ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2022, Volume 11, Number 3: 1243-1249
P-ISSN.2089-1180, E-ISSN: 2302-2914

A study of molecular docking of l-tryptophan ligand as a compound in pineapples and bananas binding with the human serotonin transporter (SERT)

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Received: 2022-07-15
Accepted: 2022-08-08
Published: 2022-09-23

ABSTRACT

Introduction: Low mood condition is related to a low level of brain serotonin. An early sign of depression with low mood symptoms is generally treated with psychotropic drugs that work as selective serotonin reuptake and monoamine oxidase (MAO) inhibitors (one of which is sertraline), to increase serotonin levels in the brain. There are some concerns regarding side effects available medication like serotonin syndrome, suicidality and aggressive behavior. Thus, development of alternative herbal products made from a combination of pineapple and banana extract with less side effect and its potential affinity with serotonin regulation is important.

Aim of the study: To determine potential herbal rich (banana and pineapple) of L-tryptophan and potential active compounds interaction with the human serotonin transporter.

Method: In the present study, using in silico molecular docking techniques, the active compound of banana and pineapple and its potential interaction with human serotonin transporter were assed. Docking study explored the bioactive compounds interactions with specific target like catechin, dopamine, epigallocatechin, gallic acid, L-tryptophan, malvidin, norepinephrine, pelargonidin, peonidin, and serotonin. Molecular docking simulations were performed using AutoDock 4.2 software. The docking method was validated first by re-docking sertraline (nature ligand) in a complex with PDB ID: 6AWO against the target receptor (SERT).

Result: The molecular docking results had showed that L-tryptophan, peonidin, and catechin could bind to esential amino acid residues in the binding pocket, with binding affinity -5.69, -8.63, -8.24 kcal/mol respectively.

Conclusion: L-tryptophan, peonidin, and catechin are the most promising compounds that have good potency as anti-depressant agents through SERT inhibitory activity. This compounds in bananas and pineapples have the potential to affect serotonin transporter receptors that play a role in mood and behavior.

Keywords: L-tryptophan, human transporter serotonin, pineapple, banana, molecular docking.
Cite This Article: Purnawati, S., Wrasiati, L.P., Lesmana, C.B.J., Megantara, S., Lesmana, R. 2022. A study of molecular docking of l-tryptophan ligand as a compound in pineapples and bananas binding with the human serotonin transporter (SERT). *Bali Medical Journal* 11(3): 1243-1249. DOI: 10.15562/bmj.v11i3.3526

INTRODUCTION

Chronic psychological distress can result in a low mood that affects work productivity and general health status, both physically and mentally. Serotonin (5HT) is a neurotransmitter that plays a role in a good mood and healthy lifestyle behavior. Neuroimaging, postmortem, and pharmacological challenge studies have all shown abnormalities of serotonin receptors and the serotonin transporter binding function in mood disorders. Serotonin transporter availability also appears to be reduced in mood disorders. The monoaminergic systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders. Abnormalities have also been demonstrated in a variety of neuropeptide, neuroendocrine, and other neurotransmitter systems in mood disorders. igh levels of amygdala activation are associated with an increased prevalence of negative mood. Some studies have demonstrated reduced gray matter volumes in parts of the orbital and medial prefrontal cortex, the striatum, and the amygdala, and enlargement of third ventricles in mood disorders.[1]

Unbalanced nutrient intake is a factor that also plays a role in individual sensitivity to low mood, even the risk of depression. Tryptophan depletion is known to negatively affect mood. A study in humans found that a decrease in the tryptophan content in the diet led to changes in irritability and aggressive behavior. An intake of nutrients containing tryptophan precursors and their binding to serotonin transporters that act on serotonin in the central nervous system (CNS) synaptic cleft correlate with mood and behavior.[2] Pineapple and banana compounds have

