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NEUROPROTECTIVE EFFECT OF CINNAMON ACTIVE COMPOUNDS VIA ACTIVATION OF SIRT1: A MOLECULAR DOCKING APPROACH

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ABSTRACT

Background: Neurodegenerative diseases are the main cause of morbidity and disability in the elderly. SIRT1 activation has been gaining popularity as novel treatment target. Cinnamon is known to possess neuroprotective abilities, however the mechanism in which it protects the brain is still limited.
Objective: This research aimed to determine the interaction between several cinnamon active compounds with SIRT1
Methods: We used *in-silico* method to determine the molecular interactions between cinnamon main compounds as the ligands to target protein SIRT1. SIRT1 3D structure was retrieved from the Protein Data Bank and 4 ligands (Cinnamaldehyde, Caffeic Acid, Epicatechin, and Trigonelline) structures were obtained from PubChem web server, and we used Resveratrol as positive control ligand. SwissADME, Pyrx, Pymol, and Biovia Discovery Studio software were utilized in this research
Results: All four ligands fulfilled Lipinski Rule of 5 criteria therefore they are suitable for oral administration. It was discovered in this study that epicathecin had higher binding affinity than the control ligand Resveratrol and interacted with SIRT1 in the similar amino acid residue as Resveratrol did. The binding pocket interaction between all ligands and SIRT1 are the same.
Conclusion: Epicathecin, as one of the main cinnamon compounds, may possess neuroprotective properties by interacting with SIRT1. We pproposed that further research be implemented to investigate epicathecin biological effects on SIRT1 in vitro or in vivo.

Keywords: Cinnamon, SIRT1, molecular docking, in silico

Introduction

Neurodegenerative diseases are the main cause of morbidity, disability, decreasing quality of life, and cognitive impairment in elderly.[1] Despite different neurodegenerative disorders have specific clinical presentations and underlying pathophysiology, they often share common features including neuronal loss or shrinkage in certain brain areas and the presence of misfolded proteins or specific inclusion bodies.[2,3] However, the exact molecular mechanism involved in the neurodegenerative process is not completely understood.

Aging is a major risk factor of neurodegenerative disease processes that was previously thought to be non-modifiable until the discovery of sirtuins.[4,5] Sirtuins are clusters of NAD+-dependent histone deacetylases which are highly conserved and widely expressed in living organisms, from bacteria to *Homo sapiens* [6] Among seven human homologs of sirtuin (SIRT1 to SIRT7), SIRT1 is the most considerably studied sirtuin in mammalian.[7] There are increasing evidence that SIRT1 plays an important roles in delaying aging process by regulating various metabolic and signaling pathways involved in stress response, neuroinflammation neuroapoptosis, and neuroprotection.[6,8,9] These findings encourage the search for novel and effective therapeutic agent based on SIRT1 activation.

Medicinal potency of natural products as alternative therapeutic agent for various diseases has been extensively investigated. Cinnamon contains various bioactive compounds, including cinnamaldehyde, cinnamyl aldehyde, cinnamic acid, tannin, epicathecin, and proanthocyanidin, which demonstrated promising potency as antioxidant, antiapoptosis, and neuroprotectant.[10–13] Despite several preclinical research demonstrating cinnamon's neuroprotective properties, the underlying mechanisms in which cinnamon protects the brain from degeneration remain elusive.

Recently, *in silico* method is becoming a popular screening method to assess the viability and feasibility of a compound

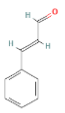
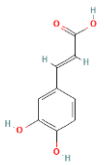
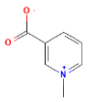
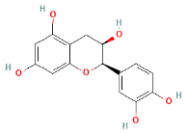
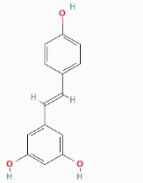
as a drug candidate.[14] In silico study may simulate the interaction, binding energy, and binding sites that occur between ligands and target protein. In this study we determined the interaction of four ligands, which are the most abundant components of cinnamon extract, to SIRT1. The goal of this research is to provide additional potential mechanism regarding neuroprotective effect of cinnamon and to see if one or more of these ligands could be used in future studies to develop new treatment options for neurodegenerative diseases.

