JURNAL RISET KEFARMASIAN INDONESIA
Ilmu Kefarmasian & Ilmu Kesehatan

Vol.8 Issue.2 (May 2026)
page 168-181
https://doi.org/10.33759/jrki.v8i2.953
e-ISSN: 2655-8289

Original Article

In Silico Evaluation of Ciplukan (*Physalis angulata* Linn.) Compounds as Potential Serotonin Reuptake Inhibitors for Antidepressant Development

Evaluasi In Silico Senyawa Ciplukan (*Physalis angulata* Linn.) Sebagai Inhibitor Reuptake Serotonin yang Potensial untuk Pengembangan Antidepresan

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Submitted : 2026-02-24
Revised : 2026-05-19
Accepted : 2026-05-30

Keywords: Depression, Antidepressant, Molecular docking, Psychotrine, Catechin, Eriodictyol

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Abstract

Depression is one of the psychiatric disorders that has become a global challenge. Patients with depressive disorders experience changes in serotonergic and noradrenergic functions in the central nervous system. Modulation of serotonin reuptake can be an effective approach in the development of antidepressant agents. Ciplukan (*Physalis angulata* Linn.) has anti-inflammatory and antioxidant properties, offering potential as a natural candidate for antidepressant development through serotonin reuptake inhibitors that can increase synaptic serotonin availability by inhibiting serotonin reuptake through hSERT. The aim of this research is to test the serotonin reuptake inhibitory activity in silico by molecular docking method to investigate the molecular interaction between active compounds in ciplukan extract with serotonin transporter. In this research, the software used is molegro virtual docker with human serotonin transporter (hSERT) target protein. The test ligands used are compounds of the alkaloid, glycoside, phenolic acid, and flavonoid groups. The comparison ligands used are SSRI drugs such as paroxetine, fluoxetine, escitalopram, and fluvoxamine. The results showed that Psychotrine, Catechin, and Eriodictyol, which are flavonoid compounds from ciplukan, have potential as antidepressants because they have the most negative rerank score, has the same significant amino acid bonds as the reference ligands, namely Asp 98 and Tyr 95 and has penetration in the blood brain barrier as shown by the results of the Lipinski analysis.

Abstrak

Depresi merupakan salah satu gangguan kejiwaan yang menjadi tantangan global. Penderita gangguan depresi mengalami perubahan fungsi serotonergik dan noradrenergik pada sistem saraf pusat. Modulasi reuptake serotonin dapat menjadi pendekatan yang efektif dalam pengembangan agen antidepresan. Ciplukan (*Physalis angulata* Linn.) mempunyai sifat antiinflamasi dan antioksidan sehingga berpotensi sebagai kandidat alami pengembangan antidepresan melalui inhibitor reuptake serotonin yang dapat meningkatkan ketersediaan serotonin sinaptik dengan menghambat reuptake serotonin melalui hSERT. Tujuan dari penelitian ini adalah untuk menguji aktivitas penghambatan reuptake serotonin secara in silico dengan metode molekuler docking untuk mengetahui interaksi molekuler antara senyawa aktif dalam ekstrak ciplukan dengan transporter serotonin. Pada penelitian ini perangkat lunak yang digunakan adalah molgro virtual docker dengan target protein human serotonin transporter (hSERT). Ligan uji yang digunakan adalah senyawa golongan alkaloid, glikosida, asam fenolik, dan flavonoid. Ligan pembanding yang digunakan adalah obat SSRI seperti paroxetine, fluoxetine, escitalopram, dan fluvoxamine. Hasil penelitian menunjukkan bahwa Psikotrin, Katekin, dan Eriodictyol yang merupakan senyawa flavonoid dari ciplukan berpotensi sebagai antidepresan karena mempunyai nilai rerank paling negatif, mempunyai ikatan asam amino signifikan yang sama dengan ligan acuan yaitu Asp 98 dan Tyr 95 serta mempunyai penetrasi pada sawar darah otak yang ditunjukkan dari hasil analisis Lipinski.

How to Cite: (*citation style* AMA 11th Ed.)

