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An Integrated Study to Extrapolate the Interaction of Nmdar with Potential Ligands for the Treatment of Alzheimer's Disease Symptoms.

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Abstract

Objective: *Alzheimer's disease (AD) is the most common neurodegenerative disease affecting the health status of older adults especially those above the age of 60 years. As an outcome, two types of medications have been developed for the treatment of its symptoms which are acetylcholinesterase (AChE) and N – methyl -D -aspartate receptor (NMDAR) antagonist. This paper uses the computational approach for understanding the interaction of NMDAR with 4 major phytocompounds (Curcumin, L-epicatechin, Ginsenosides, and Resveratrol) by molecular docking NMDAR against the ligands. Then their therapeutic analysis and pharmacological characteristics were investigated.* ***Method:*** *In this study, the target protein NMDAR was retrieved from PDB and docked against 6 phytocompounds via PyRx. The binding affinity of the target protein with each ligand was compared and analysed. Out of the 6 phytocompounds the top 4 phytocompounds were selected based on their binding affinity, which had to be lower than 6. The top 4 were then studied using ADMET and visualised using BIOVIA Discovery Studio Visualizer.* ***Results:*** *Molecular docking results of the target protein, NMDAR, with the top 4 ligands (Curcumin, L-epicatechin, Ginsenosides, and Resveratrol) showed that these ligands have the best binding affinity with the target protein.* ***Conclusion:*** *By analysing the results it can be concluded that the top 4 ligands (Curcumin, L-epicatechin, Ginsenosides, and Resveratrol) can be used for the treatment of AD symptoms. But, ligands in vitro and in vivo studies have to be carried out to understand the practical use of these ligands.*

Keywords: Alzheimer's disease (AD), N – methyl -D -aspartate receptor (NMDAR), Curcumin, L-epicatechin, Ginsenosides, Resveratrol, molecular docking, ADMET.

INTRODUCTION

Alzheimer's disease (AD) is a fatal type of dementia, caused by the abnormal build-up of proteins in and around the brain cells. The condition has an impact on the regions of the brain responsible for cognition, memory, and language. As a result, the person experiences slight memory loss, which may impair their ability to do daily tasks. The brain cells in AD eventually senesce and perish. According to research, even though having a family history of Alzheimer's does not guarantee that a person would develop the condition, people who have parents or siblings who have the disease are more likely to develop it than those who do not. Around 6.2 million Americans age 65 and older are impacted by the condition, which has an average life expectancy of 11 to 20 years following diagnosis. [1] According

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to WHO data, the condition has been shown to afflict close to 5% of men and 6% of women over the age of 60. In India, around 54% of dementia patients per 1000 people have AD. [2] Making it a major form of dementia in the sub-continent.

NMDA receptors are the brain's earliest excitatory neurotransmitters. Memory and synaptic plasticity depend on them. NMDAR hypofunction can impair memory and learning. Resulting in excitotoxic brain damage. Ageing hypofunctions NMDAR, reducing system efficiency. Amyloidopathy and oxidative stress promote NMDAR hypofunction in AD patients. Patients may develop severe, long-term NRHypo, which causes cognitive deterioration, mental problems, and neurodegeneration. AD patients can be treated by preventing corticolimbic pyramidal neuron overstimulation. Nevertheless, glutamate (glu) is crucial to Brain function. It damages central nervous system (CNS) neurons via excitatory receptors on dendritic and somal surfaces as the major CNS neurotransmitter, released at half of the brain's synapses. There are three receptor subunits for ionotropic glu, of which NMDAR is the most researched. [3] As a result, NMDAR was chosen for the study's target receptor because it is one of the key receptors for researching neurodegenerative illnesses like AD.

Curcumin, L-epicatechin, ginsenosides, and resveratrol were chosen as NMDA-binding ligands that could cure AD. First, curcumin (turmeric) is an ancient Indian herb that treats cystic fibrosis, haemorrhoids, breast cancer, dementia, traumatic brain injury, etc. Anti-inflammatory, lipophilic, and antioxidant qualities make it essential for AD treatment. Age promotes bio-metal toxicity-related oxidative stress, free radicals, inflammation, beta-amyloid activity, and brain dysregulation. These factors induce AD. Curcumin's anti-inflammatory, anti-amyloid, and metal-chelating effects may prevent neurodegeneration and microglia growth. This may boost the patient's memory. [2] Hence, curcumin is an essential AD ligand.

Second, L-epicatechin, a bioactive tea component that is part of EGCG. They are anti-oxidative and anti-inflammatory like curcumin. Long-term green tea consumption prevents amyloid beta-induced cognitive decline, hippocampus, plasma lipid peroxide, and ROS decrease. EGCG is an effective NMDAR ligand because it prevents lipopolysaccharide-induced memory loss and reduces cytokines and inflammatory proteins in untreated controls. [4-8]

Third, Chinese medicine believes ginseng gives cells energy. Ginsenosides are widely used to treat AD, despite their unknown chemical mechanism. Ginsenoside Rg1 reduces amyloid beta in AD mice and also restores mitophagy in AD cell models. It suppresses mTOR and ULK1 phosphorylation and protects AD neurons, making it a viable AD ligand. [9]

Finally, Red wine is the predominant source of resveratrol. Moderate red wine consumption can reduce dementia risk. Resveratrol activates sirtuins, mimics calorie restriction, and may influence AD regulation. It passes the blood-brain barrier and increases hippocampal amyloid-beta solubility. Resveratrol modulates A-beta, inflammatory mediators, and oxidative stress like the prior ligands. Hence, treating Alzheimer's symptoms with the four ligands and the NMDA receptor may be beneficial. [10-11]

The main aim of this study is to assess the potential of the four ligands to work as a treatment for the symptoms of AD along with the target protein via molecular docking. Additionally, to understand their pharmacological and therapeutic effects. Possibly propose a potential solution for the treatment of AD symptoms.

