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Identification of Promising Lead Compounds from *Capsicum annuum* Targeting BACE-1 for Alzheimer's Disease Therapy: A Molecular Docking Study

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Abstract

Background: *Alzheimer's disease (AD) is a neurodegenerative disorder affecting millions of people worldwide. Beta-secretase 1 (BACE-1) is an important therapeutic target for AD treatment. Capsicum annuum (CA) is a commonly consumed plant with potential neuroprotective properties. In this study, we aimed to identify potential lead compounds from CA that can target BACE-1 for AD therapy using molecular docking.* ***Methods:*** *A library of 15 compounds from CA was obtained from PubChem, and their structures were optimized using PyRx-v0.8. BACE-1 protein structure was obtained from the Protein Data Bank (PDB). Docking simulations were performed using PyRx-v0.8, and the results were analyzed using BIOVIA Discovery Studio 2019.* ***Results:*** *Among the studied 15 ligands, the best binding affinity was shown by 6 compounds. Capsaicin, Dihydrocapsaicin, Apigenin, Riboflavin, Quercetin, and Luteolin had a binding affinity of -6.4, -8.4, -8.4, -8.5, and -8.7 kcal/mol respectively. Luteolin had the highest binding score of -8.7 kcal/mol, this indicates its best possible inhibitory action with BACE-1.* ***Conclusion:*** *Our study identified Dihydrocapsaicin, and Capsaicin from CA as promising lead compounds that can target BACE-1 for AD therapy. Further in vitro and in vivo studies are needed to validate their therapeutic potential.*

Keywords: Alzheimer's disease, *Capsicum annuum*, BACE-1, molecular docking

INTRODUCTION

Alzheimer's Disease (AD) is a neurological disorder characterized by progressive memory and cognitive loss, including impaired judgement and decision making and is typically accompanied by various neuropsychiatric symptoms such as, depression, apathy, anxiety, agitation, delusions, and hallucinations [1]. The causes of Alzheimer's have not been fully understood, although it has been estimated that a combination of factors such as age-related changes in the brain, along with genetic, environmental and lifestyle factors might influence the onset of AD. From 1990 to 2019, the Alzheimer's disease burden increased worldwide, with an overwhelming population of 50 million people living with Alzheimer's in 2021 [2]. To date, only symptomatic treatment is available, which counterbalances the neurotransmitter disturbance of the disease [3]. Current treatments include symptomatic approaches such as the usage of acetylcholinesterase inhibitors and N-methyl d-aspartate (NMDA) [4]. Anticholinesterase work by preventing the action of the enzyme anticholinesterase, thereby reducing the symptoms levels of AD. NMDA antagonists function by reducing the increasing levels of NMDA receptor hypofunction. These treatments cannot completely cure Alzheimer's, but they help stabilize the symptoms for a limited period of time.

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Several studies have reported and supported the amyloid-beta (Aβ) pathway in the slow progression of AD which involves the cleavage of amyloid precursor protein (APP) into amyloid-beta peptides (Aβ) by β-secretase (β-APP-cleaving enzyme-1 (BACE1)) and γ-secretase enzymes [5]. In patients with Alzheimer's, dense Aβ aggregates develop between neurons in several regions of the brain and as a result, cell-to-cell signalling is disrupted. While symptomatic therapies work to improve cognitive functions and reduce AD symptoms there is an imminent need to develop disease-modifying therapies that can target the amyloid-beta pathway and effectively prevent or diminish Aβ aggregates in brain regions.

Common pathological features of AD include oxidative stress, accumulation of certain aggregated proteins and neuroinflammation [6]. Fighting chronic disease with phytochemicals or herbal medicine has become a hot topic recently, and numerous studies using phytochemicals for treating neurological disorders have been published. Phytochemicals with anti-oxidant properties could be beneficial in treatment since they have the ability to reduce oxidative stress and inflammation. *Justicia adhatoda L.*, *Ferula assafoetida L.*, *Amorphophallus paeoniifolius*, *Catharanthus roseus*, *Ginkgo biloba L.*, *Panax ginseng*, and *Zingiber officinale* are some plants whose extracts possess anti-inflammatory properties and could be useful in treating AD and other neurological disorders [7]. *Capsicum annuum* is one such plant, with high levels of water and carbohydrates [8]. Bell peppers supply considerable phytochemicals with high antioxidant capacities, such as phenols, flavonoids, and carotenoids. Coloured bell peppers are a good source of antioxidant compounds important for dietary consideration because they can prevent the formation of free radicals that can harm human cells. Extracts (fruits and leaves) can also modulate the immune response, exerting anti-inflammatory properties and promoting the production of antibodies [9]. More researches are necessary to help evaluate the role of phytochemical compounds in the treatment of Alzheimer's and other neurological disorders.