Alfazarah A, Nurhayati A, Wijaya BM, Sari LA, Wulan ND, Muchlashi LA. In silico evaluation of ciplukan (*Physalis angulata* Linn.) compounds as potential serotonin reuptake inhibitors for antidepressant development. *J Riset Kefarm Indones.* 2026;8(2):168-181. doi:10.33759/jrki.v8i2.953

INTRODUCTION

Mental health problems, especially depressive disorders, are becoming an increasing global challenge. Depression is one of the leading causes of morbidity that has become a global problem. The prevalence of depression in the global population is known to reach 4.4%, with an estimated 322 million people living with the condition. Meanwhile, in Indonesia, the prevalence of depression reaches 3.7% and causes morbidity of 6.6% of the population[(1)]. Depression is one of the psychiatric disorders characterized by a decrease in mood (hypotimia) and the emergence of negative feelings towards oneself. Depressive conditions are complex problems and can be caused by various triggering factors, both in terms of psychological, biological, genetic, and social. According to the *Diagnostic and Statistical Manual of Mental Disorders* edition V (DSM-V), a person is suspected of having depression if they experience five of the following ten symptoms, namely experiencing a decline in mood that continues for more than 2 weeks, increased emotional psychomotor activity in children and adolescents, loss of ability to feel happy and happy, weight loss or increase influenced by changes in appetite, sleep disturbances, easily feeling tired when doing light activities, decreased self-confidence, decreased ability to think and concentrate, and thoughts of self-harm or suicide. Depressive conditions need to be treated immediately, especially if they affect the patient's quality of life[(2)].

Based on previous clinical studies conducted on depressed patients, changes in serotonergic function in the central nervous system were found. Serotonin (5-HT) is widely distributed in the nervous system and a decrease in its amount can cause depression, phobia. In addition to decreased serotonin levels, changes in serotonin (5-HT) receptors also play a role in the mechanism of depression [(3)]. Most of the 15 serotonin receptor subtypes are known to have a role in modulating depression and can be targeted by antidepressants, for example, 5-HT_{1A} and 5-HT_{1B}. In a study that quantified 5-HT_{1A} receptor levels showed an increase in the number of 5-HT_{1A} receptors and activation of 5-$HT_{(1A)}$ receptors causes hyperpolarization which leads to decreased *firing* (neuronal activity) so that serotonin release decreases. In 5-HT_{1B} receptors where activation can reduce serotonin release through its action on the presynapse so that serotonin levels in the brain decrease [(4)].

One of the herbal plants that offers potential for antidepressant development through the mechanism of *serotonin reuptake inhibitors* that can prevent serotonin degradation is ciplukan (*Physalis angulata* Linn.). Ciplukan is a wild herbal plant that grows in tropical and subtropical regions such as Indonesia which is still not widely utilized among the community [(5)]. Ciplukan contains various potential secondary metabolite compounds such as alkaloids, glycosides, phenolic acids, and flavonoids. These compounds show a variety of antidepressant activities. Based on research conducted by Kartika *et al.* (2021) showed that alkaloid compounds have activity as antidepressants with a mechanism of action that inhibits the reuptake of serotonin in the brain [(6)]. Other research related to plants that have the potential for antidepressants shows that the content of one of the secondary metabolites, namely glycosides, is thought to be responsible for the antidepressant effect but the mechanism of action is still unclear [(7)]. Phenolic compounds are widely used as antioxidants that can reduce oxidative stress so that they can protect cells in the brain from free radicals associated with depression [(8)]. Previous research on flavonoid compounds has shown activity as an antidepressant by increasing serotonin or 5- hydroxytryptamine (5-HT), norepinephrine (NE), and Brain-Derived Neurotrophic Factor (BDNF) levels, and reducing monoamine oxidase (MAO) activity [(9)].

The management of depression can use pharmacological therapy in the form of antidepressant drugs. Selective serotonin reuptake inhibitors (SSRIs) are the first line of antidepressant drugs so they are often prescribed. The mechanism of action of SSRIs in general is by inhibiting the transport of serotonin into presynaptic neurons so that

serotonin levels in the brain increase. SSRI drugs include paroxetine, fluoxetine, escitalopram, and fluvoxamine. Antidepressant drugs are consumed for 6-9 months and some researchers even recommend 3-5 years and for life if necessary. However, long-term use may be associated with adverse effects, tolerability issues, or treatment discontinuation challenges[10]. Therefore, research on alternative treatment therapies for handling depression is urgent. This alternative therapy can be approached through wild herbal medicine in the form of ciplukan, a plant with anti-inflammatory and antioxidant properties, which has potential as an antidepressant from natural materials.

Based on the literature search regarding the biological activity of ciplukan, the author conducted in silico research with the molecular docking method which aims to investigate the molecular interactions between secondary metabolite compounds in ciplukan extract with the serotonin transporter. The molecular structure of active compounds was identified based on previous research. Furthermore, molecular simulation and docking were performed using specialized software to evaluate the strength of the interaction between the active compound and the target protein.