Methods

Study Design

This study used in silico approach to investigate the potential interaction of cinnamon main compounds with target protein SIRT1. Several cinnamon compounds chosen as ligands were based on previous studies.[10,15] Their interaction was compared to control ligand, that is Resveratrol.[7] The ligands used were acquired from Pubchem website (https://pubchem.ncbi.nlm.nih.gov/) (Table 1) and SIRT1 3D structure was acquired from Protein Data Bank (https://www.rcsb.org/) with protein code (4ZZI)[16] in .pdb format.

Table 1. Ligands with Their Molecular and Structural Formula

Compound Name (PubChem CID)	Molecular Formula	Structural Formula
Cinnamaldehyde (637511)	C_9H_8O	
Caffeic Acid (689043)	$C_9H_8O_4$	
Trigonelline (5570)	$C_7H_7NO_2$	
Epicatechin (72276)	$C_{15}H_{14}O_6$	
Resveratrol (445154)	$C_{14}H_{12}O_3$	

Compounds and Protein Preparation

Protein stabilization was performed by removing water molecules and adding hydrogen atoms in PyMol software 2.5. Residues in the target protein may affect the interaction between the protein and the ligand, therefore it must be separated from the structure before simulating the molecular interactions.[17]

Pharmacokinetic Analysis

The active compounds identified from the database were pharmacokinetically assessed using the Lipinski Rules of Five by entering the SMILEs obtained from Pubchem into the SwissADME website.[18]

Molecular Docking and Interaction Visualization

Ligand compounds' energy was minimized in order to achieve optimum binding strength. Chosen ligands were then docked specifically with SIRT1using PyRx 0.9.5 software on a grid box dimension 60 × 60 × 60 Å points and grid center at the following coordinate −0.827; 45.618; −1.076 (x, y, z). Ligand and target protein complexes were then visualized and analyzed for their specific amino acid residue interaction using Biovia Discovery Studio 2021 software. The software application has also been used to predict the interaction of ligands with specific amino acids in the active site of proteins. The ligand with the greatest binding affinity was found to have the most negative binding energy.[19]

Results

Pharmacokinetic Analysis

SwissADME was used to analyze pharmacokinetic profiles of selected compounds. The oral regiment's absorption capacity and permeability are assessed using Lipinski's 'Rule of Five' criterion. If the compounds meet the 'Rule of Five,' which is defined as molecular mass ≤ 500 g/mol, LogP value ≤ 5, hydrogen bond acceptor number ≤10, and hydrogen bond donor number ≤5, the drugs are considered outstanding in terms of absorption ability and permeability therefore suitable to oral route delivery.[20] Our findings as shown in Table 2 indicated that all four chosen ligands as well as control ligands have met Lipinski criteria without any violation.

Molecular Docking Result of Cinnamon Compounds

Protein target SIRT1 was docked three times with its control ligand and chosen compound ligands for accuracy, and then the average binding affinity was calculated and compared. Negative binding affinity value indicates how likely the ligand will form complex with the target protein.[21] The average binding affinity of 4 chosen cinnamon compounds were ranging from -6.0 to -9.2 kcal/mol (Table 3). The binding affinity score was as follow: trigonelline (-6.0 kcal/mol), cinnamaldehyde (-6.4 kcal/mol), caffeic acid (-7.1 kcal/mol), and epicatechin (-9.2 kcal/mol) compared to the control ligand resveratrol (-8.2 kcal/mol). Epicatechin was shown to be the only compound that has higher binding affinity than control ligand Resveratrol.

We simulated and visualized the binding of chosen ligands to active sites of target protein SIRT1 using Biovia Discovery Studio software (Figure 1). The same binding pocket were found in trigonelline epicatechin, cinnamaldehyde, caffeic acid, and control ligand resveratrol interaction with SIRT1.