potency for serotonergic function and also the benefit of their antioxidant content for human brain.[3] Thus, it could be a potential alternative medication using natural ingredient products derived made from local Indonesian fruit extracts which affects mood and shows potential interaction with the serotonin transporter gene-linked polymorphic region (5HTTLPR) as an expression of the serotonin transporter gene. The serotonin transporter known as 5HTT or SLC6A4 located on chromosome 17 (17q11.2) will encode the 5HTT transporter protein which functions to increase serotonin reuptake, which in turn will stop the activity of serotonin. The transcriptional activity of SLC6A4 in humans is modulated by several factors. One of these is a repeat sequence of SLC6A4 associated with the 5-HTTPLR, consisting of a short (S) and a long (L) version that affects the expression and function of 5HTT. The short-allele (S) variant 5-HTTLPR is associated with lower 5-HTT protein concentrations than the long-allele (L) variant (it could be seen in Figure 1) and is accompanied by a dramatic reduction of 5-HT reuptake that subsequently may promote 5-HT dysfunction as found in depression.[4,5]

The 5-hydroxytryptamine (5-HT) dysfunction is commonly indicated in depressed patients by lower brain availability of tryptophan. One study found a beneficial/significant effect of tryptophan challenge on mood and stress response in individuals with the S'/S' genotype (5-HTTLPR short allele). So that the effect of a phytopharmaceutical containing tryptophan on the expression of the serotonin 5-HTTPLR gene is a very interesting phenomenon to study which aims to see the effect of the phytopharmaceutical on mood.

Low mood conditions as early markers of depression are generally treated with psychotropic drugs that work as selective serotonin reuptake and monoamine oxidase (MAO) inhibitors, to increase serotonin levels in the brain (one of which is treated with sertraline[8], with the risk of possible side effects from using the drug). One example is serotonin syndrome. Other side effects can be suicidality and aggressive behavior.[9] An alternative therapy from natural ingredients is needed that affects the serotonergic system and is safe. The development preparation of pharmaceutical products (with natural ingredient) made from a combination of pineapple and banana extract (from the local fruit Indonesians) needs to do an in-silico study or molecular docking to determine the compound's bond with the human serotonin transporter receptors.

A previous study found the effect of bananas as an antidepressant-like effect.[10] The alkaloid content in bananas indicates the presence of serotonin compounds which are brain neurotransmitters that play a role in mood.[11] Another study found that bananas contain of tryptophan, serotonin, norepinephrine, dopamine which play a role in brain serotonergic function.[12] Meanwhile, other researchers found flavonoid compounds in bananas

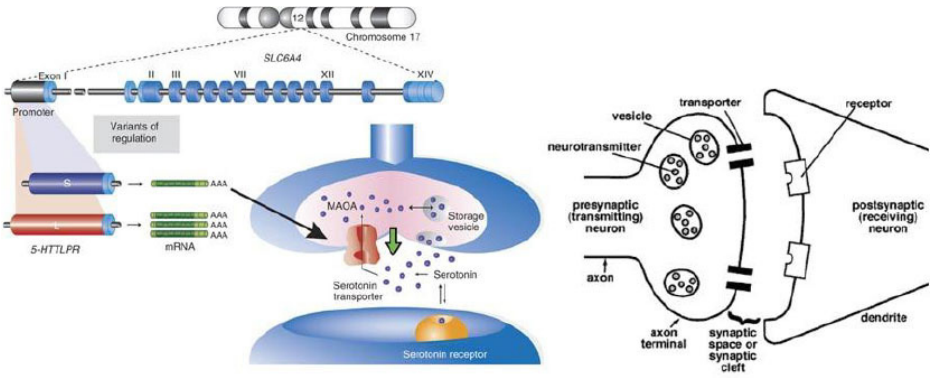

Figure 1. *Short-allele* (S) and *long-allele* (L) variant 5-HTTLPR and their function on the serotonergic system.[6]

Table 1. List of test compounds used in this molecular docking study.