METHODS

Tools and materials

The research was conducted using hardware with Windows 11 specifications, 4GB RAM, 64-bit operating system and Intel(R) Core(TM) i3- 1005G1 CPU @ 1.20GHz 1.19 GHz processor. In addition, software such as Molegro Virtual Docker, ChemDraw Ultra 12.0, and ChemDraw 3D Pro 12.0 were used. In this research, the test ligand is a compound from Ciplukan (*Physalis angulata Linn*.) with comparison ligands such as Fluvoxamine, Fluoxetine, Escitalopram, and Paroxetine. The target protein was obtained from the Uniprot database (https://www.uniprot.org/) namely hSERT (PDB ID: 5173).

Ligand Preparation and Analysis

Test ligands and standard ligands were obtained from PubChem website (https://pubchem.ncbi.nlm.nih.gov/). Furthermore, the preparation was carried out with ChemDraw Ultra 12.0 application to identifiy the physicochemical properties of the compounds. Subsequently, ChemDraw 3D 12.0 to optimize ligand geometry and perform energy minimization to obtain stable molecular conformations. The optimized ligand structures were then saved in SYBYL2 format (*.mol2) for further molecular docking analysis using Molegro Virtual Docker.

Target Protein Preparation

The target protein structure of human serotonin transporter (hSERT) with PDB ID: 5173 was obtained through the Uniprot website (The website will be connected to the protein data bank website (https://www.rcsb.org/) to download the target protein. Protein preparation water molecules were removed from the protein structure, hydrogen atoms were added, and appropriate protonation states were assigned to obtain the receptor structure suitable for molecular docking analysis. The website will be connected to the protein data bank website (https://www.rcsb.org/) to download the target protein. Protein preparation water molecules were removed from the protein structure, hydrogen atoms were added, and appropriate protonation states were assigned to obtain the receptor structure suitable for molecular docking analysis.

Molecular Docking Method Validation

Validation is done by re-docking the test ligand with the target receptor. Re tethering is done to validate the PDB file downloaded on the website https://www.rcsb.org/) and the software used as a tethering is Molegro

Virtual Docker (MVD) Ver. 5.0 as the *virtual screening docking* method studied, namely the compounds found in Ciplukan (*Physalis angulata Linn.)* The acceptance value of the re-docking is *Root Mean Square Deviation* (RMSD) < 2.0 Å.https://www.rcsb.org/) and the software used as a tethering is Molegro Virtual Docker (MVD) Ver. 5.0 as the *virtual screening docking* method studied, namely the compounds found in Ciplukan (*Physalis angulata Linn.)* The acceptance value of the re-docking is *Root Mean Square Deviation* (RMSD) < 2.0 Å.

Docking Ligand against Target Protein

Docking is done by predicting the ligand's ability to bind (affinity) to the protein (receptor) using Molegro Virtual Docker software. Ligands were prepared through geometry optimization and energy minimization before docking simulations. Docking simulations were conducted using a predicted binding cavity with a volume of 213.504 $Å^3$ and a surface area of 637.44 $Å^2$. The cavity center coordinates were x = 22.334, y = 125.798, and z = 178.100 Å. Ligands were docked flexibly into the active binding cavity to generate several possible binding conformations against the target protein. Docking simulations were performed with 10 independent runs for each ligand using the default RMSD threshold parameter in Molegro Virtual Docker. Ligand–protein interactions were evaluated using the MolDock scoring function and analyzed based on MolDock Score and Rerank Score values.

Visualization and Analysis of Docking Results

The success of this process can be seen based on the rerank score of each ligand. The rerank score value is a value that indicates the amount of bonding energy required for a compound to bind to a receptor, so that the rerank score can predict the activity of a compound on a particular receptor [(11)]. The smaller the rerank score value indicates a greater degree of compatibility between the ligand and the interacting receptor. In silico tests that are visualized and interpreted provide a representation of ligand bonds with receptors in the form of hydrogen bonds, steric interactions, and electronic interactions. Molegro Virtual Docker is a docking simulation software between protein and ligand in a fully integrated computational package. Molegro Virtual Docker has been applied to a variety of different proteins, with similar capabilities to other docking programs, such as AutoDock Vina and AutoDock4. Molegro Virtual Docker has four original scoring functions and four search algorithms. The integration between Molegro Virtual Docker and SAnDReS will increase the opportunity for detailed statistical analysis of docking results, which will improve the performance of Molegro Virtual Docker [(12)].