Thus, in this study, we aim to identify phytochemical compounds from *Capsicum annuum* plant extracts as potential drug compounds by docking the ligand molecules with BACE-1 protein.

MATERIALS AND METHODS

Retrieval of Ligands

Based on our literature review, phytochemicals with anti-oxidant and anti-inflammatory properties could exert neuroprotective effects in various brain pathologies. From our literature review, we identified fifteen such phytocompounds from the *Capsicum annuum* plant, with the help of IMPPAT database (Indian Medicinal Plants, Phytochemistry And Therapeutics) [10]. The selected phytochemicals are secondary metabolites such as flavonoids, polyphenols, terpenoids and alkaloids. The library of ligands includes, 3-Methyl-2-butanone (PubChem ID:11251), Luteolin (PDB ID: 5280445), 2-Methyl-3-pentanone (PubChem ID: 11265), Hexadecane (PubChem ID: 11006), Pentyl butyrate (PubChem ID: 10890, Octanal (PubChem ID: 454), Riboflavin (PubChem ID: 493570), Isobutyl 2-methyl butyrate (PubChem ID: 102820), Geranylacetone (PubChem ID: 19633), Capsaicin (PubChem ID: 1548943), Dihydrocapsaicin (PDB ID: 107982), 2-Acetylpyrrole (PubChem ID: 14079), and 2-Tridecanone (PubChem ID: 11622). Quercetin (PubChem ID: 5280343), and Apigenin (PubChem ID: 5280443). The ligands' PDB structures were obtained in SDF format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The ligands were then subjected to energy minimization using Universal Force Field (UFF) and converted to Autodock-compatible pdbqt format using PyRx-v0.8.

Retrieval and Preparation of Protein Target

After conducting an extensive systematic review of the literature, the protein BACE-1 (PDB ID: 1M4H) was identified as the protein target. BACE-1 is a class of hydrolase proteins which breaks down the amyloid precursor protein (APP) at the β-site [11]. This makes BACE-1 an important factor in the production and release of Aβ peptide in the brain. The three-dimensional (3D) structure of the protein was retrieved from the RCSB Protein Data Bank in PDB format. The selection of the PDB structure was made according to previous reports [12]. 1M4H has shown a reasonable resolution of 2.10 Å and

the structure was determined using the X-ray diffraction method. The protein cleaning and preparation processes were performed using BIOVIA Discovery Studio Visualizer-v21.1.0.20298, which involved the removal of water molecules, native ligand and hetero atoms, and the addition of polar hydrogen. The purified protein was then imported into PyRx-v0.8 software, where it was transformed into Autodock-compatible PDBQT format and optimized for docking purposes.

Molecular Docking and Visualization

Molecular Docking is a computational approach towards finding potential drug targets by modelling protein-ligand interactions. PyRx-v0.8 was used to carry out the docking analysis. All fifteen ligands were individually docked with the target in separate docking runs. Blind docking approach was employed to predict the binding affinity energies. The grid box dimensions for the target protein were set as 115.73 × 76.89 × 101.67 Å having centre dimensions of -3.57 × 40.74 × 11.31 Å. Results were recorded according to the Root Mean Square Deviation (RMSD) criterion and in this study, we have selected ligands with 0 RMSD values. All other docking parameters were set to default. Protein-ligand interactions having the best binding affinity scores were selected for visualisation in BIOVIA Discovery Studio. The interactions were analysed in a 2D diagram.

RESULTS AND DISCUSSION

Structural Assessment of BACE-1

BACE-1, also known as beta-secretase, is a type-I transmembrane aspartic protease enzyme that cleaves amyloid precursor protein (APP) to generate beta-amyloid peptide, which is a major component of the amyloid plaques found in the brains of Alzheimer's disease patients. The crystal structure of BACE-1 has been determined by X-ray crystallography, with PDB ID 1M4H. The BACE-1 protein structure is comprised of two domains: an N-terminal domain and a catalytic domain. Ramachandran plots and values of the purified protein structure indicated that 87.8% of residues were in favoured regions and 11.5% residues were present in allowed regions.