No.	Compound	PubChem CID
Banana fruit		
1	Catechin	1203
2	Dopamine	681
3	Epigallocatechin	72277
4	Gallic acid	370
5	L-tryptophan	1148
6	Malvidin	159287
7	Norepinephrine	439260
8	Pelargonidin	440832
9	Peonidin	441773
10	Serotonin	5202
Pineapple fruit		
1	3-methylglutaric acid	12284
2	Benzoic acid	243
3	Bromelain	44263865
4	Catechin	1203
5	Epicatechin	72276
6	Ferulic acid	445858
7	Fumaric acid	444972
8	Gallic acid	370
9	Glucaric acid	33037
10	Glyceric acid	752
11	Malonic acid	867
12	Phenylacetic acid	999
13	Protocatechuic acid	72
14	Succinic acid	1110
15	Syringic acid	10742
16	Vanillic acid	8468

that have a very important role in relation to serotonin level homeostasis.[13]

To explore and search the potential interaction of interest active compound, molecular docking is a key tool approach suitable for structural molecular biology and computer-assisted drug design. *Molecular docking* is the study to explore how two or more molecular structures (e.g., drug and enzyme or protein) fit together. The behavior of small molecules in the binding pockets of target proteins can be described by molecular docking. In a simple definition, docking is a molecular modeling technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands). The ability of a protein and nucleic acid to interact with small molecules to form a supramolecular complex plays a major role in the dynamics of the protein, which may enhance or inhibit its biological function. Molecular docking could identify the correct poses of ligands in the binding pocket of a protein and predict the affinity between the ligand and the protein.

This study aims to explore the binding of the amino acid L-tryptophan and several important compounds contained in banana and pineapple to the human serotonin transporter which is a receptor that plays a role in serotonin reuptake in the synaptic cleft.

METHOD

Molecular Docking was conducted to assess the binding energy of protein-ligand (L-tryptophan) to the serotonin transporter receptor (SERT) (the site of action of the active compound that underlies its effect on mood improvement). This in silico molecular docking test was conducted to determine the mechanism of action of the binding proteins (ligands) contained in pineapples and bananas to the serotonin transporter receptor cell membrane as a target, as well as to determine the binding energy between these compounds and the target cell membrane. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure.[14] Molecular docking was carried out through several stages including preparation and optimization of the 3D structure of the test compound, preparation of the 3D structure of the serotonin transporter (SERT), method validation, and docking of the test compound with SERT.

Data Preparation

The test compounds used were bioactive compounds sourced from banana and pineapple fruit. Bioactive compounds sourced from banana fruit were catechin, dopamine, epigallocatechin, gallic acid, L-tryptophan, malvidin, norepinephrine, pelargonidin, peonidin, and serotonin.[15,16] While the test compounds sourced from pineapple fruit were 3-methyl glutaric acid, benzoic acid, bromelain, catechin, epicatechin, ferulic acid, fumaric acid, gallic acid, glucaric acid, glyceric acid, malonic acid, phenylacetic acid, protocatechuic acid, succinic acid, syringic acid, and vanillic acid.[17,18] The whole structure of the test compound refers to the PubChem database (Table 1).

Sertraline, a selective serotonin reuptake inhibitor, was used as a standard compound in determining the potency of the test compound. The target receptor in this study was the serotonin transporter (SERT) that was retrieved from a complex with PDB ID: 6AWO. Both standard compounds and receptors were obtained from the structural extraction of the complex using Biovia Discovery Studio 2020. All test compounds were saved in .pdb file format, which was then added with polar hydrogen and Kollman charge for the receptor and Gasteiger charge for ligands using AutoDockTools 1.4.6. The entire compound structure was then saved as a file with the .pdbqt format for further process.