METHOD

Retrieval of the Ligands

The 6 major phytocompounds used for the treatment of AD were identified via literature review, they are curcumin from *Curcuma longa*, L-epicatechin from *Salacia chinensis*, ginsenosides from *Panax*

ginseng, Resveratrol from *Vitis vinifera*, Isothiocyanates from *Brassica oleracea*, and Monoterpenes from Citrus sinensis. The canonical SMILES, PubChem CID and two-dimensional (2D) models of these phytocompounds were retrieved in SDF format using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The structures were then converted to PDB file format using Open Babel software.

Protein Extraction and Purification

The three-dimensional (3D) structure of the protein of interest that is NMDAR (as shown in figure 1), (pdb Id:4KCC) was acquired using the X-ray diffraction method with a resolution of 1.89 Å, R-Value Free: 0.206, R-Value Work: 0.172, and R-Value Observed: 0.173. The structure was downloaded from Research Collaboratory for Structural Bioinformatics PDB (RCSB PDB) (https://www.rcsb.org/) in pdb format. The residues were predetermined using BIOVIA. The protein was purified in BIOVIA by removing the water molecules hetatm and the active sites. This ensured that only Chain A is retained. The purified protein was saved in pdb format. The Ramachandran plot generation and the two-dimensional structure via EMBL-EBI pdbsum (http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/).

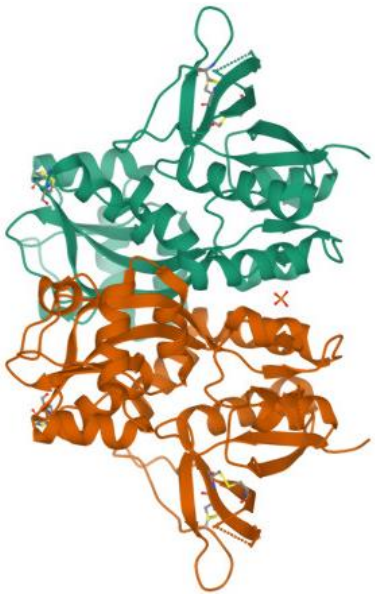

Figure 1. The 3D crystal structure of the NMDAR GluN1 ligand binding domain Apo state (pdb Id: 4KCC) was downloaded from the RCSB PDB database.

Molecular Docking

PyRx was used to carry out the molecular docking procedure after the protein and ligand had been retrieved. PyRx is primarily a virtual molecular screening application that is used to dock small-molecular libraries to find lead compounds and the operation that they offer. Here, the preselected four phytocompounds were loaded as ligands, and the target proteins 4KCC, as macromolecules. where the ligand loaded was energy minimised, and was converted to the .pdbqt form, and the grid was generated for the targeted protein.

All of the ligands were discretely docked with the target protein, and their binding affinities were evaluated. Binding affinity is the degree to which a protein and ligand can bind to one another. Therefore, meaning that the least binding results in the best possible docking conformation (Kcal/mol). The top 4 ligands with the lowest binding affinity and a value of zero for the root mean square deviation (RMSD) that is curcumin, L-epicatechin, ginsenoside and resveratrol, were chosen. The RMSD value is used to evaluate the docked conformation in comparison to other docked conformations and is visualised. The ligands were saved in the pdb file format, and the other docked conformations were evaluated based on the binding affinity and the inhibitory activity of the ligands and standard drugs.

Visualisation

PyRx was used to select the top four ligands that had the lowest binding affinity for the protein. The best model of each ligand was then saved in pdb file format. These were visualised with the help of the BIOVIA Discovery Studio software. The three-dimensional (3D) structure and the non-bond interaction were observed. The 3D model and 2D model were extracted and saved in .png format.

Physiochemical Studies (ADMET analysis)

Utilizing Lipinski's rule of five (RO5), the pharmacokinetics were analysed in ADMET (https://admetmesh.scbdd.com/). Parameters such as physiochemical properties, absorption, distribution, metabolism, medical chemistry, toxicity, and excretion were used to make predictions about pharmacodynamic properties. ADMET analysis was carried out by using ADMETlab 2.0 (https://admetmesh.scbdd.com/). The highest four docked ligands that had the lowest binding affinity for each protein were analysed.

RESULT

Selection of Phytocompounds

There was a total of 6 phytocompounds that were selected during the literature review, only 4 phytocompounds were chosen for further study based on the docking results, binding affinity and the two-dimensional chemical structure shown in Figure 2.