ADME Analysis

The ADME properties – Absorption, Distribution, Metabolism and Excretion for potential drug molecules can be predicted with the help of several in silico models. In our study, we used SwissADME (http://www.swissadme.ch/) for performing ADME analysis for the fifteen phytochemical compounds.

The predicted properties such as molecular weight (g/mol), molar volume (cm^3/mol), and molar refractivity were evaluated to justify their drug-likeness behaviour. All compounds justified the standard values according to Lipinski's rule of five. The results are presented in Table 1. The molecular mass of all fifteen phytochemical compounds was found in the range of 80 to 380. All compounds had < 5 hydrogen bond donors, except Riboflavin, which had 5 hydrogen bond donors. All 15 compounds had < 10 hydrogen bond acceptors. The molecular refractivity of all compounds was observed to be between 20 to 100. The MlogP value was in the range of +0.05 to +3.7. Only one compound, Hexadecane had a high value of +6.42, whereas the rest of the compounds had a MlogP value < 5.

Table 1. Drug-likeness analysis

Phytocompounds	Molecular weight	H-bond donors	H-bond acceptors	Molecular Refractivity	MlogP
Apigenin	270.24	3	5	73.99	0.52
3-Methyl-2-butanone	86.13	0	1	26.35	1.01
Quercetin	568.87	2	2	186.76	-0.56
2-Methyl-3-pentanone	100.16	0	1	31.16	1.39
Hexadecane	226.44	0	0	79.03	6.44
Pentyl Butyrate	158.24	0	2	46.66	2.28
Dihydrocapsaicin	307.43	2	3	90.99	2.78

Octanal	128.21	0	1	40.77	2.07
Riboflavin	376.36	5	8	96.99	-0.54
Isobutyl 2-methylbutyrate	158.24	0	2	46.66	2.28
Geranylacetone	194.31	0	1	63.86	3.34
Capsaicin	305.41	2	3	90.52	2.69
Luteolin	318.24	6	8	80.06	-1.08
2-Acetylpyrrole	109.13	1	1	30.99	-0.18
2-Tridecanone	198.34	0	1	64.80	3.54

Pharmacokinetics properties were assessed to confirm the efficacy of candidate molecules. In ADME evaluation, solubility (log mol/L), bioavailability and absorption (% absorbed) predicted values justified the strong therapeutic potential of the phytocompounds. MlogP values were considered for accurate prediction of lipophilicity. Ideally, a MlogP value < 5 is considered good for better compound absorptions, permeation, and distribution. Water solubility was predicted using the Silicos IT LogSw descriptor of SwissADME, which follows the fragmental method as opposed to the topological methods followed by ESOL and Ali methods. In the SwissADME LogSw scale, compounds with values less than -6 are considered to be poorly soluble. In our study, the log S value was predicted in the range of 0 to -4.7, indicating that most compounds are moderately soluble in water. Only Hexadecane had a log S value of -6.33, describing poor solubility in water. The pharmacokinetics study results are presented in Table 2.

The predictions of human gastrointestinal absorption (HIA) were done using the BOILED-Egg Model of SwissADME. The model returns “high” or “low” if the molecule under investigation has a high or low rate of absorption in the GI tract. All compounds, except for Hexadecane and Riboflavin showed “high”. The model returns “yes” or “no” if the molecule has a higher or lower probability of being a substrate of P-gp. From the SwissADME model, we identified that Apigenin, Quercetin, Luteolin and Riboflavin were not BBB permeant which could be a hindrance in their potential drug characteristics. It was also observed that none of the compounds forms a substrate with P-gp, which is another favourable factor for the compounds to behave as potential drug candidates. Based on this analysis, all the compounds passed the acceptable criteria for potential drug properties and were considered for docking with the target protein.