Docking Procedure

Molecular docking simulations were run using AutoDock 4.2 software.[19] The docking method was validated first by re-docking sertraline (nature ligand) in a complex with PDB ID: 6AWO against the target receptor (SERT). Re-docking was done by setting the grid box size at 40X40X40 points with a spacing centered on SERT of 0.375 Å. The docking method could be said to be valid if the minimum RMSD value obtained was 3 Å.[20]

The parameterization process, both grid parameters, and docking parameters as well as analysis of the results of docking was performed using AutoDockTools 1.4.6 software. Lamarckian Genetic Algorithm (LGA) was used to implement the interactions that occur between protein ligands. All settings were set in default mode except for the genetic algorithm value of 100. The docking results were then analyzed to identify the binding energy and inhibition constant of the interactions. Visualization of the interactions that occur between protein ligands was carried out using Biovia Discovery Studio 2020. The results then were compared against sertraline as standard.

RESULT

In this study, we investigated the secondary metabolites found in bananas and pineapples that are responsible for antidepressant activity as described in the introduction. The receptor or target protein used in this study was the serotonin transporter (SERT) which was extracted in a complex with PDB ID: 6AWO. This SERT binds to sertraline (selective serotonin reuptake inhibitor) on the interior of the transporter. Serotonin transport inhibitory activity occurs due to interactions with key amino acid residues Tyr95, Asp98, and Phe341.[21]

The validity of this molecular docking simulation method was carried out through the re-docking process of nature ligands on the complex in PDB ID: 6AWO (sertraline) against SERT. In addition, sertraline was also used as a standard in this study. The result of the re-docking process shows an RMSD value of 2.61. It indicates that the atomic shift in the molecule after the re-docking process does not exceed the specified limit (RMSD ≤ 3).[20] An overview of the sertraline compound overlay before and after the re-docking process can be seen in Figure 2.

The results of this molecular docking study are presented in Table 2. From all test compounds, none of the compounds obtained had a lower binding affinity compared to sertraline as standard. However, some compounds showed their best potency compared to other compounds. Peonidin showed the lowest binding affinity value among other active compounds in bananas and pineapples. Peonidin can form hydrogen interactions

with Tyr95 residues on SERT, even the type of interaction is stronger when compared to the interaction between sertraline-SERT. This indicates that peonidin has the potential as a SERT inhibitor with high effectiveness compared to other test compounds.

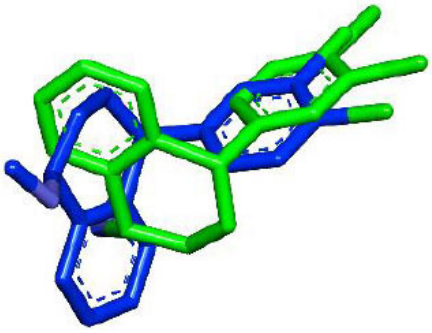

Figure 2. Overlay nature ligand (sertraline) before (blue) and after (green) re-docking process.

An interesting finding was observed, catechin, besides showing the lowest binding affinity gain compared to other active compounds in pineapple, also showed the most similar binding motif compared to the sertraline-SERT interaction. Another fact, these catechins are also contained in bananas. Catechins interact through a hydrogen bond with the Asp98 residue and Pi-Sigma interaction with the Tyr95 and Phe341 residues. It indicates that catechins have potency as more selective SERT inhibitors, but are thought to have lower effectiveness when compared to peonidin.

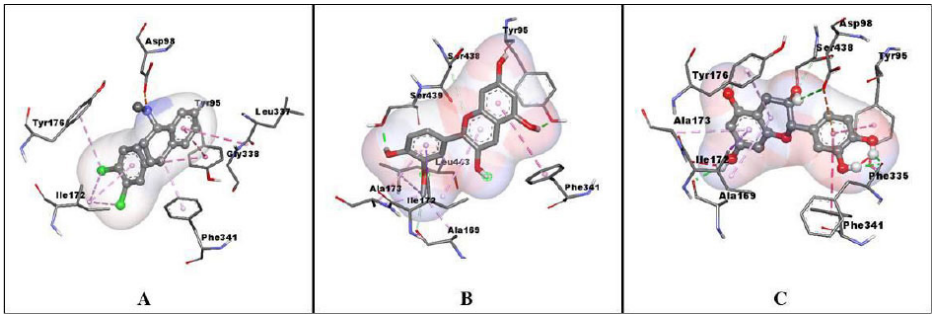

Figure 3. (A) Interaction between sertraline-SERT, (B) Interaction between peonidin-SERT, and (C) Interaction between catechin-SERT.