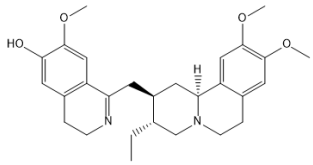
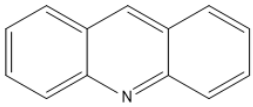
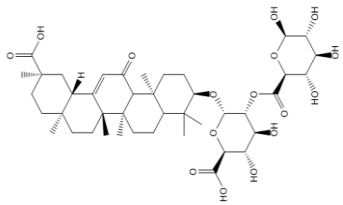
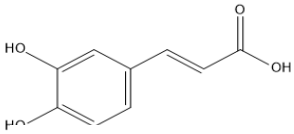
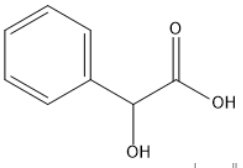
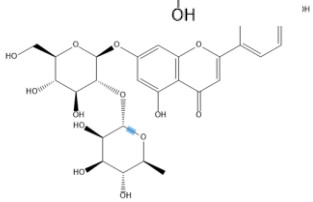
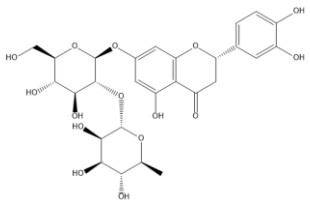
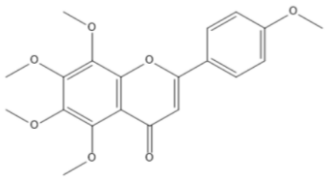
RESULT AND DISCUSSION

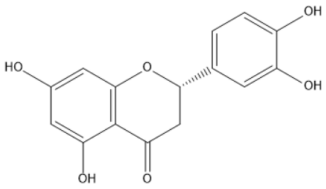
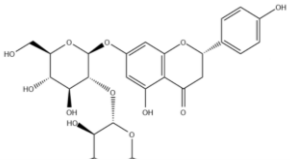
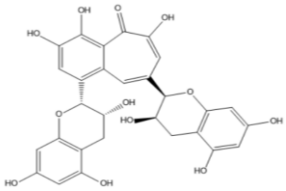
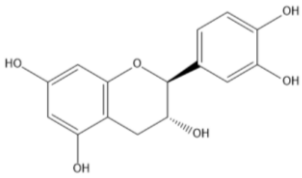
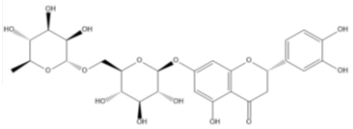
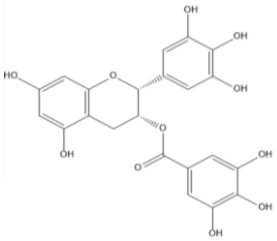
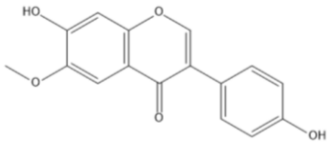
Ligand Preparation and Analysis

In this study, molecular binding of 16 active compounds found in Ciplukan (*Physalis angulata Linn*.) plants that have been studied previously in previous studies with test ligands against the hSERT (PDB ID : 5I73) was carried out. As in **Table 1**. the selection of metabolites from Ciplukan extract (*Physalis angulata Linn*.) was selected 16 compounds with the largest concentration taken from 4 identified secondary metabolites, namely 2 compounds in metabolites of the Alkaloid group from 12% alcohol isolate with filtration methods including Psychotrine and Acridine, 2 compounds in metabolites of the Phenolic Acid group from 70% acetone isolate with filtration methods including Captopril acid and E-strophantin acid, 2 compounds in metabolites of the glycoside group from 0,1 M with filtration method including Astringin acid and Mandelic acid and 10 compounds in Flavonoid metabolites from distilled water isolates with filtration method including Rhoifolin, Neoriocitrin, Tangeretin, Eriodictyol, Naringin, Theaflavins, Catechin,

Eriocitrin, Epigallocatechin gallate, and Glycitein where 16 compounds selected have previously been identified in previous studies [13].

Table 1. Secondary Metabolites of Ciplukan (*Physalis angulata Linn*.) [13].

Compound Structure	Compound Name	Concentration (% w/w)
	*Psychotrine*	6.353%
	*Acridine*	5.630%
	*Glycyrrhizin*	6.435%
	*Caffeic Acid*	4.362%
	*Mandelic Acid*	7.484%
	*Rhoifolin*	7.398%
	*Neoriocitrin*	6.200%
	*Tangeretin*	5.800%

Compound Structure	Compound Name	Concentration (% w/w)
	*Eriodictyol*	3.300%
	*Naringin*	3%
	*Theaflavins*	2.800%
	*Catechin*	2.700%
	*Eriocitrin*	2,500%
	*Epigallocatechin gallate*	2%
	*Glycitein*	0.003%

While the comparison ligand used is a *Selective Serotonin Reuptake Inhibitor* (SSRI) class drug, namely Citalopram, Fluvoxamine, Fluoxetine, Escitalopram, and Paroxetine. Test ligands and standard ligands were obtained from the PubChem website which were then prepared using the ChemDraw Ultra 12.0 application to obtain 2D structures as in **Table 1.** and determine the chemical physical properties of ligand compounds. Furthermore, using ChemDraw 3D 12.0 to minimize the energy of the ligand compound and get the total energy value and then stored in SYBYL2 format (*.mol2).