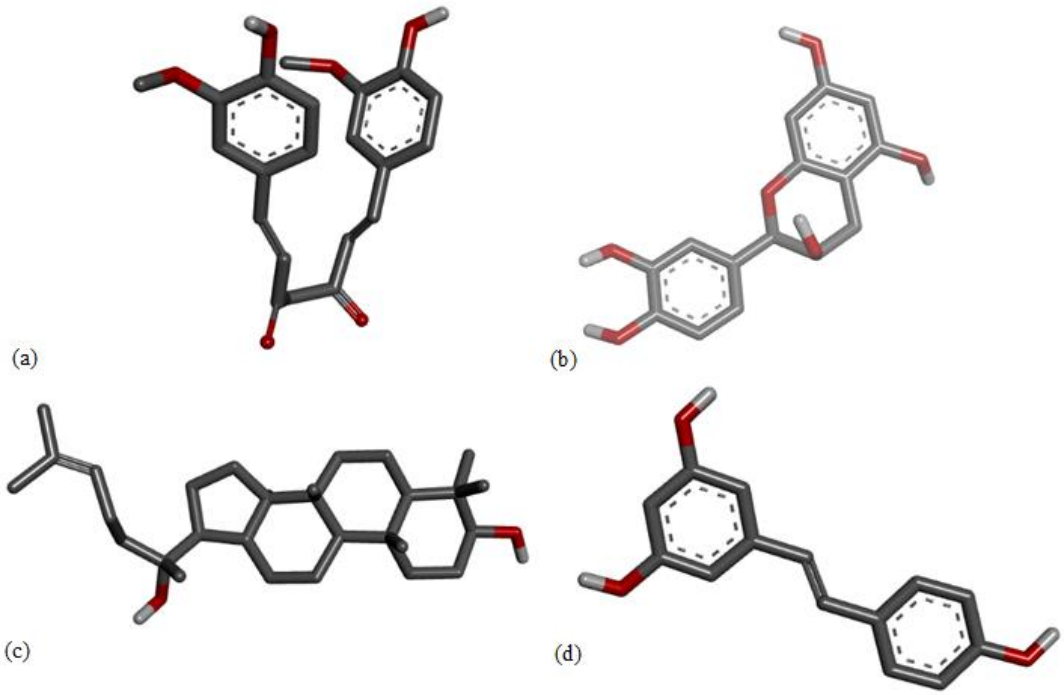

Figure 2. The chemical structures of the top 4 phytocompounds. A) Curcumin, B) L-epicatechin, C) Ginsenosides and D) Resveratrol.

Protein Retrieval and Purification

The 3D crystal structure of the target protein NMDAR that was retrieved from PDD (pdb Id: 4KCC) and purified using BIOVIA Discovery software is subjected to structural analysis as shown in figure 3. The protein's Ramachandran plot, Secondary Structure and hydropathy plot are analysed in the structural analysis.

The water molecules hetatm and the active sites of the protein were removed using BIOVIA to obtain the purified form of the NMDAR protein.

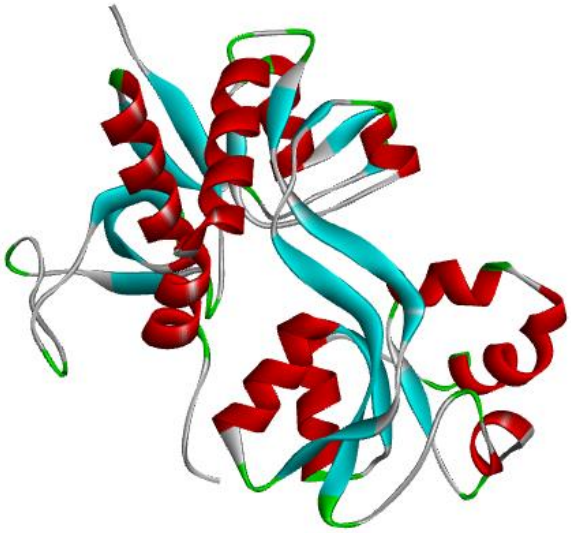

Figure 3. The 3D structure of the purified protein was downloaded from BIOVIA Discovery Studio.

The Ramachandran Plot

The Ramachandran plot for the protein NMDAR was downloaded from the EMBL-EBI pdbsum. As shown in figure 4 the 3D structure has 91.7% of residues in the most favoured regions [A, B, L] that is 222 residues, 8.3% in the additional allowed region [a, b, l, p] 20 residues, 0.0% in the generously allowed region [~a,~b,~l,~p] and 0.0% in the dissolved region [XX]. The Non-glycine and non-proline residues were 242 which is 100% and the End-residues (excl. Gly and Pro) are 6. The total number of residues is 275 with 17 glycine residues and 10 proline residues (Figure 4).