Table 2. Pharmacokinetics Profiles of Chosen Ligands

Compound	Mol. Weight (g/mol)	H Bond Donor	H Bond Acceptor	Log P	Fulfill Lipinski Criteria
Resveratrol	228.24	3	3	2.48	Yes
Cinnamal-dehyde	132.16	0	1	1.899	Yes
Caffeic Acid	180.16	3	4	1.196	Yes
Epicatechin	290.27	5	6	1.546	Yes
Trigonelline	137.14	0	2	-0.330	Yes

Table 3. Molecular Docking Result of Cinnamon Compound Ligands Compared to Resveratrol (Control) Ligand

Compound	Binding Affinity (Kcal/mol)	Interaction with Amino Acid	
		Hydrophobic Bond	Hydrogen Bond
Resveratrol	-8.2	ILE347, **PHE273, ALA262**, HIS363, VAL445	**ILE347**
Epicatechin	-9.2	**ALA262, PHE273,** HIS363, PHE297	ASN346, ARG274, VAL421
Caffeic Acid	-7.1	**ALA262, PHE273**	**ILE347**, ASP348, ASP 272
Cinnamaldehyde	-6.4	**ALA262, PHE273**	ASP348, **ILE347**
Trigonelline	-6.0	**PHE273, ALA262**	ASP348, **ILE347**, GLN345