Target Protein Preparation

The target protein that binds to SSRI class drugs is the *human serotonin transporter* (hSERT) with PDB ID

5273[14].The target protein was downloaded through the RCSB-PDB database according to the PDB Protein ID. Furthermore, the target protein was inserted into the Molegro Virtual Docker software without including the cofactor and water molecule. A cavity detection was performed on the target protein which is where the ligand binds.

Analysis of *docking* results

The *docking* process of test ligands and comparison ligands with proteins is performed using Molegro Virtual Docker software to predict the ability of ligands to bind (affinity) to proteins (receptors). The process resulted in a *Rerank Score* and ligand-protein interactions. While the Total Energy was obtained from ChemDraw 3D 12.0 in the ligand preparation process.

Total energy indicates the stability of the ligand structure. However, not all ligands that have low total energy can interact well with their receptors. Rerank Score (RS) describes the binding energy. Bond energy is the amount of energy required for the ligand to bind to the receptor. A lower rerank score indicates a higher affinity of the ligand for the protein [15].

Table 2. Total energy value of ligand based on ChemDraw 3D 12.0 and docking result data of ligand with target protein using Molegro Virtual Docker.

Goals	Compound	Total Energy (kcal/mol)
Comparison Drug	*Paroxetine*	24.0987
	Fluvoxamine	24.0560
	Escitalopram	20.2398
	Fluoxetine	17.0929
Test Compound	*Epigallocatechin gallate*	4.3898
	Naringin	56.7073
	Rhoifolin	57.5105
	Neoriocitrin	49.8027
	Psychotrine	41.8010
	Catechin	-5.6718
	Theaflavins	41.1073
	Eriocitrin	19.9354
	Glycitein	33.1620
	Tangeretin	59.9918
	Eriodictyol	5.1657
	Caffeic Acid	-7.3263
	Acridine	1.8092
	Mandelic Acid	-4.0612
	Glycyrrhizin	128.2716

The comparison drug, fluoxetine, has the highest rerank score among the other comparison drugs, namely -

95.919 kcal/mol. However, it does not mean that fluoxetine is worse than other drugs because fluoxetine is a widely used SSRI class drug. There are eleven test ligands that have more negative RS than the comparator drug fluoxetine. The test ligands are compounds of Epigallocatechin gallate (-118.511), Naringin (-98,112), Neoriocitrin (-97,570), Theaflavins (-139.055), Eriodictyol (-100.485), Glyyrrhizin (-142.189), Psychotrine(-107.655), Rhoifolin (-137.997), Eriocitrin (-129.939), Catechin (-96.419), Tangeretin (-100.399). Among these compounds, Glyyrrhizin has the best RS value of –142.189 kcal/mol. The more negative rerank scores observed in these compounds may suggest favorable predicted interactions with hSERT. Comprehensive molecular docking results are detailed in **Table 3.**

Table 3. Amino acid residue analysis using Molegro Virtual Docker

Compound	Rerank Score (kcal/mol)	Hydrogen bond	Steric Interaction	Electrostatic Interaction
Paroxetine	-102,361	Ala 96, Ser 439	Asp 98, Ala 96, Tyr 95, Ile 172, Ser 439	-
Fluvoxamine	-107,822	Ala 96, Ser 336	Ala 96, Ser 336, Asp 98, Phe 335, Tyr 95	-
Fluoxetine	-95,919	-	Phe 335, Asp 98, Tyr 95	-
Escitalopram	-106,692	-	Tyr 95, Ala 96	Asp 98
Epigallo catechin gallate	-118,511	Ala 169, Asn 177, Tyr 95, Phe 335, Tyr 175, Ser 436	Ala 169, Asn 177, Ser 439, Tyr 95, Phe 335, Asp 98, Ser 438, Tyr 176, Ile 172, Tyr 175	-
Naringin	-98,112	Glu 495. Arg 104, Gln 332, Glu 493, The 497	Glu 494, Asp 328, Gln 332, Glu 493, Arg 104, Val 501, Thr 501, Thr 497, Tyr 175	-
Neoriocitrin	-97,570	Tyr 176, Glu 493, Trp 103, Asp 98, Phe 325, Tyr 95	Glu 493, Trp 103, Asp 98, Tyr 176, Gly 100, Gln 332, Ser 336, Asn 101 Phe 335, Tyr 95, Ser 438	-
Theaflavins	-139,055	Tyr 175, Pro 499, Glu 493, Gln 332	Tyr 175, Pro 499, Leu 502, Gly 498, Glu 493, Thr 497, Phe 556, Arg 104, Glu 494, Gln 332	-