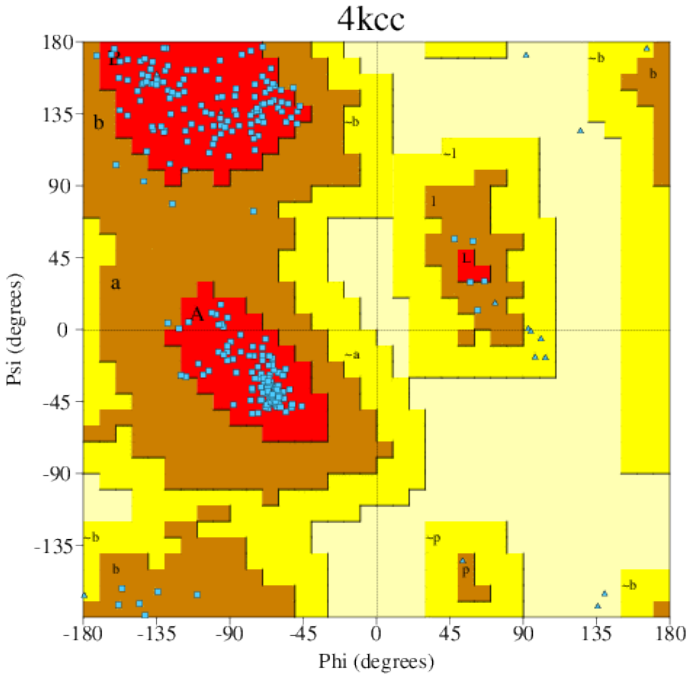

Figure 4. The Ramachandran plot for the protein of interest NMDAR (pdb Id: 4KCC).

The Secondary Structure

As shown in Figure 5(a), the secondary structure of the target protein depicts the presence of 4 Sheet, 1 beta alpha beta, 2 beta-hairpin, 2 psi loops, 3 beta bulges, 14 strands, 11 helices, 8 helix-helix interacs, 18 beta turns, 1 gamma turn and 3 disulphides.

The Hydropathy plot

In the hydropathy plot, which is a form of quantitative analysis, the hydrophobic and hydrophilic tendencies of an amino acid sequence are displayed. The hydropathy plot of the target protein NMDAR has been analysed via BIOVIA Discovery Studio Visualizer which can be seen in Figure 5(b).

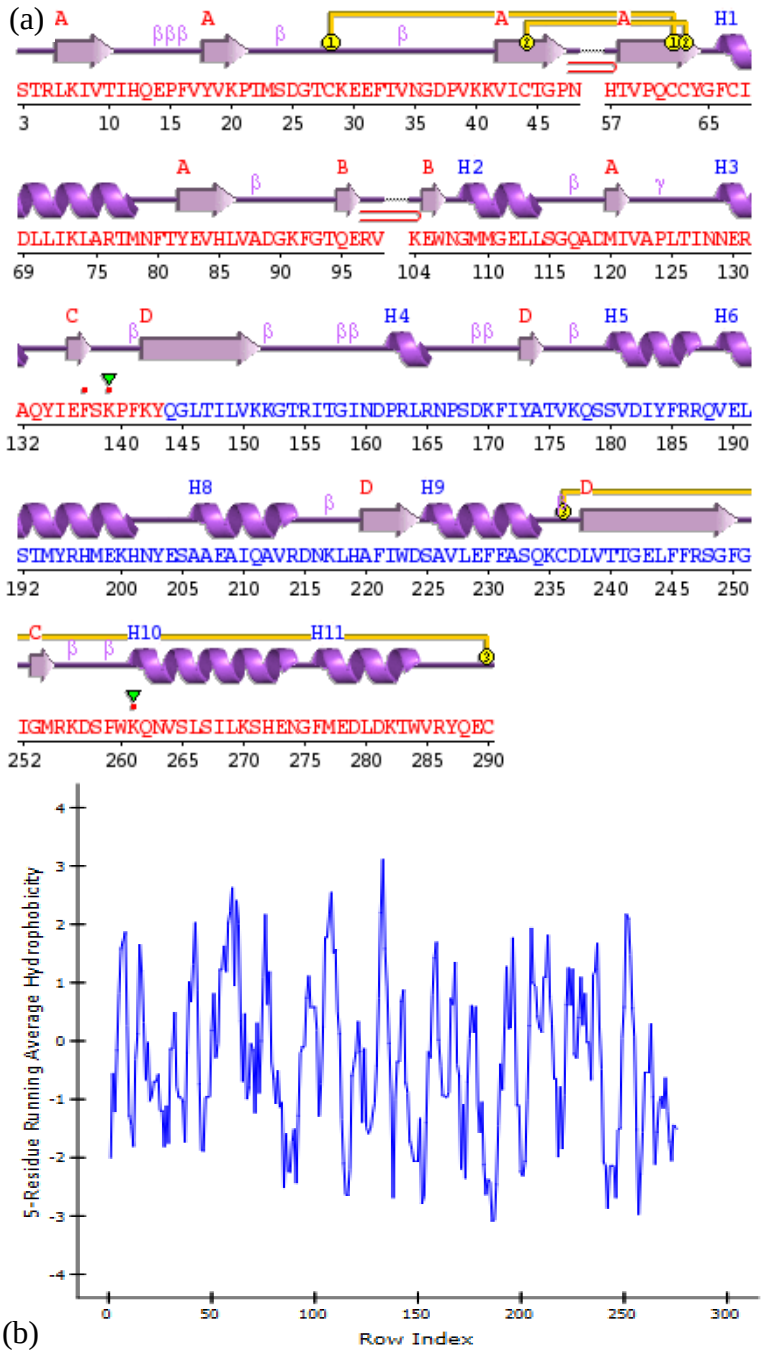

Figure 5. The structural analysis of EGFR. (a) the secondary structure and (b) the hydropathy plot of the target protein.