Table 2. Pharmacokinetics assessment

Phytocompounds	**logS**	**GI absorption**	**BBB permeant**	**P-gp Substrate**	**Bioavailability**
Apigenin	-3.94	High	No	No	0.55
3-Methyl-2-butanone	-0.93	High	Yes	No	0.55
Quercetin	-3.16	High	No	No	0.55
2-Methyl-3-pentanone	-1.36	High	Yes	No	0.55
Hexadecane	-6.33	Low	No	No	0.55
Pentyl Butyrate	-2.76	High	Yes	No	0.55
Dihydrocapsaicin	-5.59	High	Yes	No	0.55
Octanal	-2.6	High	Yes	No	0.55
Riboflavin	-2.62	Low	No	No	0.55
Isobutyl 2-methylbutyrate	-2.01	High	Yes	No	0.55
Geranylacetone	-3.18	High	Yes	No	0.55
Capsaicin	-4.87	High	Yes	No	0.55
Luteolin	-0.97	Low	No	No	0.55
2-Acetylpyrrole	-1.88	High	Yes	No	0.55
2-Tridecanone	-4.66	High	Yes	No	0.55

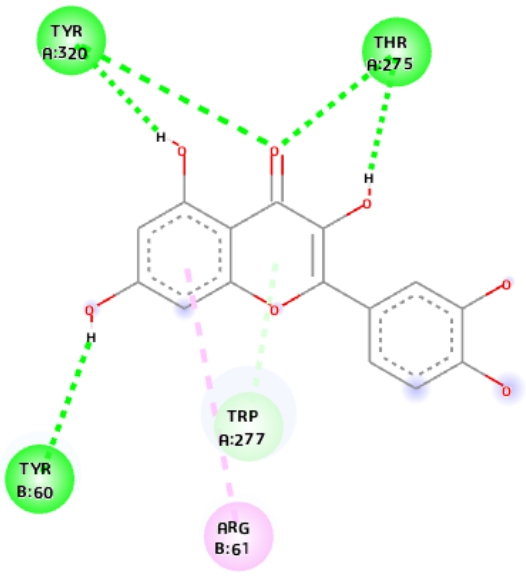
Molecular Docking

All fifteen compounds were docked with BACE-1 crystallized protein structure. The docked complexes were analyzed on the basis of lowest binding energy (kcal/mol). The best pose selection from all the docking complexes was also conducted on the basis of lowest binding energy values. The binding energy values were in the range of -4.2 to -8.7 kcal/mol, which is considered good. Only the ligands which had relatively lower binding energy scores were considered best among the fifteen compounds. The docking results are represented in Table 3.

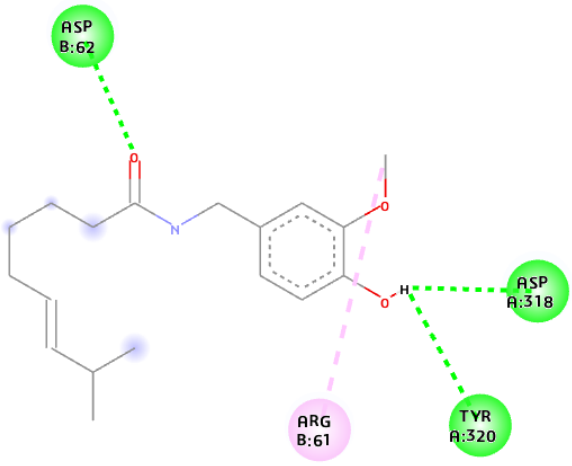
Table 3. Molecular docking with BACE-1

Phytocompounds	Binding Affinity (Kcal/mol)
Apigenin	-8.4
3-Methyl-2-butanone	-4.2
Quercetin	-8.5
2-Methyl-3-pentanone	-4.1
Hexadecane	-4.6
Pentyl Butyrate	-4.6
Dihydrocapsaicin	-7.1
Octanal	-4.6
Riboflavin	-8.4
Isobutyl 2-methylbutyrate	-4.7
Geranylacetone	-6
Capsaicin	-6.4
Luteolin	-8.7
2-Acetylpyrrole	-4.8
2-Tridecanone	-4.9

