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RESEARCH ARTICLE

Molecular docking study on curcumin and its derivatives as inhibitors of BACE1 in the treatment of Alzheimer's disease

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder, and it is the main cause of dementia in the elderly. At present, no proper cure is available to stop the progression of AD. The neuronal damage in AD is due to the deposition of β-amyloid peptide and tau protein within the brain. Curcumin a curry spice has several beneficial activities such as antioxidant, antimicrobial, anti-inflammatory, and chemotherapeutic properties. **Aims and Objectives:** The main objective was to perform molecular docking of curcumin and its derivatives with BACE1 to determine its binding efficacy and the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the selected curcumin derivatives. **Materials and Methods:** Three-dimensional structure of the BACE1 was retrieved from RCSB database in protein data bank format. Total 200 ligand derivatives of curcumin were generated using the software advanced chemistry development/ChemSketch. The rapid virtual screening of the compounds was performed using the docking tool iGEMDOCK version 2.0. The ligands with low binding energy were selected and were analyzed for the drug-relevant properties. The final docking of the ligands was performed using the software AutoDock 4.0, based on the drug-like properties and the binding affinity. **Results:** Among the four ligands, based on the drug-likeness, the ligand (6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyohenyl) hepta-1,6-diene-3, 5-dione was the best. It had excellent binding energy with good ADMET properties. **Conclusion:** In this study, using the molecular docking method, a new compound has been identified to inhibit BACE1. This compound can be an effective drug candidate for controlling AD.

KEY WORDS: Molecular Docking; Curcumin; Alzheimer's Disease; BACE1

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder affecting the cholinergic neurones, and it is the main cause of dementia in the elderly population. It affects more than 5% of people over 65 years, and this increases to 20% in people over 80 years of age.[1] By 2050, it is predicted that globally 1 in every 85 people will be affected with AD.[2] It is a genetically complex disease which progresses at a slow pace for about 7–10 years leading to a state of complete helplessness. At present, no proper cure is available to stop the progression of AD.

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It is difficult to ascertain the early course of the disease as the patient is an unreliable informant. The early features of the disease include confusion, mood swings, impaired memory, preoccupation with the past events, and general withdrawal. This further leads to deterioration of cognitive function,

progressive impairment of daily living activities and several neuropsychiatric symptoms.[3]

In AD, deposition of abnormal proteins, both inside and outside of the neurons causes neuronal damage. The hallmark pathological lesions of AD are known as the plaques and tangles. Senile plaques are extracellular accumulations of amyloid protein; it consists of insoluble amyloid beta protein (Aβ). Neurofibrillary tangles are intracellular aggregates of the hyperphosphorylated protein tau which interferes with normal axonal transport of the various components that are needed for proper neuronal function and survival; this ultimately causes the neurons to die.[4-6] The β secretase or β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1), is the rate-limiting enzyme which causes the production of the toxic Aβ by cleaving APP. Therefore, inhibitors of BACE1 are being considered as having the potential to lower cerebral Aβ concentrations, which will be useful in treating and preventing AD.[7,8]

For centuries in India, medicinal plants and their ingredients have been used to cure a lot of ailments including those associated with learning and memory.[9] Therefore, plant-derived products can be useful therapeutic options in the treatment of AD.

Curcumin is a hydrophobic polyphenol, which is derived from the rhizome of the *Curcuma longa* herb, it is also known as turmeric. It is the member of the ginger family.[10,11] Traditionally curcumin (Turmeric) is used as a curry spice in various Indian food preparations. At present, the US Food and drug administration has listed turmeric as ''generally recognized as safe'' coloring and flavoring agent in the food.[12,13] Curcuminoid consists of three main compounds of which curcumin is the main curcuminoid, other compounds are demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC). Curcumin has several beneficial activities such as antioxidant, antimicrobial, anti-inflammatory, analgesic, nephroprotective, and chemotherapeutic properties.[14-21]