Molecular Docking

As part of this docking study, six different ligands were input into the PyRx software and matched up against the NMDAR proteins. After performing the docking analysis, the optimal docking orientation for the compound was determined to be the conformation that had the least amount of

binding affinity while also having zero roots mean square deviation (RMSD). After the docking was finished, both the RMSD and the binding affinity were recorded. From the 6 phytocompounds, those that are shared by all of the target proteins and have a lower binding affinity that is 6 or higher were chosen and displayed in Table 1.

Table 1. The binding affinity of the top 4 phytocompounds with the target protein NMDAR.

Ligand	Name of Ligand	Binding Affinity
NMDA_Pdbqt_969516_uff_E=272.07	Curcumin	-7.3
NMDA_Pdbqt_1203_uff_E=230.94	L-epicatechin	-8
NMDA_Pdbqt_3086007_uff_E=797.18	Ginsenosides	-9.8
NMDA_Pdbqt_445154_uff_E=172.22	Resveratrol	-6.9

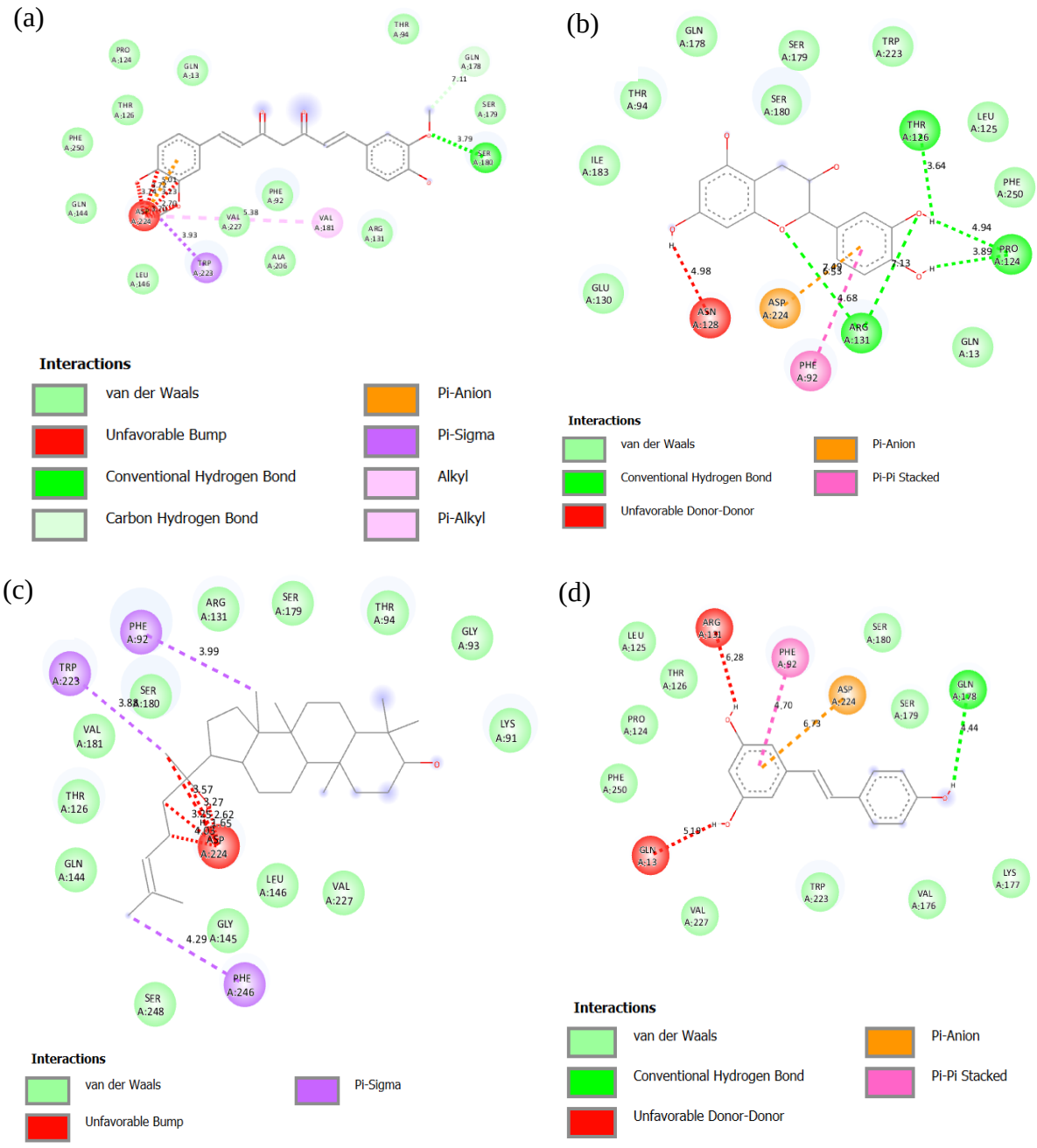

Figure 6. The 2D structure of the target protein's interaction with the top 4 ligands, and the bond length of each interaction. A) Curcumin, B) L-epicatechin, C) Ginsenosides and D) Resveratrol.

Visualisation

The top four phytocompounds were chosen for the target protein from the six different phytocompounds. These compounds were then put through the visualisation process using the BIOVIA Discovery Studio Visualizer. The 2D & 3D models of the interactions, as well as information regarding the category and type of interactions, and the bond for the corresponding amino acid residues in the ligand, were successfully obtained (Figure 6 &7).