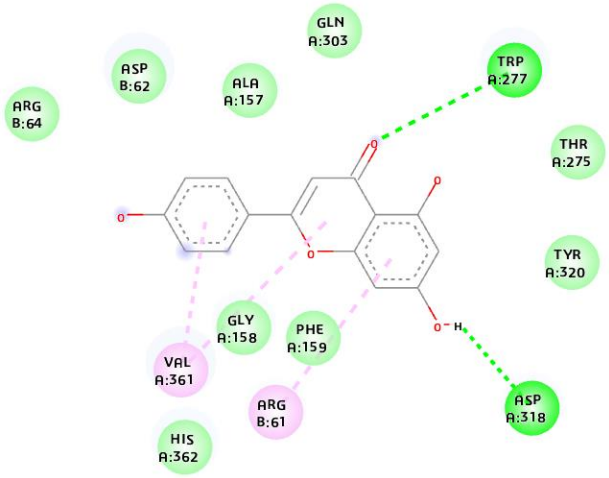
Among the fifteen ligands, the best binding affinity was shown by six compounds. Capsaicin, Dihydrocapsaicin, Apigenin, Riboflavin, Quercetin, and Luteolin had a binding affinity of -6.4, -8.4, -8.4, -8.5, and -8.7 kcal/mol respectively. Luteolin had the highest binding score of -8.7 kcal/mol, this indicates its best possible inhibitory action with BACE-1. These compounds were visualised using BIOVIA Discovery Studio and the 2D interaction diagrams were studied. The interactions can be visualised in Figure 1.