Compound	Rerank Score (kcal/mol)	Hydrogen bond	Steric Interaction	Electrostatic Interaction
Eriodictyol	-100,485	Asn 177, Ala 169, Ser 439, Tyr 95, Ser 438, Tyr 176	Ser 439, Asn 177, Ala 169, Phe 341, Ala 96, Asp 98, Ser 438, Tyr 95, Tyr 176	-
Glycyrrhizin	-142,189	Arg 564, Ala 401, Tyr 107, Gln 562, Lys 490	Arg 104, Glu 494, Leu 563, Gln 562, Lys 490, Tyr 107, Lys 399, Gln 111, Arg 564, Ala 401, Ile 108	-
Psychotrine	-107,655	Ser 438	Tyr 95, Ser 438, Tyr 176, Asp 98, Phe 335, Gln 332	-
Glycitein	-90,757	Ala 96	Tyr 95, Phe 335, Ser 336, Asp 98, Ala 96	-
Rhoifolin	-137,997	Glu 493, Thr 497, Tyr 95, Asp 98, Ser 438	Arg 104, Gly 498, Thr 497, Phe 335, Glu 493, Tyr 95, Gly 338, Phe 341, Ile 172, Asp 98, Ser 438	-
Caffeic Acid	-74,146	Asp 98, Gln 332	Gln 332, Ser 336, Asn 101, Phe 335, Asp 98	-
Eriocitrin	-129,939	Asp 98, Glu 493, Tyr 175, Tyr 95, Ala 169	Asp 98, Phe 335, Ser 336, Ala 96, Arg 104, Glu 493, Thr 497, Tyr 175, Tyr 95, Ile 172, Ala 169	-
Catechin	-96,419	Asn 177, Ser 439, Ala 169, Asp 98	Asn 177, Ser 439, Ala 173, Ala 169, Asp 98, Ala 96, Tyr 95	-
Tangeretin	-100,399	-	Ser 336, Phe 335, Gln 332	-
Mandelic Acid	-68,965	Asn 351, Lys 85, Phe 347	Lys 85, Asn 351, Phe 88, Phe 347	-

Compound	Rerank Score (kcal/mol)	Hydrogen bond	Steric Interaction	Electrostatic Interaction
Acridine	-79,797	Arg 104	Ser 336, Gln 332, Arg 104	-

	Similarity of Interaction with amino acid **Ala 96** through Hydrogen Bonds and Steric Interactions
	Similarity of Interaction with amino acid **Ser 439** through Hydrogen Bonds and Steric Interactions
	Similarity of Interaction with amino acid **Asp 98** through Steric Interactions
	Similarity of Interaction with amino acid **Ala 96** through Steric Interactions
	Similarity of Interaction with amino acid **Ile 172** through Steric Interactions
	Similarity of Interaction with amino acid **Phe 335** through Steric Interactions
	Similarity of Interaction with amino acid **Ser 336** through Steric Interactions

Ligand interactions with amino acids in protein are crucial for the biological activity of a compound. From the analysis of ligand interactions with amino acids, it is known that of the 11 compounds with lower rerank scores than the reference drug, only 8 compounds showed interactions with hSERT similar to the natural ligand (reference drug). In hSERT inhibition, the amino acids Asp 98 and Tyr 95 are very significant for antidepressant activity. These amino acids bind to the protonated amine functional group in SSRIs. At physiological pH, this group is positively charged so it interacts with negatively charged amino acid residues in the hSERT protein. From the analysis of ligand interactions with amino acids, it is known that of the 11 compounds with lower rerank scores than the reference drug, 7 compounds showed interactions with the amino acids Asp 98 and Tyr 95. These compounds are epigallocatechin gallate, neorioctrin, eriodictyol, psychotrine, rhoifolin, eriocitrin, and catechin.

Based on the analysis of the results of the epigallocatechin gallate, neorioctrin, eriodictyol, psychotrine, rhoifolin, eriocitrin, dan catechin compounds which are flavonoid metabolite group compounds from Ciplukan, demonstrated favorable interactions with hSERT target protein. These compounds showed relatively negative rerank scores and interacted with several amino acid residues involved in the binding pocket, including Asp 98 dan Tyr 95 which are associated with hSERT. These may suggest a possible resemblance in binding mechanisms toward hSERT such as comparator drugs. However, molecular docking only predicts the possibility of ligand-target interaction and does not directly indicate clinical efficacy and biological activity. Therefore, these compounds may be considered as potential candidates as serotonin reuptake inhibitors with further investigation.

