International Journal of Biomedical Data Mining

Saddala et al., Int J Biomed Data Min 2016, 5:2
http://dx.doi.org/10.4172/2090-4924.1000120

Research article Open Access

Selenoergothionein as a Potential Inhibitor against Amyloid β-Protein (Aβ): Docking and Molecular Dynamics Studies

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Rec date: Apr 06, 2016; **Acc date:** Apr 30, 2016; **Pub date:** May 07, 2016

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, encircling the deterioration of cognitive functions and behavioral changes, characterized by the aggregation of amyloid β-protein (Aβ) into fibrillar amyloid plaques in elected areas of the brain with the lipid-carrier protein apolipoprotein E (apoE), the microtubule associated protein tau, and the presynaptic protein α-synuclein. High levels of fibrillary Aβ, the main constituent of senile plaques, are deposited in the AD brain that outcome in the thrashing of synapses, neurons and destruction of neuronal role. Aβ is derived from the amyloid precursor protein through sequential protein cleavage by aspartyl protease, β-secretase and presenilin-dependent β-secretase triggering a spill of events such as oxidative damage, neurotoxicity, and inflammation that contributes to the progression of AD. Therefore the Aβ protein may be a target for anti-Alzheimer drugs. Aβ protein was retrieved from the Protein Data Bank and energy minimized and subjected to molecular dynamic simulations using NAMD 2.9 software with CHARMM27 force field in water. The Aβ protein structure was energy minimized by 25,000 steps for 500 ps and pretend 100,000 steps for 2ns. The ergothionein and selenoergothionein, which were found to exhibit amyloid inhibitory effect, were selected and the 3D structure files of those compounds were retrieved from Zinc database. The two compounds were then docked into the active site of Aβ protein with AutoDock Vina in PyRx Virtual Screening tool. The two compounds were showed best binding energies of -9.8, and -7.9 kcal/mol correspondingly. The binding interactions of compounds with active site of Aβ protein model suggested that the amino acid residues (SER8, GLN15, and LYS16) play a key role for drug design. The predicted pharmalogical properties of two compounds, among them selenoergothionein is well within the range of a drug molecule with good ADME profile. Therefore, would be interesting towards progress of persuasive inhibitor against Aβ protein.

Keywords: Aβ protein; MD simulations; Molecular docking; Zinc database; NAMD; VMD

Introduction

Neurodegenerative disorders (NDs) are irregular or ancestral and characterized by the persistent and progressive loss of neuronal subtypes [1] and includes principally Alzheimer's disease (degeneration of basal forebrain cholinergic neurons). NDs possibly will crash a variety of brain functions, such as association (as in Parkinson's disease) or memory and cognition (as in Alzheimer's disease). Neuro-regenerative therapies consist of neuroprotection, nuritogenation and neurorestoration of neuronal subtypes chiefly through traumatic brain and spinal cord injuries. Alzheimer's disease (AD) is a progressive neurodegenerative anarchy, encircling the corrosion of cognitive functions and behavioral changes, characterized by the aggregation of amyloid β-protein (Aβ) into fibrillar amyloid plaques in elected regions of the brain with the lipid-carrier protein apolipoprotein E (apoE), the microtubule coupled protein tau, and the presynaptic protein α-synuclein [2-4]. Elevated levels of fibrillary Aβ, the main constituent of senile plaques, are deposited in the AD brain that outcome in the failure of synapses, neurons and destruction of neuronal role [5]. Aβ is resultant from the amyloid precursor protein from side to side chronological protein cleavage by aspartyl protease, β-secretase and presenilin-dependent β-secretase triggering a tumble of actions such as neurotoxicity, oxidative damage, and inflammation that contributes to the succession of AD. Aβ fibrillization involves the pattern of dimers and petite oligomers followed by enlargement into protofibrils and fibrils by the use of a complex multistep-nucleated polymerization that ultimately forms Aβ plaques or deposits [6]. minor kind of aggregated Aβ, known as Aβ oligomers, also characterize the primary toxic species in AD [7].

Anti-amyloidogenic rehabilitation chiefly involves the lessening of Aβ creation, inhibiting secretase, escalating Aβ consent, or overcrowding Aβ aggregation (with antibodies, peptides, or small organic molecules that selectively join and inhibit Aβ aggregate and fibril formation) via inhibition of the nucleation-dependent polymerization model [7,8]. Consequently, the employ of little molecules and peptides that can persuade the Aβ peptide to fold into an α-helical or random, comprehensive chain structure and the damaging β-sheet structures to appearance inexplicable amyloids (Figure 1) may possibly proffer a hopeful substitute to the pharmacotherapy for AD as inhibitors of Aβ oligomerization [9].

Away from each other from the dose-dependent inhibition of the pattern of Aβ fibrils from Aβ40 and Aβ42 and their extensions, deterioration of preformed Aβ fibrils is also an fascinating beneficial interference [10]. A quantity of tiny molecules have been reported to inhibit Aβ fibrillogenesis or to amend Aβ fibrillization in that way inhibiting Aβ-mediated cellular toxicity ensuing from soluble amyloid oligomers or prefibrillar aggregation intermediates [11,12].