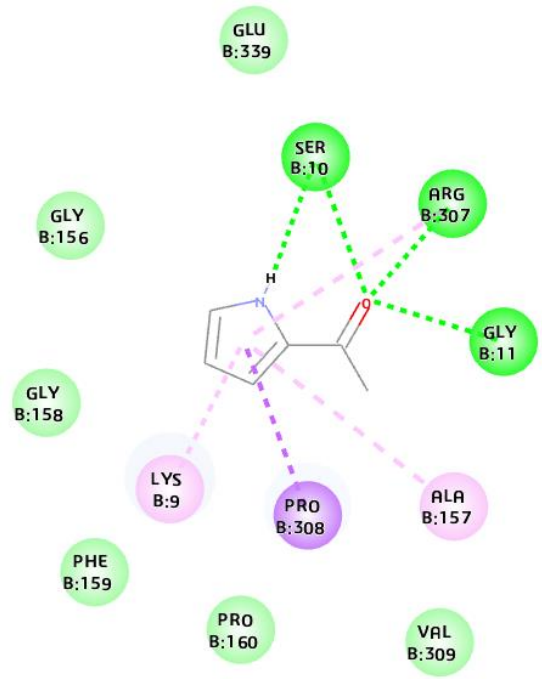
Quercetin



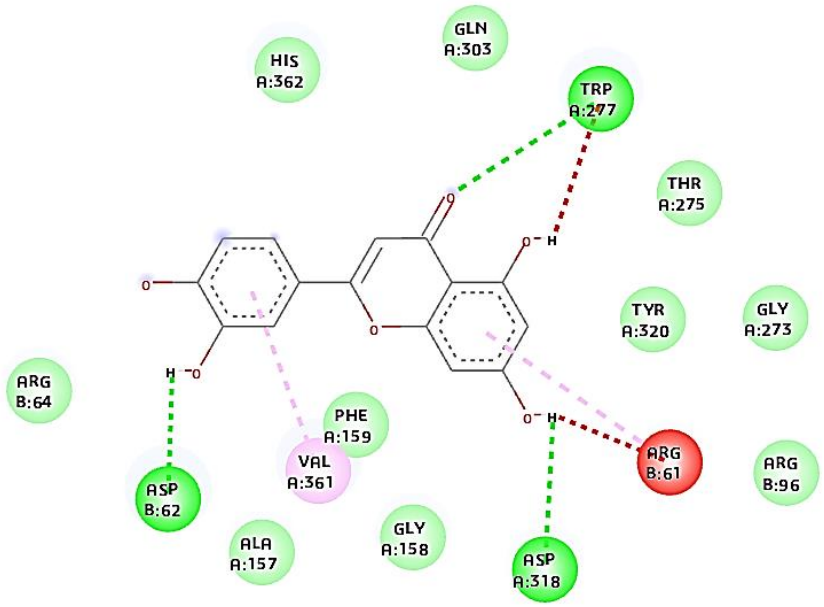
Capsaicin



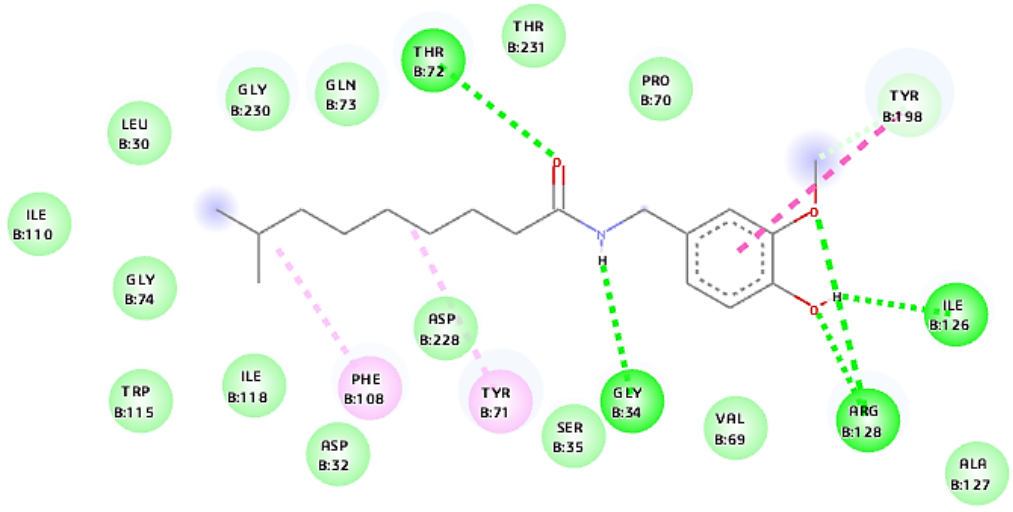
Apigenin



Riboflavin



Luteolin



Dihydrocapsaicin

Figure 1. Protein-ligand interaction visualization in BIOVIA Discovery Studio.

The ligand Quercetin displayed three H-bonding with BACE-1 at Tyr320, Thr75, Tyr60 and one π-alkyl bonding at Arg61. Dihydrocapsaicin showed one π-π T-shaped bonding at Trp277 and three H-bonding (Tyr60, Tyr320, Thr275). Apigenin showed two π-alkyl bonding (Val361 and Arg61) and two H-bonding (Trp277 and Asp318). Riboflavin showed one π-sigma bonding at Pro308, two π-alkyl bonding at Lys9 and Ala159 and three H-bonding at Ser10, Arg307 and Gly11. Capsaicin displayed one alkyl bonding at Tyr60, one π-alkyl bonding at Arg61, six carbon-hydrogen bonding at Asp363, Gln303, Trp277, Gly158, His362, and Thr 275 and two H-bonding. Luteolin showed one unfavourable donor-done bonding at Arg61, one π-alkyl bonding at Val361 and three H-bonding at Asp62, Asp318 and Trp297.

DISCUSSION

Alzheimer's disease is a neurodegenerative disorder that affects the brain, causing a gradual decline in cognitive abilities, memory loss, and changes in behaviour. One protein that plays an important role in the development of Alzheimer's disease is beta-secretase 1 (BACE-1). BACE-1 cleaves the amyloid precursor protein (APP) to form beta-amyloid peptides. Beta-amyloid peptides are the main component

of amyloid plaques that accumulate in the brains of Alzheimer's patients. These plaques are toxic to neurons, leading to their death and the subsequent cognitive decline that characterizes the disease [13].

Studies have shown that BACE-1 levels are increased in the brains of Alzheimer's patients and that reducing BACE-1 activity can prevent the formation of beta-amyloid plaques. Therefore, BACE-1 has become an attractive target for the development of Alzheimer's treatments. Several drugs targeting BACE-1 have been developed, but so far, clinical trials have been disappointing. One reason for this may be that BACE-1 has other important functions in the brain, such as regulating synaptic plasticity, that are disrupted by blocking its activity [14]. Despite these challenges, the role of BACE-1 in the pathogenesis of Alzheimer's disease is clear. Further research is needed to fully understand the complex functions of BACE-1 in the brain and to develop effective therapies that can target this enzyme without causing unwanted side effects.

The present study aimed to identify potential lead compounds from *Capsicum annuum* that can target BACE-1 for Alzheimer's disease therapy. In silico molecular docking was performed to evaluate the binding affinity of fifteen phytochemical compounds with BACE-1, and the ADME properties of these compounds were also analyzed. The crystal structure of BACE-1 used in this study (PDB ID 1M4H) had high-quality refinement and was validated by Ramachandran plots. The results of ADME analysis showed that all fifteen phytochemical compounds were drug-like and had desirable pharmacokinetic properties, including good water solubility and bioavailability. These results suggest that these compounds could be potential candidates for Alzheimer's disease therapy.

