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New Insights on N-Methyl-D-Aspartate (NMDA) Receptor Under Combinatorial Molecular Docking and MD Simulation Studies Using Natural Bioactive Compounds Against Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases pose a significant challenge, and novel therapeutic strategies are urgently needed. N-methyl-D-aspartate (NMDA) receptor is reported to play a critical role in the central nervous system and has emerged as a potential target for drug discovery. This study explored the potential scope of natural bioactive compounds as ligands for the NMDA receptor using current advances of docking studies with molecular dynamic (MD) simulations. An extensive virtual screening of 500 natural compounds were executed based on wide scientific literature and bibliography search. Docking simulations identified promising candidates with favorable binding affinities, with the top compounds - DL-Alanosine, and Zeinoxanthin (PubChem CIDs 153353 and 5281234) exhibiting exceptionally high docking scores of -6.6 and -6.4, against NMDA respectively. Further, MD simulations suggested the stability of the top-scoring compounds in complex with the NMDA receptor. These findings will provide a new insights to researchers and scientists on proceeding with new alternatives on the investigation of natural bioactive compounds as therapeutic lead candidates for targeting various receptors like NMDA in neurodegenerative diseases. However, in vitro and in vivo studies are warranted to validate these results and elucidate the underlying mechanisms of action.

Keywords- neurodegenerative diseases, NMDA receptor, natural bioactive compounds, in silico docking, molecular dynamics simulations, beta-carotene, catechins.

I. INTRODUCTION

Cancer and neurodegeneration are often seen as opposing ends of a spectrum, with cancer characterized by uncontrolled cell proliferation and neurodegeneration by excessive cell death [1]. Brain tumors, either primary (originating in the brain) or secondary (metastatic from other organs), are a major category of cancers affecting the central nervous system [2]. In contrast, Alzheimer's disease (AD) is a progressive neurodegenerative disorder [3]. Intriguingly, recent research suggests surprising commonalities between these seemingly disparate pathologies.

One such shared feature is the presence of active cell cycles in both AD and cancer [4]. While uncontrolled cell division is a hallmark of cancer, increased cell cycle entry has also been documented in clinically diagnosed AD cases [5]. This finding challenges traditional views

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and raises questions about the underlying mechanisms. Furthermore, epidemiological studies have revealed an inverse relationship between AD and cancer incidence, suggesting that a shift in pathophysiology towards one disease may offer protection from the other [5]. These observations highlight the complex interplay between cellular processes and disease development.

Bioinformatics approaches offer a promising avenue for developing novel therapeutic strategies to combat these debilitating diseases. By leveraging computational tools to analyze vast datasets generated from biological research, researchers can identify potential drug targets and pathways crucial for disease progression.

Traditionally, drug discovery often relied on synthetic compounds designed to mimic the effects of illegal narcotics. However, these synthetic drugs can have serious health consequences, including mental health issues, addiction, and even suicidal thoughts [6]. This has led to a paradigm shift towards exploring natural bioactive compounds as an alternative source for drug discovery.

Bioactive compounds are naturally occurring substances present in the food chain that demonstrably impact human health [7]. Examples include vitamins and polyphenols, which have been linked to various health benefits through numerous pharmacological studies [8][9]. Furthermore, certain bioactive compounds exhibit anti-aging properties with potential applications in the cosmetic industry [10].

The focus on bioactive compounds aligns well with bioinformatics approaches. Bioinformatics empowers researchers to formulate hypotheses and navigate the vast amount of data generated in this exciting field of drug discovery.

II. METHODS

1.1. Sample Collection:

Bioactive compound data was retrieved from public databases, including the National Center for Biotechnology Information (NCBI) [11] and PubChem[12]. These databases offer a comprehensive collection of biomolecules with readily available structural and functional information.