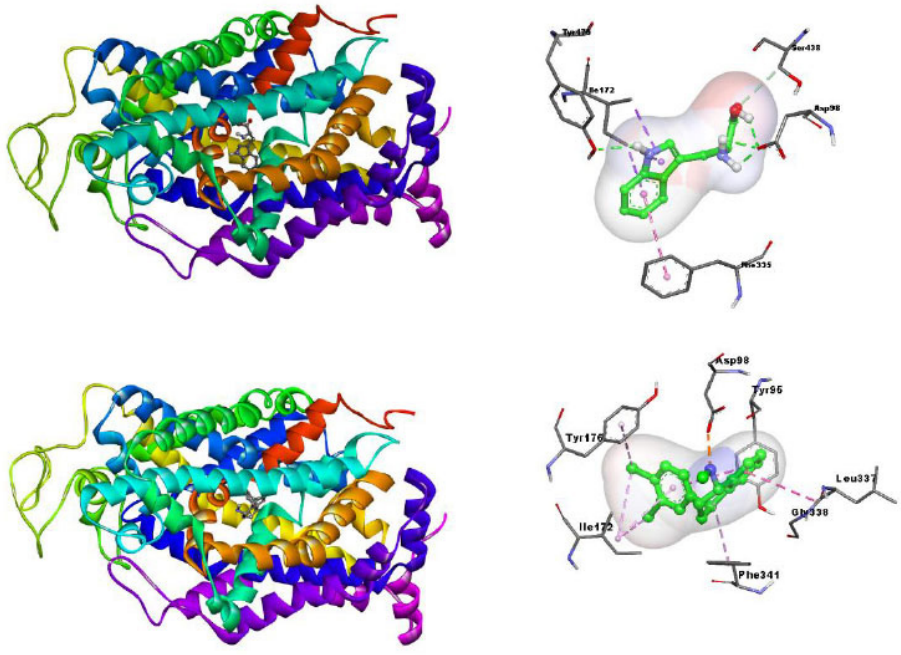

Figure 4. (A) Interaction between L-tryptophan (3D)-SERT, (B) Interaction between L-tryptophan (2D)-SERT, (C) Interaction between Sertraline (3D)-SERT, (D) Interaction between Sertraline (2D)-SERT.

DISCUSSION

The main finding of this study was L-tryptophan amino acid and these two flavonoids, peonidin and catechin are the most promising compounds that have good potency as anti-depressant agents through SERT inhibitory activity. The potency of peonidin, catechin, and also tryptophan is estimated to be lower than sertraline. However, the advantage is that these two compounds have a better safety profile compared to sertraline.[21,22] In addition, besides the need for further analysis to prove the potency of these two compounds, efforts can also be made to improve the activity of these two compounds through various modifications, both chemically and physically.

The findings of this molecular docking study provide an overview of the mechanism of action of the effects of the active compounds in bananas and pineapples (especially L-tryptophan) by regulating synaptic cleft concentrations of serotonin, norepinephrine, and dopamine with their target of action being their binding to the human transporter serotonin receptor. We found that L-tryptophan has a bond energy of -5.69 kcal/mol; it bonds to hydrogen atoms via amino acid residues Asp98, Tyr175. That means this compound with low binding affinity gain compared to other active compounds in pineapple. This finding also showed that L-tryptophan have similar binding motif compared to the sertraline-SERT interaction. The binding of L-tryptophan compounds and catechins to serotonin transporter receptors especially in the hippocampus and amygdala illustrates that these compounds affect serotonin transporter receptors due to serotonin concentrations in the synaptic cleft that play a role in mood function. Although others compounds which were more lower binding affinity gain have been found in our study, such as peonidin and catechin, are potentially to explore from Indonesian pineapples and banana extract for further explorative study. This study is in line with the previous in silico study that found the possible relevance of in-silico studies

Table 2. Molecular docking results of banana's and pineapple's active secondary metabolites towards SERT (PDB ID: 6AWO).