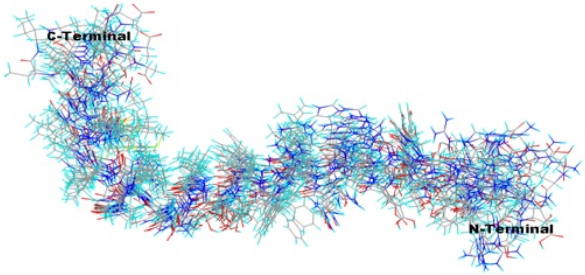

Figure 1: Self-assembly of amyloid β-protein (1IYT).

In this cram, we developed the novel and persuasive inhibitor aligned with amyloid β-protein during computational approaches such as molecular docking, molecular dynamics simulations.

Materials and Methods

Protein preparation and MD simulations

The three dimentional structure of the amyloid β-protein (1IYT) was taken from the PDB (Protein data bank) (http://www.rcsb.org/pdb). The Accession no. of the amyloid β-protein PDB ID is 1IYT. The existing crystallographic water was removed. It was refined by molecular dynamics in a solvated layer and equilibration methods using NAMD 2.9 (Nanoscale Molecular Dynamics) software [13] using CHARMM27 [14] (Chemistry at Harvard Macromolecular Mechanics) force field for protein in water [15]. Protein was energy minimized with 2500 runs for 500ps and simulation with 1000000 steps for 2ns. Spherical periodic boundary conditions were included in this study. Finally, the structure having the least RMSD of Cα trace was generated by employing the molecular dynamics simulations which improve the quality of the target protein. The trajectory investigation was analyzed by depiction the graph between Time in Ps on X-axis and RMSD (Å) on Y-axis as revealed in Figure 2. The excellence structure of Aβ was worn for additional investigation.

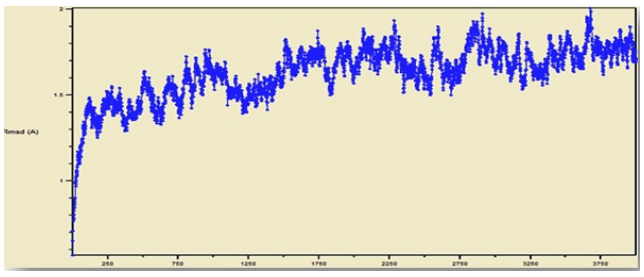

Figure 2: Root mean square deviation (RMSD) during the molecular simulations of 1IYT. Time (Ps) was taken in X-axis and RMSD was taken in Y-axis.

Simulation parameters

The MD simulations method was equilibrated at 260 k for 12 ps with amyloid β-protein atoms firm, followed by 20 ps MD exclusive of restraints. The method was afterward simulated for 110 ps at 310 k through the subsequent parameters. The standard equations of action were included by a leap frog integrator using a time step at 1 fs. The desire based ver let-I/r-RESPA technique was worn execute various time stepping: 4 fs long-range electrostatic: 2fs for small range non-bonded forces, and 1 fs for bonded force. The swift mission was worn to cutoff the Lennard-Jones possible, with the first cut off at 10 Å and the second cutoff at 12 Å. Short range relations were considered at intervals of 4 fs. Every one bonds concerning hydrogen atoms were controlled to their equilibrium bond parameters by the SHAKE beside them. Langevin dynamics was engaged to sustain the pressure at 1 atm, with a Langevin pisten phase of 100 fs and fluctuation decay time of 50fs. Trajectories were recorded each 200 fs. Consequently the dynamics performance and structural changes of the protein was analyzed by the computation of energy and the RMSD (root mean square deviation). The developed protein is publicized in Figure 3.

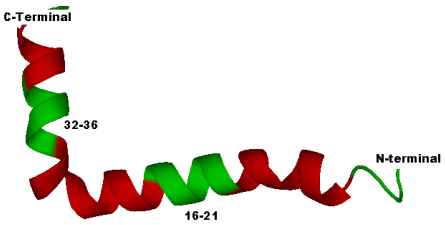

Figure 3: 3D structure of 1IYT. The amyloidogenic district (16-21 and 32-36) is decorated in green colour.

Ligand Preparation

The polyphenolic compounds such as ergothionein and selenoergothionein, which were found to exhibit amyloid inhibitory effect, were selected and the 3D structure files of those compounds were retrieved from Zinc database [16], it contains more than 4.6 million compounds in prepared to dock and offer 3D formats at the URL http://ZINC.dock.org. The structures of the compounds are mentioned below in Figure 4.

Figure 4: The prepared compounds shown in sticks model.

Protein- Ligand docking Analysis

Docking is a computational process which analysis the favored direction of one particle to a next when bound to each other to shape a constant complex. Docking has been broadly worn to propose the binding modes of protein inhibitors. The majority docking algorithms are capable to spawn a great amount of potential structures, as a result they also need a means to score every structure to recognize those that of most importance. Docking was performed by AutoDock Vina [17].