1.2. Homology Modeling and Physiochemical Characterization:

Homology modeling, a computational technique, was employed to predict the three-dimensional (3D) structure of query proteins based on their sequence similarity to known template proteins [13]. This approach typically involves four key steps: Target identification, Sequence alignment, Model building, and Model refinement [14]. The Swiss-Model server [15] was utilized for homology modeling. Additional bioinformatics tools, including UniProt [16], ProtParam [17], Ramachandran plot, SOUSI [18], and SOPMA [19], were used to assess the protein sequences' physicochemical properties.

1.3. Library preparation:

Virtual high-throughput screening (vHTS), also known as screening of virtual chemical libraries, is one of the most frequently used applications of computational drug discovery. This in silico screening approach allows researchers to prioritize compounds with potential biological activity for further evaluation. A library of 500 bioactive compounds derived from various sources, such as plants, bacteria, and algae, was constructed using the PubChemdatabase[12].

1.4. Bioactive Compound Selection:

The Osiris software suite, a comprehensive drug discovery informatics platform encompassing aspects from drug design to preclinical development, was employed to filter the initial library [20]. This software facilitated the retrieval of relevant information about the bioactive compounds, including potential mutagenic properties. Based on this in silico analysis, a subset of 231 compounds was selected for further investigation.

1.5. Drug-Likeness Assessment:

The druggable nature of the selected compounds was evaluated using Drulito, a software tool specifically designed to assess drug-likeness properties [21]. This in silico approach helps determine whether a compound possesses the requisite characteristics to be a viable drug candidate. A total of 253 compounds were analyzed with Drulito, further refining the selection process.

1.6. Receptor Preparation:

Google Scholar was utilized to identify a suitable target receptor for subsequent docking simulations. Chimera software [22] facilitated receptor preparation. This involved importing the receptor's PDB file, performing energy minimization using SPDBV [23] and finalizing the receptor structure through additional energy minimization and hydrogen/charge addition steps within Chimera.

1.7. Ligand Preparation:

Avogadro software [24] was used to prepare the ligand molecules for docking simulations. Ligand structure files (SDF format) retrieved from the library were processed and saved in PDB format using Avogadro. Subsequently, Chimera was employed to add hydrogens and charges to the ligands, resulting in the generation of final ligand preparation files.

1.8. Molecular Docking:

CASTp server [25] was used to identify potential binding pockets within the target receptor. Following this, Chimera facilitated the docking of ligands into the identified binding pockets. The docking scores were calculated and recorded for each ligand-receptor complex.

1.9. Analysis of Ligand-Receptor Interactions:

Open Babel software [26] was employed to extract relevant information about ligand-receptor interactions from the docking results (PDBQT format). Biovia Discovery Studio software [27] was then utilized

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to visualize and analyze these interactions in detail, including the identification of bond angles. Both 2D and 3D representations of the interactions were generated for further analysis.

1.10. Molecular Dynamics Simulation:

The iMOD server [28] was utilized to perform molecular dynamics simulations on the docked ligand-receptor complexes. The prepared files were uploaded to the server for simulation, and the resulting data were retrieved for further analysis.

II. RESULT

2.1. Receptor Selection and Properties:

The N-methyl-D-aspartate (NMDA) receptor, a key glutamate receptor and the brain's primary excitatory neurotransmitter, was chosen as the target receptor for this study [29].

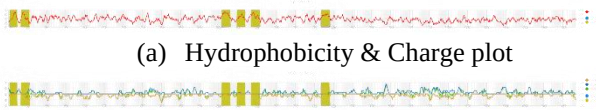
NMDA receptors play a crucial role in synaptic plasticity, a cellular process believed to underlie memory formation [30]. The selected receptor sequence possessed a length of 1484 amino acids. ProtParam, a bioinformatics tool from the ExPASy server (17), was employed to analyze the physicochemical properties of the NMDA receptor sequence. The GRAVY value, indicative of overall hydrophobicity, was determined to be -0.388, suggesting a slightly hydrophilic nature. Additionally, the allopathic index of 74.55 indicated a potential for blood-brain barrier penetration as shown in Table 1.