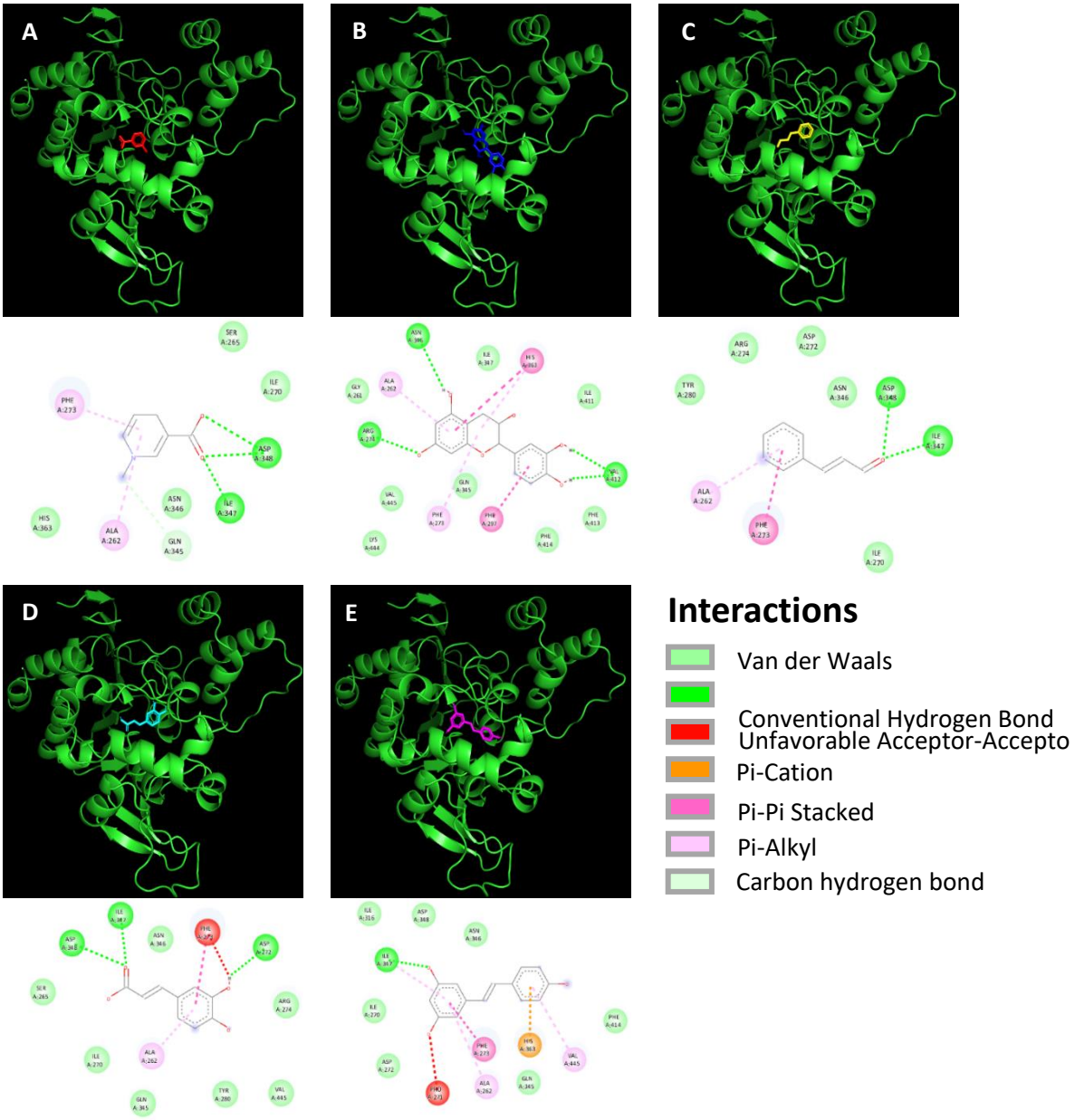


Figure 1 Interaction Visualization and Active Site Residues Between Ligands and SIRT1: (A) Trigonelline (B) Epicatechin (C) Cinnamaldehyde (D) Caffeic acid (E) Resveratrol (Control)

Resveratrol forms hydrogen bond interaction with SIRT1 at ILE347 as well as hydrophobic interactions at PHE273, ALA262, HIS363, and VAL445 amino acid residue (Figure 1E). All four chosen ligands were shown to form similar hydrophobic interactions with SIRT1 as Resveratrol did, namely at similar amino acid residues ALA262 and PHE273 (Figure 1A-D).

Discussion

Pharmacokinetics is the study of how drugs are used to interact with the body based on four aspects: absorption, distribution, metabolism, and excretion (ADME). Once the drug distribution is finished, it reaches the target site and binds to particular target, usually a protein and then causes alteration and modification of certain cellular action/pathway. This process is called pharmacodynamics.[22] ADME is a crucial study that determines how medications will be delivered to the target sites thus provide the best therapeutic impact. Compounds pharmacokinetic profiles can be predicted by analyzing their physicochemical characteristics. Many criteria were created and performed in the early stages of drug development stages, one of the which is Lipinski's Five law/ Rule of Five (RO5). RO5 suggested that a compound is said to have good GI absorption, high oral bioavailability, and membrane permeability.[23] The RO5 violation may results in poor absorption of the compounds, however it does not mean that molecules which do not obey RO5 can't be a drug. In our study, all the selected ligands met the Lipinski's rule.

In general, recognizing suitable compounds for drug development in silico is based on three criteria: binding affinity, molecular linkage connections, and therapeutic characteristics.[19] Ideal compounds are more likely to have negative binding affinity, strong hydrogen and hydrophobic bond interactions, and high ADME characteristics.[24] Present study found that only epicathecin (-9.2 kcal/mol) had higher binding affinity than the control ligand Resveratrol (-8.2 kcal/mol) which means that epicathecin can form stronger bonding to SIRT1 than resveratrol. Binding affinity of –6 kcal/mol is generally accepted as a cut-off in ligand-binding studies.[17] Thus, the other three ligands (trigonelline, cinnamaldehyde, and caffeic acid) can also be said to possess some SIRT1 activator effects, despite their binding affinity were not as strong as epicatechin and control ligand resveratrol. Epicathecin also interacted with SIRT1 in the similar amino acid active sites as Resveratrol did, namely ALA262 and PHE273. The binding pocket interaction between all ligands and SIRT1 are also the same as Resveratrol and SIRT1 which further support the assumption that the ligands have similar effect toward SIRT1. Our findings are supported by previous study using animal models that reported trans-cinnamaldehyde administration cause an increase in SIRT1 expression.[25] However, a randomized clinical trial of cinnamon supplementation failed to show beneficial effect.[26] These conflicting result intrigued further studies of cinnamon compounds neuroprotective effect especially as SIRT1 activator.

Conclusion

Based on the molecular docking result, it is illustrated that epicathecin may possess neuroprotective properties by interacting with SIRT1. We suggested that further research be conducted to investigate epicathecin biological effects on SIRT1 *in vitro* or *in vivo.*

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