Molecular docking interaction with NMDAR, 4KCC

a) ***Curcumin:*** As shown in figure 7(a), curcumin's 3D interaction with 4KCC can be visualized. Curcumin forms a conventional Hydrogen bond with Ser180, with bond distance of 3.79.
b) ***L-epicatechin:*** As shown in figure 7(b), L-epicatechin's 3D interaction with 4KCC can be visualized. L-epicatechin forms a conventional Hydrogen bond with Arg131, Pro124, and Thr126. With the bond distance of 7.49 and 7.13 with Arg131, 4.94 and 3.89 with Pro124 and finally 3.64 with Thr126.
c) ***Ginsenosides:*** As shown in figure 7(c), ginsenoside's 3D interaction with 4KCC can be visualized. Ginsenoside forms Pi-Sigma interactions with Phe92, Trp223, and Phe246. With a bond length of 3.99, 3.88 and 4.29 respectively. Ginsenoside has no conventional Hydrogen bond.
d) ***Resveratrol:*** As shown in figure 7(d), resveratrol's 3D interaction with 4KCC can be visualized. Resveratrol forms a conventional Hydrogen bond with Gln178, with bond distance of 4.44.

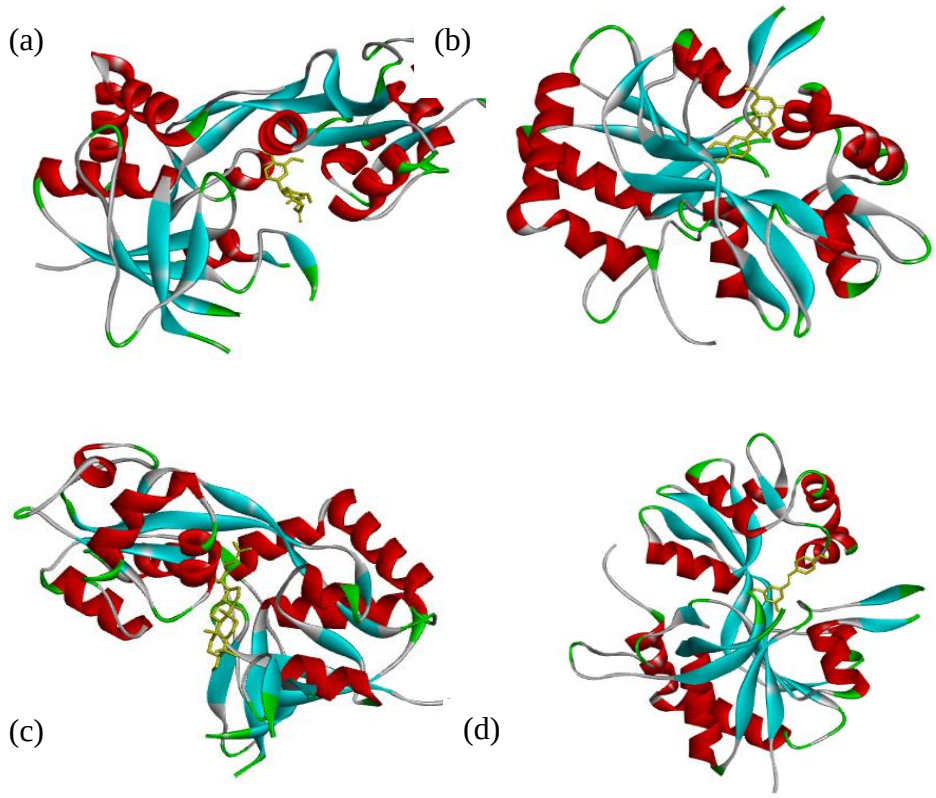

Figure 7. The 3D structure of the target protein's interaction with the top 4 ligands. A) Curcumin, B) L-epicatechin, C) Ginsenosides and D) Resveratrol.

ADMET Analysis

The four different phytocompounds were selected, along with their own unique PubChem ID. As can be seen in Tables 2, 3, 4, 5, 6, and 7, these phytocompounds were analysed with ADMETlab 2.0 to determine their physiochemical properties, medicinal chemistry, absorption, distribution, metabolism, excretion, and toxicity.

Table 2. Medicinal chemistry of top 4 ligands.

Ligands	QED	SYNTH	Fsp3	Lipinski Rule	Pain Alert
Curcumin	0.548	2.426	0.143	Accepted	0
L-epicatechin	0.510	3.344	0.200	Accepted	1
Ginsenosides	0.440	4.675	0.933	Accepted	0
Resveratrol	0.692	2.112	0.000	Accepted	0

Table 3. Physiochemical properties of top 4 ligands.

Ligand	MW	Vol	nHD	nHA	nRot	nRing	nHet	fChar	Flex	TPSA	LogS
Curcumin	368.130	381.036	2	6	8	2	6	0	0.500	93.060	-3.921
L-epicatechin	290.080	279.249	5	6	1	3	6	0	0.059	110.380	-2.990
Ginsenosides	444.400	508.154	2	2	4	4	2	0	0.190	40.460	-4.775
Resveratrol	228.080	241.503	3	3	2	2	3	0	0.154	60.690	-2.273

MW: Molecular weight, nHA: number of hydrogen acceptors, nHD: number of hydrogen bond donors, nRot: number of rotatable bonds, nRing: number of rings, nHet: number of heteroatoms, fChar: formal charge, Flex: flexibility, TPSA: topological polar surface area, LogS: logarithm of aqueous solubility value, PAINS: Pan Assay Interference Compounds

Table 4. Absorption of top 4 ligands.