Table 1 - Parameters computed by using ProtParam Tool:

Protein	No.of amino acids	Molecular weight	Theoretical pI	Instability index	Aliphatic index	Grand average of hydropathicity (GRAVY)
NMDA	1484	166367.24	6.47	48.76	74.55	-0.388

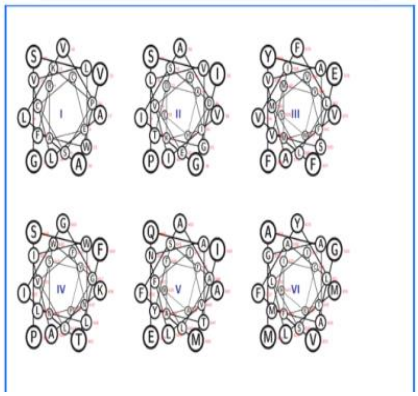
2.2. Secondary Structure Prediction

The online tool SOSUI [18] was employed to predict the secondary structure of the NMDA receptor based on its amino acid sequence. This analysis provided insights into the protein's folding patterns and potential functional domains as shown in Figure 1.



(a) Hydrophobicity & Charge plot

(b) Net charge density



(c) Wheel plot of transmembrane helices

Figure 1: (a) Hydrophobicity of NMDA receptor (b) Net charge density of NMDA (c) Wheel plot of transmembrane helices.

2.3. Prediction of Solvent Accessibility

SOPMA (Self-Optimized Prediction Method with Alignment) software was utilized to analyze the solvent accessibility of the NMDA receptor's amino acid residues [19]. This analysis helps identify regions of the protein that are exposed to the solvent and potentially accessible for ligand binding. The results, including graphs and parameters like window width and the number of states, are not shown here but can be included as a supplementary figure if deemed necessary shown in Table 2 and Figure 2.

Table2: Secondary structure elements calculated using SOPMA

Protein	NMDA
Alpha helix (Hh)	29.04%
310 helix (Gg)	0.00%
Pi helix (Ii)	0.00%
Beta bridge (Bb)	0.00%
Extended strand (Ee)	15.63%
Beta turn (Tt)	4.31%
Bend region (Ss)	0.00%
Random coil (Cc)	51.01%
Ambiguous states (?)	0.00%
Other states	0.00%

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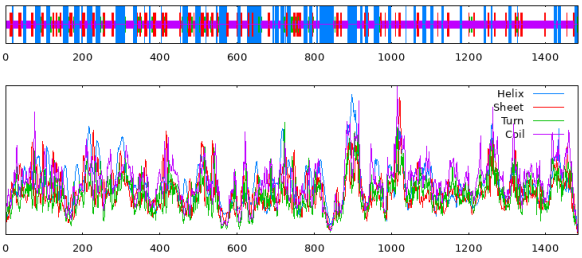

Figure 2: Secondary structure prediction of NMDA receptor having different patterns of helix, sheet, turn, coil.

2.4. Computational modeling of 3D Protein structure of NMDA receptor using Swiss Model:

The Swiss-Model server was employed to generate a 3D structural model of the NMDA receptor through homology modeling shown in Figure 3. This model serves as a valuable tool for understanding the receptor's spatial conformation and potential ligand binding sites.

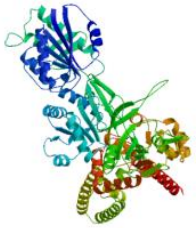

Fig3: 3D structure of NMDA receptor.

2.5. Virtual Library Construction and Docking

A virtual library of 500 bioactive compounds was established using the PubChem database. These compounds encompassed diverse classes, including alpha-hydroxy acids (AHAs), beta-carotene, caffeic acid, catechins, chlorogenic acid, collagen, coumaricacid,elastin, euhalothece 362, flavonols, fucoidan, fucoxanthin, ginseng saponin, glycerine, hyaluronic acid, keratin, lanolin, mycosporine glycine, nucleic acid, palythinol, 334, protocatechuic acid, retinoic acid, scytonemin, vitamin A, vitamin B. The Osiris and Drulito software tools were employed for further library curation and drug-likeness assessment. Subsequently, AutoDockVinasoftware[31] was utilized to perform in silico docking simulations of the virtual library compounds with the NMDA receptor as shown in Figure 4,5,6,7,8. Docking scores were calculated to evaluate the predicted binding affinities between ligands and the receptor.

