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Original Article

PREDICTION OF ANTI-ALZHEIMER'S ACTIVITY OF FLAVONOIDS TARGETING CD33 THROUGH IN-SILICO APPROACH

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ABSTRACT

Objective: Alzheimer's disease (AD) is a progressive, fatal brain disorder that would be putting a growing strain on health and social care systems. Present anti-AD agents are limited in their application due to their adverse effects, toxicity, and limited targets in AD pathology. As a result, it is important to develop an AD-fighting compound. Some flavonoids (such as kaempferol, myricetin, quercetin, and syringetin) have been shown to be effective in the treatment of Alzheimer's disease.

Methods: We chose 284 flavonoids from the NPACT database for molecular docking studies in order to examine their binding interactions with the Alzheimer target protein CD33.

Results: These compounds exhibited significant docking interactions with a variety of targets implicated in the pathogenesis of AD. We chose the top three compounds (Rutin, Morin, and,4,4'-Trihydroxydihydrochalcone) based on the scoring parameter.

Conclusion: These compounds exhibited favorable pharmacokinetic properties, indicating that they could be attractive drug candidates for the treatment of Alzheimer's disease.

Keywords: Alzheimer's disease, CD33, Flavonoids, Molecular docking

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative brain condition characterized by neurological symptoms such as diminished cognition and memory, communication, behavior, and personality, as well as depression, anxiety, and dementia [1]. As per one study, there were 36 million million people with dementia worldwide in 2010, and the number is expected to double every 20 y, eventually reaching more than 115 million people with AD in 2050 [2]. AD is a complex multifactorial neurodegenerative disorder that is characterized by the development of amyloid amyloid-peptide (Aβ), extracellular plaque, within the brain parenchyma [3]. New evidence suggests that impaired Aβ clearance, rather than its overproduction, is the central pathogenic event in AD, as Aβ clearance rates decline in AD patients but remain unchanged in healthy controls [4]. Latest genome-wide analyses (GWASs) reported a cluster of differentiation 33 (CD33) as a significant genetic locus associated with late-on*set al.* zheimer's disease (LOAD) in white populations [5], and these results have been providing accurate information in other ethnic groups [6]. CD33 is a type I transmembrane protein in the sialic acid-binding family of immunoglobulin-like lectins (Siglecs) designed to mediate the interaction between cells and cells and to inhibition normal immune cells function [7]. CD33 in the brain is expressed primarily in microglial cells, and strong evidence suggests that CD33 enables Aβ pathology in AD by affecting Aβ-mediated microglia clearance [8]. In the brain, concentrations of CD33 protein in AD patients were increased, revealing the rise in the number of CD33 immunoreactive microglial cells [9]. With regard to transcription level, it was shown that CD33 mRNA was significantly increased in AD, which suggested that CD33 transcription in microglial cells could be improved [9]. The results indicated that CD33 levels may be associated with the etiology and pathogenesis of AD. Flavonoids are one of the researchers' largest nutrient families, with more than 5,000 members already recognized. Recently, long-term flavonoid consumption has been associated with tentative evidence that certain chronic neurodegenerative diseases can be delayed, including age-related dementia. This may usually be traced to the flavonoid's ability to contrast certain common features characterizing the pathogenesis of AD and other neurodegenerative conditions, such as oxidative stress, and/or its activity on some molecular mechanisms on the basis that these diseases are pathogenesized [10]. Therefore, molecular docking studies have been used to identify the activity of many flavonoids against AD target protein CD33.

MATERIALS AND METHODS

Protein preparation

The crystal structure of CD33 was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb). Following the screening procedure, the target protein (PDB Code: 5IHB) was selected and prepared for molecular docking simulations in such a way that all heteroatoms (i.e. non-receptor atoms such as water, ions, etc.) were removed.

Ligand preparation

The 284 flavonoids compounds from NPACT database were downloaded in SDF format and translated to PDB format using the Online Smile Translator. According to the technique, energy minimization of ligands was indeed accomplished using ChemBio 3D Ultra 12.0.

Molecular docking

Molecular docking analysis has been performed using the Autodock module available in PyRx Version 0.8 [11, 12]. Blind docking has been executed to study insights into the molecular interaction between ligand and the target receptor protein. Blind docking was performed against the CD33 (PDB ID: 5IHB) protein data bank structure with selected flavonoids compounds. The size of the docking grid has been expanded to fit the entire protein within the

grid with dimensions. Genetic Algorithm (GA) has been used for screening of the highest suitable blind docking conformers. Through molecular docking, maximum conformers have been considered for each compound to predict the best conformers in genetic algorithms. For each best one compound was selected for further interaction analysis

RESULTS AND DISCUSSION

We used PyRx to perform molecular docking between flavonoid compounds and the CD33 target. Allowing the ligand to interact with the particular target is the fundamental step in the ligand-based drug design (LBDD) process. Docking is a process that utilizes an algorithm to determine the molecular interactions (intermolecular interactions) between the ligand and the target. By looking for suitable conformations of the protein, the ligand molecule interacts with the target at a particular binding site. The pattern of interaction between the amino acid residues of the target protein and the ligand molecule determines the ligand-target binding. Molecular docking provides a quantitative prediction of the binding energetics and also ranks (scores) docked compounds according to their binding affinity for the ligand-target complex. The binding energetics are primarily determined by the formation of hydrogen bonds between amino acid residues and the ligand molecule. The results of the docking study indicated that the best three compounds complexes were chosen based on the scoring parameter and hydrogen bond interaction. Rutin, Morin, and 2,4,4'-Trihydroxydihydrochalcone docking scores and interaction fig. have been seen in fig. 1 and table 1.