Ligand	CaCo-2	MDCK	PgP-inh	Pgp-sub	HIA	F(20%)
Curcumin	-4.834	1.6e-05	0.284	0.014	0.06	0.011
L-epicatechin	-5.971	4.3e-06	0.007	0.002	0.096	0.99
Ginsenosides	-4.842	8.7e-06	0.138	0.0	0.014	0.911
Resveratrol	-4.916	1.4e-05	-	--	---	--

MDCK: Madin-Darby Canine Kidney Cells, PgP-inh: P-glycoprotein inhibitor, PgP-sub: PgP Substrates, HIA: Human Intestinal absorption, F(20%): Human Oral Bioavailability 20%.

Table 5. Distribution of top 4 ligands.

Ligands	BBB	PBB	VD	FU
Curcumin	0.103	99.799%	0.369	1.049%
L-epicatechin	0.025	92.065%	0.661	8.871%
Ginsenosides	0.766	99.276%	1.566	1.833%
Resveratrol	0.032	97.268%	0.822	2.620%

BBB: Blood Brain Barrier, PBB: Plasma Protein Binding, VDss: Volume Distribution, FU: Fraction unbound in plasma.

Table 6. Metabolism and excretion of top 4 ligands.

Ligand	CYP1A2-Sub	CYP1A2-Inh	CYP3A4-Inh	CYP3A4-Sub	CL
Curcumin	0.758	0.593	0.674	0.517	13.839
L-epicatechin	0.295	0.219	0.315	0.215	17.911
Ginsenosides	0.325	0.024	0.141	0.296	21.150
Resveratrol	0.11	0.976	0.943	0.163	15.661

Table 7. Toxicity of top 4 ligands.

Ligand	CYP1A2-Sub	CYP1A2-Inh	CYP3A4-Inh	CYP3A4-Sub	CL
Curcumin	0.758	0.593	0.674	0.517	13.839
L-epicatechin	0.295	0.219	0.315	0.215	17.911
Ginsenosides	0.325	0.024	0.141	0.296	21.150
Resveratrol	0.11	0.976	0.943	0.163	15.661

HER: Human Ether-a-go-go related gene, H-HT: Human Hepatotoxicity, DILI: Drug-induced liver injury, IGC50: 50% growth inhibition, LC50%: 50% death.

DISCUSSION

In this study, we focus on understanding Alzheimer's disease and proposing a possible solution to the disease's symptoms. AD is the most prevalent form of dementia. Originally it was hypothesised that the disease is primarily caused by the combined presence of amyloid and tau. However recent studies have shown that is not always the case. The core mechanisms of the disease are affected by factors which are age-related, disease-promoting and protective. Various biomarkers are available for the disease such as

amyloid-beta 42, and tau protein which are the core cerebrospinal biomarkers and amyloid-beta oligomers and synaptic markers can also be used as novel candidate biomarkers. The 2 prominent tools used for the diagnosis of the disease is MRI and fluorodeoxyglucose PET. [12] Even though the disease can be diagnosed and there is only a hand fun of licensed treatments available to treat the disease. More biological and neuroimaging biomarkers have to be developed to support clinical diagnosis. Reports showed that there are potential risks and protective factors for the disease, but further research has to be carried out to understand if interventions can substantially lower the risk of the disease. [13]

Statical data shows that the cases of AD worldwide will triple by 2050. In the primary phase of the disease, amyloid-beta accumulation and the spread of tau pathology occur simultaneously. Reports state that there is about 60-80% association of the disease with heritable factors. More than 40 AD-associated genetic risk loci have been identified including *APOE* alleles, which have the strongest association with the disease. Though lifestyle factors do not directly affect AD pathology, they have a significant positive impact on patients. Many pharmacological treatments have been developed targeting the anti-amyloid-beta, anti-inflammatory and anti-tau properties. [14]

NMDAR is a subtype of glutamate receptor that is extremely important to synaptic plasticity as well as the processes of learning and memory. Cognitive decline, memory loss, and synaptic dysfunction are the hallmarks of Alzheimer's disease (AD), a progressive neurodegenerative disorder. According to findings from recent research, a dysfunction in NMDARs may play a role in the pathogenesis of Alzheimer's disease (AD). As a result, targeting NMDARs may be a promising therapeutic strategy for treating this disease. Modulating NMDARs has been shown in several preclinical studies to be effective in improving cognitive function and lowering amyloid beta (A) pathology in models of Alzheimer's disease. For example, it has been demonstrated that the NMDAR antagonist memantine can improve cognitive function and reduce A deposition in models of Alzheimer's disease [15]. In addition, recent research has shown that AD models treated with the NMDAR co-agonist D-serine exhibited improvements in cognitive function and a reduction in A pathology [16]. According to the findings of these studies, modulating NMDARs could be a promising therapeutic approach for Alzheimer's disease (AD).