Based on the docking scores, the top five compounds with the most favorable binding affinities (highest negative scores) were selected for further analysis. These compounds included PubChem CIDs 153353 (an AHA analog), 5281234 and 5281227 (beta-carotene analogs), 3593 (a catechin analog having a negative score of -6.2), and 446467. PubChem CID 153353 emerged as the top candidate with a docking score of -6.6, followed by CID 5281234 (-6.4), 446467 (-5.5), 5281227 (-5.5) as shown in Table 3.

Table 3: Docking result of receptors with ligands molecule

Pubchem CID	IUPAC name	Molecular weight	Docking score
153353	Androst-4-en-3-one, 9,11-epoxy-17-hydroxy-17-methyl-, (11alpha,17beta)-	316.4	-6.6
5281234	Zeinoxanthin	552.9	-6.4
3593	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one	302.28	-6.2
446467	2-[(1E,3E,5Z,7E)-3,7-dimethylnona-1,3,5,7-tetraenyl]-1,3,3-trimethylcyclohexene	270.5	-5.5
5281227	Canthaxanthin	564.8	-5.5

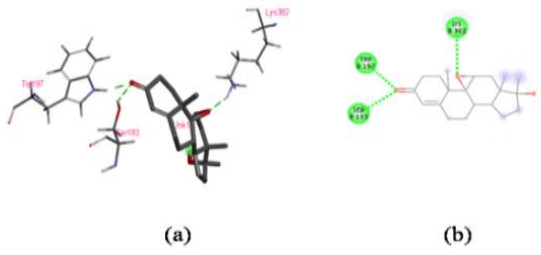

Figure 4: (a) 3d and (b)2d Molecular interaction between NMDA and PubChem CID 153353.

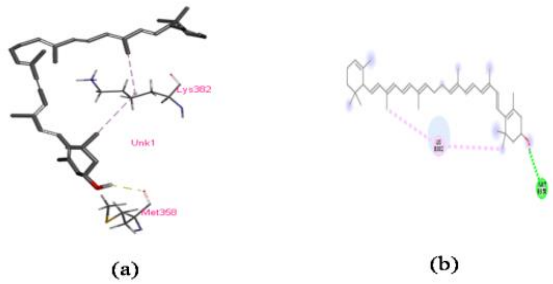

Figure 5: (a)3d and (b)2d Molecular interaction between NMDA and pubchemcid5281234.

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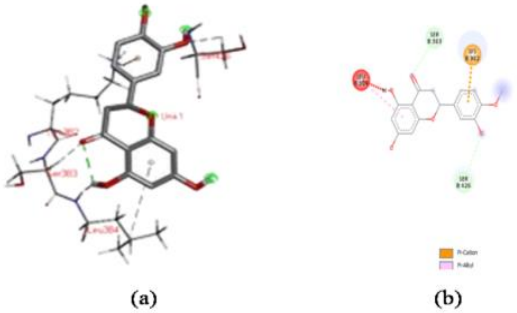
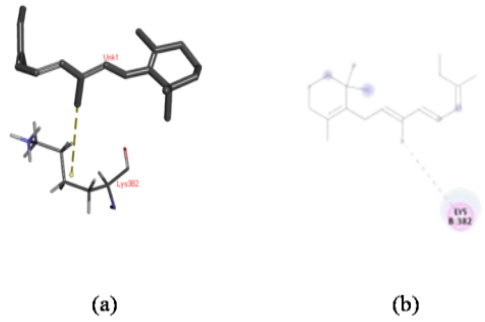


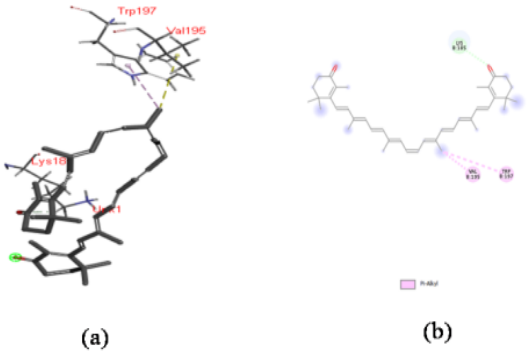
(a) (b)

Figure 6: (a) 3d and (b) 2d Molecular interaction between NMDA and pubchemcid3593.