Table 1: Molecular docking results of CD33 with selected flavonoids

S. No.	Compound name	Score	H-bond interaction	Distance Å
1	Rutin.1	-10.322	LYS-77	2.2
			GLY-88	2.8
2	Morin.1	-6.801	GLY-69	2.2
			ASP-70	2.1
			GLN-80	2.7
			SER-128	2.4
			LYS-130	2.8
3	2,4,4'-Trihydroxydihydrochalcone.1	-5.482	GLY-88	1.6

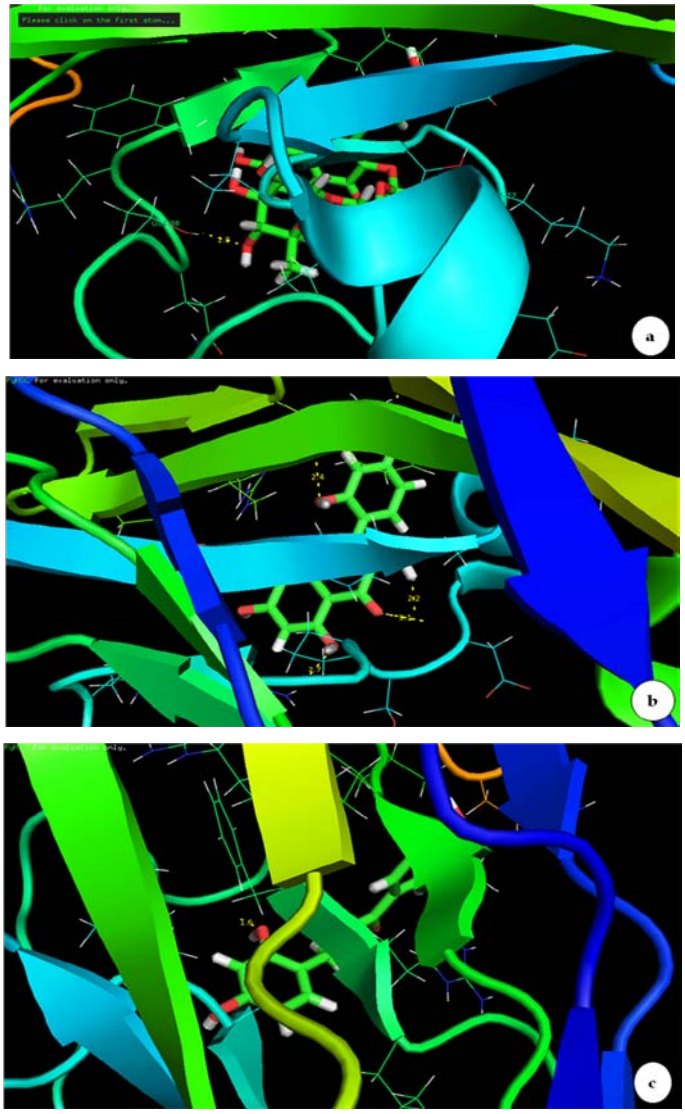

Fig. 1: Molecular interaction of CD33 with a) Rutin b) Morin c) 2,4,4'-Trihydroxydihydrochalcone

When the selected flavonoids docked with the active site of the CD33 proteins, they used a versatile ligand docking technique. All docked flavonoids developed H-bonding interactions with CD33 protein amino acid residues LYS-77, GLY-88, GLY-69, ASP-70, GLN-80, SER-128 and LYS-130. This demonstrated that flavonoids often interact with amino acid binding sites and therefore these residues have become important for flavonoid inhibitors' selectivity. Compared to the other two compounds Morin formed the five hydrogen interactions with CD33 target protein. The distance of the hydrogen bond interaction occurs within 3Å means that compounds formed the very strong interaction with target protein. In the present study, the hydrogen bond distance of selected the three flavonoids (Rutin, Morin, and 2,4,4'-Trihydroxydihydrochalcone) occurs within 3A◦. Therefore, it was confirmed that selected flavonoids bound with CD33 very strongly. Hence, these compounds may acts as lead compounds to identify a drug for Alzheimer's.

CONCLUSION

The field of molecular docking has developed over the last three decades to aid in the design of structurally dependent drugs. Automated docking is commonly used to predict biomolecular complexes, to conduct structural and functional analyses, and to help in drug design. It has evolved into a critical component of drug discovery and development, as it is used to accurately predict protein-ligand complexes. To identify robust and efficient AD medications, various phytocompounds were compared using PyRx. The target ligands were imbedded into the CD33 receptor's catalytic site and the protein-ligand interactions were analyzed. Rutin, Morin, and 2,4,4'-Trihydroxydihydrochalcone molecules demonstrated superior results due to their high hydrogen bond count. Thus, molecular docking detected a large number of additional promising, efficacious, and selective new drugs in the form of flavonoids against Alzheimer's disease, thereby shortening the drug discovery process. Appropriate *in vitro* studies, such as ADMET research, that demonstrate drug absorption, delivery, metabolism, and excretion within a living organism may also be considered further as a lead in the drug discovery phase.

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Nil

AUTHORS CONTRIBUTIONS

Ms. Akila and Ms. Malar Vizhi did the experimental work and Dr. Vijayalakshmi and Ms. Clara Mary assisted in manuscript writing. Dr. Rajalakshmi did the research guidance and critical revision of the manuscript.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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