As amyloid plaques cause oxidative damage to the brains of the AD patients, also generation of free radicals by Aβ, abnormalities in the mitochondria of the cells, inflammation and abnormal changes which affects the natural antioxidant defense are ultimately responsible for the pathophysiology of AD.[22] Thereby, substances which have antioxidant properties like curcumin can be potential therapeutic targets useful in slowing the disease progression. Moreover, in several studies conducted, it was observed that there was a lower incidence of AD and improved cognitive function in the population who consumed curries comprising curcumin on a regular basis as compared to the population who have not.[23,24]

At present the drugs available for treatment of mild to moderate AD patients are cholinergic activators such as rivastigmine, donepezil and galantamine, which produce their effect by inhibiting acetylcholinesterase and thereby increase the availability of acetylcholine in the synapses, to compensate the cholinergic deficit which happens due to the loss of neurones. Memantine, an antagonist of N-methyl-D-aspartate receptors in the brain is useful for moderate to severe AD. However, all these drugs give only temporary relief and are associated with a lot of side effects.[25] Therefore, there is an urgent to need to develop effective and safer alternative drugs for the prevention and treatment of AD.

Molecular docking is a very important tool useful in the structure-based rational drug designing. These programs give a prediction of how a large molecule such as a receptor or enzyme interacts with a smaller molecule ligand such as a drug candidates or inhibitors to form a stable complex. These methods have been useful in the development of several drugs, which later underwent clinical trials.[26]

The main objective of this study was to perform molecular docking of curcumin and its derivatives with BACE1, to determine its binding efficacy and the ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of the selected curcumin derivatives.

MATERIALS AND METHODS

This work was done in the bioinformatics facility of Tagore Medical College and Hospital

Protein Preparation

From the RCSB database, the three-dimensional (3D) structure of the BACE1 was retrieved in protein data bank (PDB) format. (http://rcsb.org/pdb/explore)[27] The PDB code is 3IN3. Figure 1 shows the 3D structure of BACE1, magenta colored are the Alpha helices, Beta sheets are yellow, the turns are blue, and the other residues are white colored.

Active Site Prediction

The binding sites of BACE1 were predicted using 3DLIGANDSITE, a web server.[28]

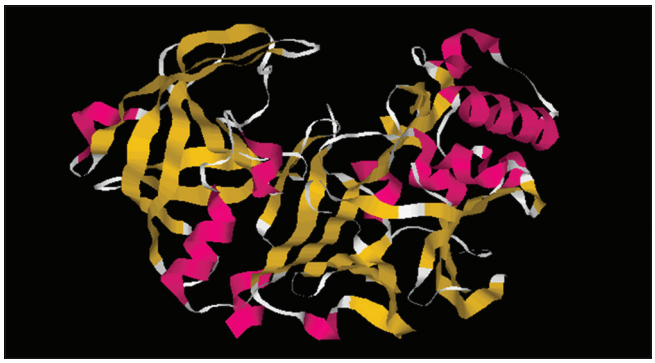

Figure 1: The 3D structure of BACE1(β-site APP cleaving enzyme 1 or β-secretase)

Optimization of Ligand

The structure (Figure 2) and properties of curcumin and its derivatives (ligand) were obtained from PubChem database. Its zinc ID is 20230445, Compound ID is 124072 and the IUPAC name is 1,7-bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-dione. The molecular weight is 372.417 g/mol, and Xlogp value is 2.8.

Total 200 ligand derivatives of curcumin were generated using the software advanced chemistry development (ACD)/ChemSketch.[29] Ligands were then converted from mol 2 format to PDB format using the software OPEN BABEL (www.vcclab.org/lab/babel/start.html).[30]

Rapid Protein-Ligand Docking

The rapid virtual screening of the compounds was performed using the docking tool iGEMDOCK version 2.0.[31] Population size of 150 was set with 70 generation and with one solution for the quick docking. For further study, the ligands with low binding energy were selected based on the "Lipinski's rule of five," the selected ligands were then analyzed for the drug-relevant properties. The ligands were then taken up for further molecular docking study based on the binding affinity and the drug-like properties.

The Final Docking

Docking of the ligands was performed using the software AutoDock 4.0,[32] to obtain its binding energy and the possible conformations and orientations at the binding site. Using the software, the polar hydrogen atoms were then added to BACE1 and merged with its non-polar hydrogen atoms. The rotatability of all the ligand bonds were checked. Lamarckian genetic algorithm method was used for all the calculations of the drug-ligand flexible docking.[33] The docking search was completed after the best conformation with the lowest docked energy was chosen.