(a) (b)

Figure 7: (a)3d and (b)2d Molecular interaction between NMDA and pubchemcid 446467.

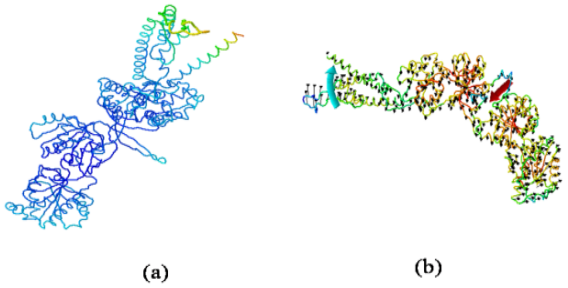


(a) (b)

Figure 8: (a)3d and (b)2d Molecular interaction between NMDA and pubchemcid 5281227.

2.6. Molecular Dynamics Simulations

The two top-scoring compounds (PubChem CIDs 153353 and 5281234) were subjected to additional analysis using the iMOD server. Molecular dynamics simulations were performed to evaluate the stability and dynamic behavior of the ligand-receptor complexes over time. The simulations yielded data on various parameters, including deformability, B-factors, and atom indices. The eigenvalue for both complexes was determined to be 2.764866e-06(shown in Figure 9, 10, 11, 12)



(a) (b)

Fig9: 3-D structure of NMDA and PubChemCID 153353 from iMOD Server.

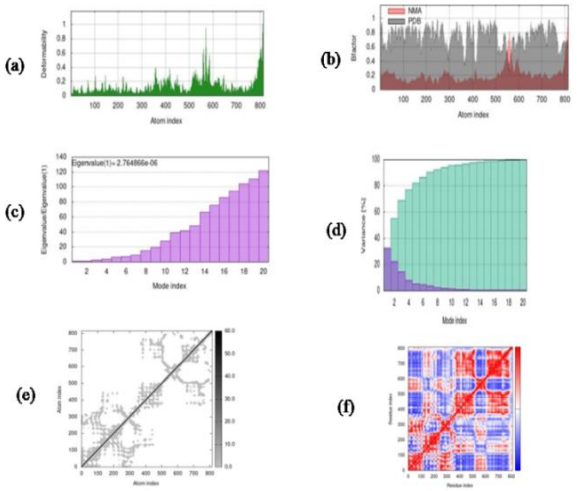
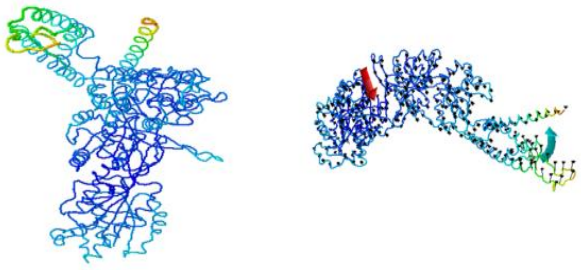


Figure 10: Best docked molecular dynamics simulations done through iMODS server of 153353 against NMDA receptor depicting (a) Deformability (b) bfactor (c) Eigenvalue (d) Varience (e) Atom index (f) Covarience matrix



(a) (b)

Figure 11: 3-D structure of NMDA and PubChemCID 5281234 from iMOD Server.

