in comprehending the pharmacokinetics of proteins related to Alzheimer's and Parkinson's diseases is characterized by remarkable opportunities for innovation and scientific advancement. The integration of molecular docking with artificial intelligence, molecular dynamics, pharmacokinetic modeling, personalized medicine, systems biology, and large-scale computational resources is expected to transform neurodegenerative disease research. These developments will enhance our understanding of protein–ligand interactions, accelerate the identification of novel therapeutics, and support the development of more effective, safer, and patient-specific treatment strategies.[41]

As computational technologies continue to evolve, molecular docking will remain a cornerstone of modern drug discovery, contributing significantly to the fight against some of the most challenging neurological disorders affecting humanity.

Acknowledgment

None.

Conflict of interests

The author declares no conflicts of interest.

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