The ready compounds were docked into the active site of the refined of amyloid β-protein (1IYT). Lamarkian genetic algorithm was used as a number of individual population (150), max number of generation (27000), max number of energy evaluation (25000000), Gene mutation rate (0.02), Cauchy beta (1.0), crossover rate (0.8) and GA window size (10.0).The grid was set whole amyloid β-protein due to the multi-binding pocket at X=3.42, Y=-56.23, Z=98.32 and dimension (Å) at X=89.92, Y=98.56, Z=98.32 and exhaustiveness 8. The pose for a given compound recognized on the center of top binding energy. Only ligand flexibility was taken into relation and the proteins were measured to be firm bodies. The ensuing complexes were clustered according to their root mean square deviation (RMSD) principles and binding energies, which were considered with the AutoDock scoring utility. Additional categorization by MD simulations was conducted by complexes that were chosen according to their binding energies and the contacts through with the neighboring residues. The PyMol viewer (http://www.pymol.org/) was engaged to evaluate the docked structures.

Results and Discussion

The target protein (1IYT) was in use from the protein data bank (PDB), and afterward the water molecules were detached and minimized and subjected to molecular dynamics simulation by NAMD tool. The refined protein was used for further docking of prepared compounds. The two compounds such as Ergothionein and Selenothionein were used for further molecular docking studies.

The ready compounds were in use and docked into target protein (Aβ) active site with AutoDock Vina in PyRx Virtual Screening tool by which both the compounds were embedded within the active site of the amyloid β-protein. The selenothionein compound was found, to require lower energy as compared to the ergothionein. The two compounds such as selenothionein and ergothionein have -10.8 kcal/mol and -7.9 kcal/mol energies respectively.

The molecular docking studies were obtained the best compounds based on binding affinity. The compound selenoergothionein was bound with the binding affinity -9.7 kcal/mol by the three hydrogen bond interactions with SER8, GLN15, and LYS16 residues of Aβ protein. The compound ergothionein was bound with the binding affinity -7.9kcal/mol by the formation of two hydrogen bond interactions with GLN15 and LYS16 residues within the active site of Aβ protein (Figure 5). The protein and ligand interactions, binding affinity values, and hydrogen bond lengths are represented in Table 1.

The lead compounds fulfilled the Lipinski's rule of five with zero violations and also the octanol/water partition coefficient (miLogp), a helpful parameter for predicting the drug transport properties like bioavailability, absorption, permeability and penetration. In addition to topological molecular polar surface area (TPSA), a number of atoms, their molecular weight (MW), a number of H donors and number of H acceptors. A topological parameter is a number of rotatable bonds and it describes the molecular litheness of these compounds represented in Table 2.

S.No.	Compound	Interactions Protein----Ligand	Binding energies (Kcal/mol)	H-bond length (Å)	H-bond angle	No. of H-bonds
1.	Selenoergothionein	SER_8CO------N_3H_6 $GLN_{15}HN$----C_7O_9 $LYS_{16}HN$----C_7O_9	-10.8	3.21 3.09 2.99	101.69 173.41 108.05	3
2.	Ergothionein	$GLN_{15}HN$-------C_7O_9 $LYS_{16}HN$-------C_7O_9	-7.9	3.11 2.99	174.78 107.03	2

Table 1: Amyloid (1IYT) and ligand interactions, binding energies, H-bond length, H-bond angle and No. of H-bonds.

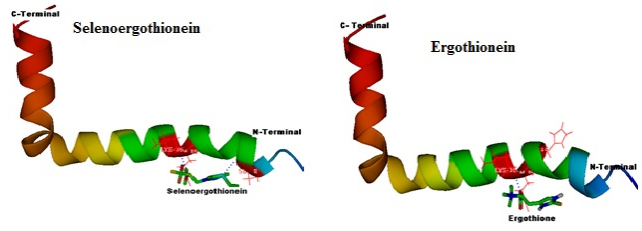

Figure 5: Docking complex of amyloid β-protein (1IYT) with selective inhibitors.

Our analysis exposed that the elected compounds have exhibited considerable binding affinity with in the active site of Aβ protein, when compared to query compound ergothionein. Based upon this study, it is concluded that selenoergothionein compounds may be used as leads for developing effective anti-Alzheimer drugs.

Name	Selenoergothionein	Ergothionein
miLogP	-5.14	-5.41
TPSA	68.81	71.71
NATOMS	15	15
MW	275.19	229.31
NON	5	5

Nohnh	1	2
N violation	0	0
N rotb	4	4
Volume	209.35	205.67

Table 2: Docked compounds of ADME properties by using Molinspiration server.

Conclusions

In the present work, we have selected for potent anti Aβ inhibitors through molecular docking studies and MD simulation studies. The newly identified Aβ protein is an important target in a drug design part therapeutic intervention of Alzheimer disease. Inhibition of Aβ protein could result in reducing plaque formation. Among docked compounds selenoergothionein have the highest binding affinity and obey the drug properties compared to ergothionein. Therefore, the selenoergothionein compound is hopeful drug molecule like ergothionein against Alzheimer disease.

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