Compound	Binding Affinity (kcal/mol)	Inhibition Constant	Ligand-Receptor Interaction	
			Hydrogen Bond	Others
Sertraline	-10.3	28.21 nM	-	**Tyr95', Asp98***, Ile172", Tyr176", Leu337', Gly338"', **Phe341"**
Banana				
Peonidin	-8.63	469.97 nM	Tyr95, Ser439	Ala169****, Ile172**, Ala173", Phe341', Ser438****, Leu443"
Catechin	-8.24	906.3 nM	Asp98, Ala169, Phe335	Tyr95', Ile172**, Ala173"", Tyr176", Phe341', Ser438****
Pelargonidin	-8.2	975.63 nM	Tyr95	Ile172*, Ala173", Phe341', Ser438****
Malvidin	-7.91	1.58 uM	Asp98, Gly442	Tyr95", Ala169", Ile172**, Ala173", Tyr176', Phe335****, Phe341**, Leu443"
Serotonin	-7.44	3.51 uM	Asp98, Ser439	Ile172**, Ala173"
Epigallocatechin	-7.25	4.84 uM	Asp98, Tyr175, Phe335, Ser438, Thr497	Ile172**, Phe341**
Dopamine	-6.15	31.04 uM	Ala96, Asp98, Ser336	-
Norepinephrine	-5.85	51.19 uM	Tyr95, Ala96, Asn101	Phe335****, Phe341', Ser438****
L-Tryptophan	-5.69	66.94 uM	Asp98, Tyr175	Ile172**, Phe335', Ser438****
Gallic Acid	-3.9	1.38 mM	Tyr95, Ala96, Asp98, Ser336	-
Pineapple				
Catechin	-8.24	906.3 nM	Asp98, Ala169, Phe335	Tyr95', Ile172**, Ala173"", Tyr176", Phe341', Ser438****
Epicatechin	-7.87	1.71 uM	Ile165, Phe341, Ser438, Ser439	Ala169**, Ile172**, Ala173", Val343"
Ferulic Acid	-5.34	122.68 uM	Phe341	Ala169", Ile172", Ala173**, Tyr176**, Leu443"
Vanillic acid	-4.33	664.61 uM	Gly442	Ala169", Ile172", Ala173", Tyr176**, Ser438****, Leu443"
Syringic acid	-4.21	827.01 uM	Ser439	Ala169", Ile172**, Ala173", Tyr176**, Gly442****
Phenylacetic acid	-4.15	903.05 uM	Asn177, Ser439	Ile172", Tyr176', Ser438'
Protocathechuic acid	-4.08	1.03 mM	Ala96, Ser336	Phe335***, Phe341'
Benzoic acid	-4.04	1.1 mM	Asn177, Ser439	Ala169", Ile172**, Ala173"
Gallic Acid	-3.9	1.38 mM	Tyr95, Ala96, Asp98, Ser336	-
3-methylglutaric acid	-2.56	13.25 mM	Asn177, Ser439, Gly442	Ile168"', Ala169", Ile172", Ala173", Tyr176, Phe341"', Val343"', Leu443"', Val446"'
Glyceric acid	-2.27	21.7 mM	Tyr175	-
Fumaric acid	-2.18	25.3 mM	Ala169	Ala173""
Succinic acid	-2.04	31.98 mM	-	Ala169"', Ile172"', Ala173"', Tyr176"', Asn177"', Phe263"', Ser439"', Gly442"', Leu443"'
Malonic acid	-1.45	86.27 mM	Asn177, Ser439, Leu443	-
Glucaric acid	-0.56	391.32 mM	Tyr175, Thr497	-