The molecular docking results revealed that six phytochemical compounds (Capsaicin, Dihydrocapsaicin, Apigenin, Riboflavin, Quercetin, and Luteolin) had the best binding affinity with BACE-1, with Luteolin showing the highest binding score. This indicates that Luteolin has the best inhibitory action with BACE-1, and could potentially be used as a lead compound for developing Alzheimer's disease therapy. The interaction diagrams of the six compounds showed that they interacted with the active site of BACE-1 through hydrogen bonding and pi-alkyl bonding. The compounds Quercetin and Dihydrocapsaicin formed three and four hydrogen bonds with BACE-1, respectively, indicating their strong binding affinity with the protein.

Our study explores the potential of Capsicum annuum, a commonly used spice, as a source of lead compounds for Alzheimer's disease therapy. The study provides important insights into the molecular mechanism of BACE-1 inhibition by these compounds, which can help in the design and development of more potent inhibitors. The use of molecular docking for the evaluation of binding affinity of these compounds with BACE-1 is also an important contribution, as it provides a cost-effective and efficient way of screening potential drug candidates. From the ADME analysis, a better understanding of the compounds' pharmacokinetic and pharmacodynamic characteristics can be provided. This information can be used to design drugs that have improved bioavailability and efficacy. From the ADME analysis, it was discovered that ligands with the ability to permeate the Blood-Brain Barrier (BBB) are more suitable as drug components [15]. However, in our study, we identified that out of the selected fifteen compounds, ten compounds were BBB permeant. Capsaicin and Dihydrocapsain show high binding energy of -6.4 Kcal/mol and -7.1 Kcal/mol respectively and are both BBB permeants, making them the best-suited molecules to be considered for drug discovery. The study also highlights the importance of in-silico methods in drug discovery and the potential of phytochemical compounds as drug candidates. The study's findings can pave the way for the development of more potent and effective BACE-1 inhibitors for Alzheimer's disease therapy.

Overall, the present study provides valuable insights into the potential lead compounds from Capsicum annuum for developing Alzheimer's disease therapy. The study's findings can pave the way for the development of more potent and effective BACE-1 inhibitors for Alzheimer's disease therapy. These compounds showed good drug-like properties and strong binding affinity with BACE-1, making them promising candidates for further experimental validation. Further studies are needed to explore the efficacy and safety of these compounds in vivo and in clinical trials.

CONCLUSION

Alzheimer's disease (AD) is a complex and multifactorial neurodegenerative disorder, for which there is no definitive cure yet. Current therapeutic options only provide symptomatic relief and do not address the underlying pathology of the disease. Therefore, the search for new treatments and preventive strategies for AD is a major area of research. Phytocompounds derived from plants have emerged as a promising alternative due to their multifaceted neuroprotective properties and low toxicity profiles [16]. The results of the present study highlight the potential of phytocompounds from Capsicum annuum as a source of lead compounds for the development of novel drugs for AD therapy. The six compounds (Capsaicin, Dihydrocapsaicin, Apigenin, Riboflavin, Quercetin, and Luteolin) identified in this study have shown promising inhibitory action on BACE-1, a key enzyme involved in the production of beta-amyloid plaques, a hallmark of AD. These compounds are also reported to behave as anti-oxidants and anti-inflammatory agents, which are potential neuroprotective properties [17–19]. Molecular docking studies have shown strong binding affinities of these compounds with BACE-1, suggesting their potential as inhibitors of beta-amyloid production.

Furthermore, the ADME analysis of these compounds has predicted their drug-like properties, indicating their suitability for further development as therapeutic agents. These phytocompounds have also shown good pharmacokinetic properties, with high gastrointestinal absorption rates, water solubility, and bioavailability.

In conclusion, phytocompounds derived from Capsicum annuum show great potential as novel therapeutic agents for AD, and further studies are warranted to validate their efficacy and safety. The future research direction in this field can focus on optimizing the identified lead compounds through structure-activity relationship (SAR) studies, in vivo pharmacological evaluations, and clinical trials to determine their efficacy in treating and preventing AD. The use of phytocompounds in combination with other therapies and drug delivery systems could also be explored to improve their bioavailability and efficacy.

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