RESULTS

Total 200 derivatives of the alkaloid curcumin were generated, and the rough docking was done, of which four derivatives with highest total binding energy (kcal/mol) were selected.

Table 1 summarizes the results of the rapid virtual screening of the compounds done using the iGEMDOCK software. It shows the binding energies of curcumin and the four ligands with BACE1. It is clear from the results that the four ligands have low binding energy, so were taken for further docking studies.

The docking poses of the parent curcumin and its four derivatives are displayed in Figure 3 and 4. The structure and IUPAC names of the four ligands are displayed in Figure 5.

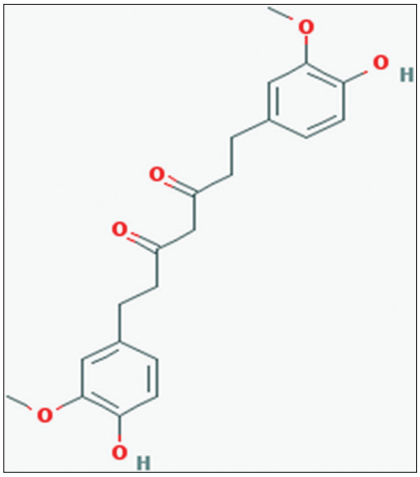

Figure 2: Structure of curcumin

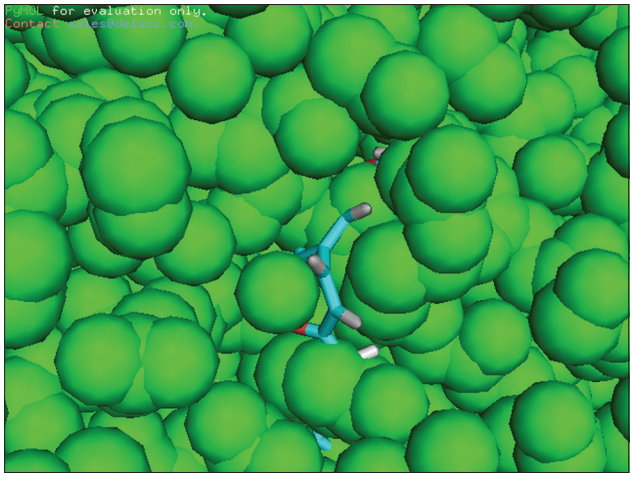

Figure 3: Docked pose of the parent curcumin

DISCUSSION

Total 200 ligands were derived from alkaloid curcumin using ACD/Chemsketch software and converted to PDB format using the format conversion software OPEN BABEL. The results of the rough docking using iGEMDOCK showed that four ligands had low binding energies (Table 1) and hence were taken for further docking studies. Accurate docking for the selected four ligands was done using Autodock 4.0 software (Table 2). Parent curcumin and the four ligands were checked for the drug-relevant properties based on the Lipinski's rule of five. From the Table 3, it is evident that both curcumin and the four ligands satisfy the Lipinski's rule. They were then tested for the ADMET properties, mutagenicity and tumorigenicity using the Swiss ADME tool (Table 4).[34] Using the Data warrior software,[35] the drug-likeness was determined. All possess good drug-likeness.

Due to diverse pathological processes AD is a complex disease, for which at present no effective treatment is available to cure or prevent it.[36] As AD occurs due to increased accumulation of beta-amyloid protein, which is formed by the cleavage of APP, mediated by the enzyme

Table 1: The results of the iGEMDOCK

Ligand	Total binding energy (kcal/mol)	Vander Waals force	H Bond	Electrostatic bond
1,7-bis (4-hydroxy-3-methoxyphenyl) heptane-3,5-dione	−91.4088	−78.6584	−12.7505	0
(6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	−161.637	−121.858	−39.7788	0
(2E)-7-(4-hydroxy-3-methoxyphenyl)-2-[(4-hydroxy-3-methoxyphenyl) methylidene]-3,5-dioxohept-6-enoyl chloride	−159.495	−135.786	−23.7088	0
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenoxy} phosphonous acid	−158.788	−133.055	−25.7325	0
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenyl} phosphonic acid	−157.208	−122.324	−34.8835	0