A molecule must reach its target in the body in sufficient amounts and remain in the body in its bioactive form for an adequate period. This analysis was conducted using SwissADME. Furthermore, the physicochemical properties of the compounds were predicted according to the Lipinski's Rule of Five, which serves as an indicator of a compound’s ability to penetrate cell membranes through passive diffusion. Compounds that do not meet these criteria may exhibit impaired oral drug absorption. Based on the results of the Lipinski analysis on **Table 4**, eight

compounds were found to fullfill the criteria of Lipinski's Rule of Five. In the Lipinski analysis of 7 compounds that had lower rerank scores than the reference drug and interacted with the amino acids Asp 98 and Tyr 95, it was found that only 3 compounds had Lipinski values that met the requirements, including psychotrine, catechin, and eriodictyol.

Tabel 4. *Lipinski Rule of Five* of Secondary Metabolite Compounds from *Physalis angulata Linn.*

Compound	Molecule Weight < 500	Lipophilicity (MLOGP) < 5	H-Bond Acceptors < 10	H-Bond Donors < 5	Rotatable Bonds < 10	Lipinski Yes
Epigallocatechin gallate	458.37	-0.44	11	8	4	No
Naringin	580.53	-2.77	14	8	6	No
Rhoifolin	578.52	-2.96	14	8	6	No
Neoriocitrin	596.53	-3.24	15	9	6	No
Psychotrine	464.60	2.77	6	1	6	Yes
Catechin	290.27	0.24	6	5	1	Yes
Theaflavine	564.49	-0.79	12	9	2	No
Eriocitrin	596.53	-3.24	15	9	6	No
Glycitein	284.26	0.77	5	2	2	Yes
Tangeretin	372.37	0.63	7	0	6	Yes
Eriodictyol	288.25	0.16	6	4	1	Yes
Caffeic Acid	180.16	0.70	4	3	2	Yes
Acridine	179.22	3.06	1	0	0	Yes
Mandelic Acid	152.15	0.78	3	2	2	Yes
Glycyrrhizin	822.93	0.02	16	8	7	No