Compound	Binding Affinity (kcal/mol)	Inhibition Constant	Ligand-Receptor Interaction	
			Hydrogen Bond	Others
Bromelain	25.71	-	Ala169, Ser439, Gly442, Cys473	Tyr95", Asp98*, Ile172"", Tyr176"", Phe335"", Phe341"", Val343", Ser438"", Ala441", Glu493"", Thr497""

*Salt Bridge/Pi-Anion; **Pi-Lone Pair; ***Pi-Lone Pair, ****Carbon Hydrogen Bond; 'Pi-Pi T-shaped/Amide-Pi Stacked/Pi-Pi Stacked; "Alkyl/Pi-Alkyl; ""van der Waals; ""Unfavourable Donor-Donor

in search of DMT analogues against the 5-HT1B receptor, which may be associated with alterations such as depression and anxiety.[24] According to those study, it could be clearer that mood disorders are characterized by central neurobiochemical alterations, especially serotonergic dysfunction, and it is related to serotonergic neurotransmission. Besides that, a wide variety of active metabolites are isolated from any herbal have identified with inhibitory effect of monoamine oxidases (MAO) and serotonergic stimulants and improvements in mood.[24-26] Our molecular docking study is correlated with brain serotonin homeostasis regulation mechanism to maintain serotonin levels based on improvement of 5-HTTLPR (gene of serotonin transporter receptors). Another theory said that there is a direct relationship between dietary tryptophan and brain 5-HT synthesis, the supply of 5-HT in the brain can be exhausted by decreasing the availability of tryptophan.[27] So, that the pharmaceutical product that contain of tryptophan and other active ingredients (made from natural ingredients) where it is compatible with human serotonin transporter receptors (based on our molecular docking study) has potency for mood lifting.

Based on the RMSD analysis of trajectories after simulation by molecular dynamics, it is important to note that our study with RMSD value of 2.61 (or RMSD ≤ 3), shows similar results to the ones reported by Wang et al for serotonin 5-HT1B inhibitor and receptor complexes with RMSD values between 1.4 and 3 Å.[28] The value is mean the similarity between two or more protein structures, and the lower RMSD, the better the model is in comparison to the target structure.

Clinical significance of our study is that based on the discovery that L-tryptophan has a bond energy of -5.69 kcal/mol to human serotonin transporter receptors; and it bonds to hydrogen atoms via amino acid residues Asp98 and Tyr175. It could be a novel to discovery of potential pharmaceutical product from natural resources (a combination of banana and pineapple, our previous and ongoing research) which its effect to improve low mood symptom related to tryptophan depletion among worker (in industrial setting) or community in general.

CONCLUSION

Taken together, this molecular docking study has revealed that L-tryptophan has a bond energy of -5.69 kcal/mol; it bonds to hydrogen atoms via amino acid residues Asp98, Tyr175. L-tryptophan, peonidin, and catechin are the most promising compounds that have good potency as anti-depressant agents through SERT inhibitory activity. However, the potency of the L-tryptophan, peonidin, and catechin is estimated to be lower than sertraline. The catechins in bananas and pineapples as well as the L-tryptophan compound have the potential to affect the human serotonin receptor transporter that plays a role in mood and behavior.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS CONSIDERATION

This in-silico or molecular docking study is a type of study that utilized AutoDock 4.2 software operated by Medical Faculty expert personnel. There is no human trials nor animal testing involved in this research, therefore this study doesn't violate the ethics of research. This study is part of our multi years study of "*MyBrome-banana*, an extract of pineapple and banana and its effect on mood and the serotonin transporter gene (5-HTTLPR)" a preparation of first phase of clinical trial with ethic document no 1866/UN14.2.2.VII.14/LT/2021.

FUNDING

The authors thank to Institute of Research and Community Services (LPPM) of Udayana University for funding this research.

AUTHOR CONTRIBUTION

All authors equally contribute to the study. SP and LPW (research concept and manuscript drafting), CBJL (final manuscript review and English translation), SM (molecular docking expert adviser and manuscript draft review), and RL (expert adviser during in silico study and manuscript draft review).

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