NMDAR-induced excitotoxicity may contribute to cell death associated with certain neurodegenerative diseases. The cell signalling downstream of NMDAR promotes cell survival and plasticity. Research shows that the overactivation of NMDARs located external to the synapse plays a major role in NMDAR toxicity whereas those in the interior contribute to cell survival. This increases the possibility of intervention of NMDAR therapeutically. Ensuring that excessive extrasynaptic NMDAR activity is prevented can provide therapeutic benefits, especially in AD. [17] This makes targeting NMDAR difficult. The only known medication based on NMDAR approved for AD treatment is memantine. Many single-target therapies for AD have proven to be unsuccessful. Due to the convoluted nature of AD pathophysiology, there is a hunt for a diversified pharmacological target. [14]

Keeping this in mind, this study focuses on the 4 major phytocompounds (Curcumin, L-epicatechin, Ginsenosides, and Resveratrol) that can be used as ligands and interact with NMDAR (the target protein) for the treatment of AD symptoms. In general, Curcumin is a naturally occurring polyphenol compound that is derived from the turmeric plant. It has been demonstrated to be neuroprotective, anti-inflammatory, and antioxidant properties. Recent studies have shown that curcumin could also modulate the function of NMDARs, which are linked to the development of AD and play an important part in the processes of learning and memory. Curcumin has been shown in several preclinical studies to modulate NMDAR function and enhance performance in animal models of AD. For example, it has been demonstrated that curcumin increases NMDAR-dependent long-term potentiation (LTP) in the hippocampus hence improving the process of learning and memory [3]. Furthermore, it has been demonstrated that curcumin can reduce the neuronal toxicity caused by A by modulating the function of NMDAR in AD models [18]. Hence, curcumin's ability to modulate NMDAR function may make it

a promising therapeutic strategy for Alzheimer's disease (AD). However, additional research is required to evaluate the efficacy and safety of curcumin in patients with Alzheimer's disease.

Recent research has indicated that catechins could have neuroprotective effects and modulate the activity of NMDARs, which play an important role in the processes of learning and memory and are linked to the development of AD. For instance, it has been demonstrated that EGCG, a major catechin that can be found in green tea, can inhibit NMDAR-mediated Ca2+ influx and reduce A-induced neuronal toxicity in models of AD [19]. Additionally, it has been demonstrated that EGCG can improve cognitive function and lower deposition in an AD mouse model [20]. Therefore, catechins, and especially EGCG, may be able to promote a good potential therapeutic strategy for AD by modulating the function of NMDAR. However, additional research is required to evaluate the efficacy and safety of catechins in patients with Alzheimer's disease.

Ginsenosides are bioactive compounds that can be found in Panax ginseng. These compounds have been demonstrated to have a wide range of therapeutic effects, one of which may be beneficial in the treatment of AD. The modulation of NMDARs is one of the proposed mechanisms of action. Several studies have been done to investigate the impact of ginsenosides on the function of NMDAR, and they have found encouraging results. It was discovered in a study that, Ginsenoside Rg1, for instance, was found to be capable of increasing NMDAR-mediated currents in cultured hippocampal neurons [21]. Ginsenoside Rb1 was also able to improve NMDAR-dependent long-term potentiation (LTP) in the hippocampus of rats, according to the findings of another research study [22]. According to these findings, ginsenosides might possess the ability to enhance cognitive function in AD patients by enhancing the function of NMDAR. To fully comprehend the impact of ginsenosides on NMDARs as well as their therapeutic potential applications for AD, however, additional research is required.

Several studies have been conducted to investigate the effects of resveratrol on the function of NMDAR. In one study, it was discovered that resveratrol protected cultured hippocampal neurons from NMDAR-mediated excitotoxicity [23]. Yet another study, for instance, discovered that resveratrol could improve NMDAR-dependent long-term potentiation (LTP) in the hippocampus of rats [24]. This shows that resveratrol may have the potential to improve cognitive function in AD patients by improving NMDAR function and protecting against excitotoxicity.

The fact that the top four phytochemicals for the target protein had lower binding affinities and promising results in ADMET analysis indicates that these phytochemicals have the potential to work on the target protein, NMDAR. Therefore, the phytocompounds Curcumin, L-epicatechin, Ginsenosides, and Resveratrol have the potential to undergo further investigation in vitro and in vivo to develop new treatments for the symptoms of AD.

CONCLUSION

AD is a neurodegenerative disease that affects the older population. It causes dementia and leads to difficulties in handling day-to-day activities. Though no proper medication has been discovered for the treatment of AD, a potential way to improve the lives of the patients will be by reducing the symptoms. Based on the results, it can be concluded that ginsenosides have the best binding affinity with the target protein (NMDAR), which is -9.8. This is followed by catechins (-8), curcumin (-7.3) and resveratrol (-6.9), as seen in table 1. These ligands have the potential to bind with NMDAR and the result from ADMET analyse (documented in table 2 to table 7) indicates that these phytocompounds have the potential to treat AD. Further *in vivo* and *in vitro* research has to be carried out on the ligands to extrapolate their interaction with NMDAR and to create a novel drug for the treatment of AD.

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Conflict of interest

The authors declare no conflict of interest.

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Abbreviation

A-beta	Amyloid-beta
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADMET	Chemical absorption, distribution, metabolism, excretion, and toxicity
CNS	Central Nervous System
EGCG	Epi Gallo Catechin Gallate
LTP	Long-term potentiation
NMDAR	*N* – methyl -D -aspartate receptor
RCSB PDB	Research Collaboratory for Structural Bioinformatics PDB
RMSD	Root Mean Square Deviation

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