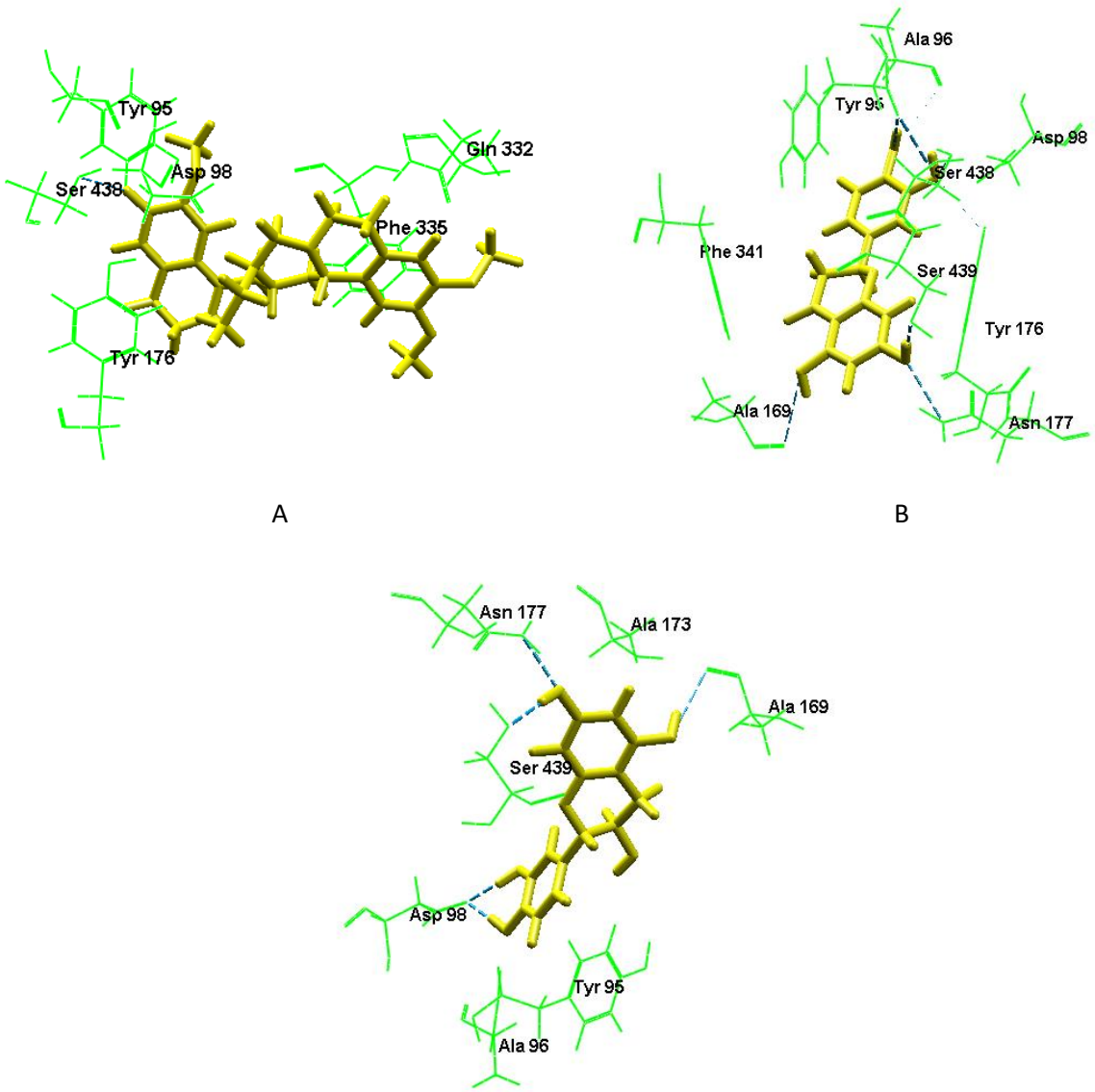


Figure 1. Visualization of test ligand binding (a) Psychotrine with hSERT; (b) Eriodictyol with hSERT; (c) Catechin with **hSERT.** Compound Psychotrine interacts with Asp 98 and Tyr 95 through Steric Interactions. Compound Eriodictyol interacts with Asp 98 and Tyr 95 through Steric Interactions. Compound Catechin interacts with Asp 98 and Tyr 95 through Steric Interactions.

Docking Validation Analysis

Validation of Docking Results can be determined from the RMSD value of natural ligand with target protein. The RMSD is used to determine the prediction of successful bonding of natural ligand compounds with target proteins and is an important parameter in the docking program. RMSD is said to be good if ≤ 2 Å where the greater the RMSD value, the greater the deviation and prediction error of natural ligand interaction with the target protein [(18)]. It is known in the results of **Table 4** that the RMSD of the natural ligand with the target protein is ≤ 2 Å, which means that there is minimal deviation or prediction error between the interaction of the ligand and the target protein, so it can be concluded that the results can be validated properly.

Table 4. *Re-docking* Results of Natural Ligand with Target Protein

Target Protein	Protein Code	Natural Ligan	Binding Affinity	RMSD (≤ 2 Å)
hSERT	5I73	68P_701	-23,695	0.821121

LIMITATION

This study has several limitations that should be considered when interpreting the result. First, this study addresses a relatively novel research topic. Therefore, supporting literature is still limited. This limitation restricts comprehensive comparison with previous studies and may affect the depth of discussion. Further studies are required to strengthen the evidence and validate the findings of this research.

Second, this study was conducted using a computational (in silico) method with molecular docking without experimental validation using in vivo and in vitro methods. Therefore, the results of this study are predictive and may not fully represent the actual pharmacological effect under physiological conditions.

CONCLUSION

Of the 15 compounds identified in ciplukan extract and evaluated through molecular docking analysis, psychotrine, catechin, and eriodictyol demonstrated more negative rerank sores, has the same significant amino acid bonds as the reference ligands, namely Asp 98 and Tyr 95 and has penetration in the blood brain barrier as shown by the results of the Lipinski analysis. These findings suggest that the flavonoid compounds may exhibit favorable binding affinity toward the target receptor. However, the resin this study are predictive in nature and based solely on in silico molecular docking analysis. Therefore, further validation through in vitro and in vivo studies is required to confirm their potential antidepressant activity.

FUNDING

This research has passed the 2024 Pekan Kreativitas Mahasiswa (PKM-AI) Incentive and is supported by Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi (Kemendikbudristek).

ACKNOWLEDGMENTS

Thank you to all team members and all parties who have contributed to the process of preparing this research, especially to our supervisor apt. Luthfi Ahmad Muchlashi, S.Farm., M.Farm who has guided and directed the author in conducting this study and research so that it can be presented in the form of a scientific article.

AUTHOR CONTRIBUTION STATEMENT

Azki Alfazahrah: Conceptualization, Methodology, Supervision, Investigation, Data Curation, and Formal Analysis. Alifda Nurhayati : Data Curation, Investigation, Literature Review, and Writing – Original Draft. Bianti Meylia Wijaya : Conceptualization, Data Curation, Investigation, Formal Analysis, and Writing – Review & Editing. Larasati Atum Sari : Investigation, Literature Review, Data Curation, and Writing-Original Draft. Nabila Dinar Wulan : Data Curation, Investigation, Target Protein Analysis, and Control Ligand Analysis. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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