Table 2: The results of accurate docking using AutoDock showing the binding affinities of curcumin and the four ligands with BACE1

Ligand	Total binding energy (kcal/mol)	Mode	RMSD lower bond	RMSD upper bond
1,7-bis (4-hydroxy-3-methoxyphenyl) heptane-3,5-dione	−7.4	0	0.0	0.0
(6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	−13.0	0	0.0	0.0
(2E)-7-(4-hydroxy-3-methoxyphenyl)-2-[(4-hydroxy-3-methoxyphenyl) methylidene]-3,5-dioxohept-6-enoyl chloride	−14.5	0	0.0	0.0
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenoxy} phosphonous acid	−14.2	0	0.0	0.0
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenyl} phosphonic acid	−13.9	0	0.0	0.0

Table 3: Lipinski's properties of curcumin and the four ligands

Ligand	Molecular weight (g/mol)	xlogp	H Bond donor	H Bond acceptor
1,7-bis (4-hydroxy-3-methoxyphenyl) heptane-3,5-dione	372.417	2.8	2	6
(6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	413.382	4.06	2	8
(2E)-7-(4-hydroxy-3-methoxyphenyl)-2-[(4-hydroxy-3-methoxyphenyl) methylidene]-3,5-dioxohept-6-enoyl chloride	430.84	4.25	2	7
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenoxy} phosphonous acid	448.364	3.93	4	9
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenyl} phosphonic acid	448.364	3.93	4	9

Table 4: ADMET properties of curcumin and the four ligands.

Ligand	Drug-likeness	Mutagenic	Tumorigenic	Irritant
1,7-bis (4-hydroxy-3-methoxyphenyl) heptane-3,5-dione	−4.774	No	No	No
(6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	2.4963	No	No	No
(2E)-7-(4-hydroxy-3-methoxyphenyl)-2-[(4-hydroxy-3-methoxyphenyl) methylidene]-3,5-dioxohept-6-enoyl chloride	−6.803	No	No	No
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenoxy} phosphonous acid	−13.371	No	No	No
{2-hydroxy-5-[(6Z)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-1-yl]-3-methoxyphenyl} phosphonic acid	-10.227	No	No	No