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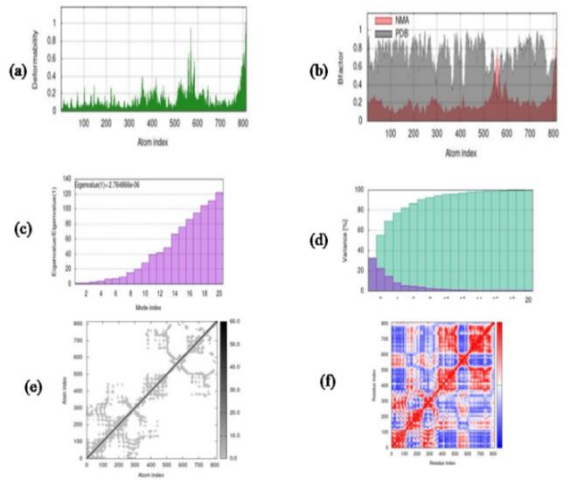

Figure 12: Best docked molecular dynamics simulations done through iMODS server of 5281234 against NMDA receptor depicting (a) Deformability (b) bfactor (c) Eigenvalue (d) Varience (e) Atom index (f) Covarience matrix

III. DISCUSSION

The N-methyl-D-aspartate (NMDA) receptor is a complex subtype within the glutamate receptor family, and the glutamate system itself represents a highly intricate network within the central nervous system (CNS) [32]. This complexity likely reflects the NMDA receptor-glutamate system's critical roles in various fundamental CNS functions. Importantly, the system also plays a role in protecting against the damaging effects of excessive NMDA receptor-mediated neurotransmission [32]. However, NMDA receptor function diminishes with age, potentially contributing to age-related memory decline [33].

Calcium acts as a crucial intracellular messenger in neurons and other brain cells, influencing synaptic transmission, development, differentiation, exocytosis, and learning and memory processes. Disruptions in calcium homeostasis have been implicated in various neurodegenerative and psychiatric disorders, as well as brain aging [34][35][36].

In Alzheimer's disease (AD), excessive glutamate release by neurons overstimulates NMDA receptors, leading to increased calcium influx and subsequent neuronal cell death [37]. Memantine, a medication used to treat moderate-to-severe AD symptoms, has shown some promise in mitigating these effects [38].

The present study explored the potential of natural bioactive compounds, such as beta-carotene and catechin derivatives, as ligands for the NMDA receptor using in silico docking simulations from natural resources like carrots, spinach lettuce, tomato, strawberries, black grapes, apricots, green tea, etc. Natural products often offer advantages over synthetic drugs due to their generally better tolerability profiles [39].

Beta-carotene, a well-known antioxidant and anti-cancer agent, emerged as a promising candidate in this study. Calcium/calmodulin-dependent protein kinase IV (CAMKIV) is an enzyme involved in the formation of calcium-calmodulin complexes and plays a role in both cancer and neurological diseases. Beta-carotene's ability to bind to the CAMKIV active site with high affinity suggests its potential as a therapeutic target [39].

This study employed in silico techniques, which offer valuable insights but require validation through in vitro and in vivo experiments. Future studies should investigate the identified compounds' biological effects on cellular models and potentially animal models relevant to neurodegenerative diseases. Additionally, exploring the potential mechanisms by which these compounds may exert their effects would be of great interest.

IV. CONCLUSION

The N-methyl-D-aspartate (NMDA) receptor has emerged as a promising target for therapeutic development in neurodegenerative diseases such as Alzheimer's disease. This study employed in silico docking simulations to explore the potential of natural bioactive compounds as ligands for the NMDA receptor. The findings suggest that certain plant-derived compounds, including beta-carotene and catechin derivatives, may exhibit favorable binding affinities with the receptor. These natural products offer potential advantages over synthetic drugs due to their generally safer side-effect profiles.

The top-scoring compounds (PubChem CIDs 153353 and 5281234) displayed promising docking scores (-6.6 and -6.4, respectively) and exhibited stability during subsequent molecular dynamics simulations. However, in silico techniques require validation through biological experiments. Future research should focus on in vitro and in vivo studies to evaluate the identified compounds' biological effects on relevant cell and animal models of neurodegenerative diseases. Additionally, investigating the mechanisms by which these compounds exert their effects is crucial for further development.

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