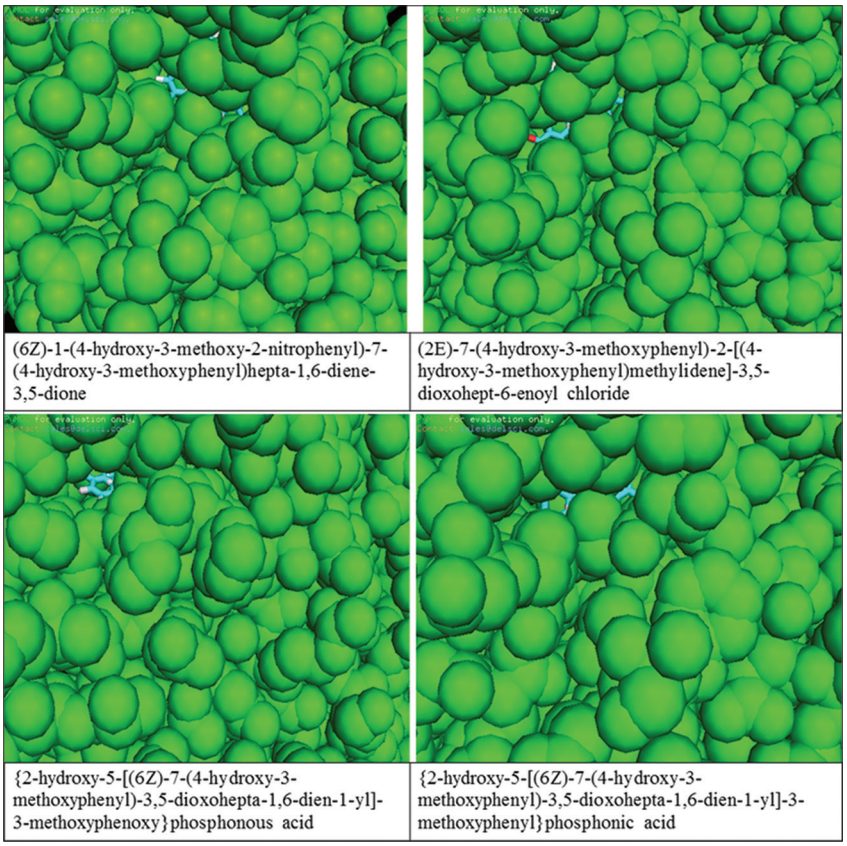

Figure 4: Docking pose of four ligands with BACE1

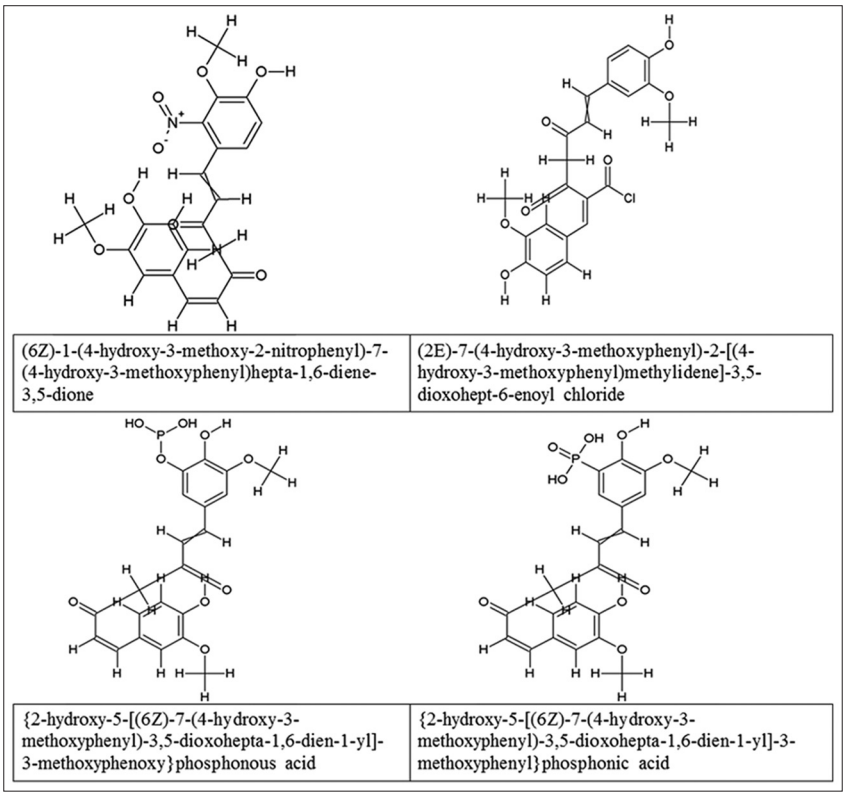

Figure 5: The structure and IUPAC name of the four curcumin derivatives

BACE1.[37] Therefore, inhibitors of BACE1 can be useful in preventing the pathogenesis of AD.[38,39] Hence, BACE1 can be an effective drug target, which will be useful for the development of newer drugs for AD.

In this study among the four ligands, based on the drug-likeness, the ligand (6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyohenyl) hepta-1,6-diene-3, 5-dione was the best. It had excellent binding energy with good ADMET properties. It can be used as an efficient drug in the treatment of AD. The limitations are that the present study is only a virtual throughput screening, further high throughput screening is required followed by studies on cell lines and animal models of the disease for further confirmation as a potential drug.

CONCLUSION

There is an urgent need to explore new therapeutic compounds which will offer safer, efficacious and cost-effective treatment, that will improve the life quality of AD patients. In this study, using the molecular docking method, a new compound (6Z)-1-(4-hydroxy-3-methoxy-2-nitrophenyl)-7-(4-hydroxy-3-methoxyohenyl) hepta-1,6-diene-3, 5-dione has been identified to inhibit BACE1. Therefore, this compound can be an effective drug candidate for controlling AD.

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