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Research Article

Molecular Docking Study on Ciplukan Fruit (Physalis Angulata L) Using Receptor AChE for Anti-Alzheimer Agents

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ABSTRACT

Neurodegenerative diseases, especially Alzheimer's, have become a global problem with an ever-increasing number of patients, as many as 46 million people worldwide. Alzheimer's is a multifactorial disease, so it has several treatment approaches, such as controlling acetylcholine levels with acetylcholinesterase enzyme inhibitors. The application of chemical drugs is used for healing therapy but can cause side effects. Therefore, using active constituents derived from plants is tested as a potential drug in neurodegenerative disease therapy. The reasons for choosing herbal medicines are the availability of materials, more economical prices, and low toxic effects. Ciplukan fruit (Physalis angulata L) contains polyphenolic compounds from the flavonoid class, which can reduce oxidative stress and have the potential to prevent or treat Alzheimer's disease. Molecular docking simulation was performed with AChE (PDB ID: 4EY7) and receptors based on target proteins for Alzheimer's treatment. The in silico testing phase begins with receptor preparation using the Molegro Molecular Viewer 2.5 application, method validation using the AutoDockTools 1.5.6 application, ligand preparation using the Marvin Sketch application and Lipinski screening, ligand binding to the receptor using the AutoDockTools 1.5.6 application, analysis and visualization of docking results using the BIOVIA Discovery Studio Visualizer. The results showed that the compounds Ergost-5-en-3-ol with a value of -12.85 kcal mol and 1-dehydrohydrocortisone with a value of -10.23 kcal/mol from Ciplukan Fruits (Physalis angulata L) have potential as drug candidates with AChE enzyme inhibition mechanism.

Keywords: Alzheimer's Disease; Acetylcholine; AChE receptor; Ciplukan Fruits; Molecular Docking

Introduction

Neurodegenerative diseases are characterized by progressive degeneration of the structure and function of the central or peripheral nervous system. Common neurodegenerative diseases include Alzheimer's disease and Parkinson's disease [1]. Alzheimer's disease (AD) is commonly associated with decreased cognitive functions such as speech, focus, judgment, and memory [2]. It has been reported that 50 million people worldwide are affected by AD, which is growing, adversely affecting the quality of life, productivity, and economy [3-5].

The pathological changes that trigger AD are unknown, but several hypotheses have been proposed, including a deficiency of cholinergic neurons in the central nervous system. This is because acetylcholine (ACh) plays essential roles in memory, focus, information sensing, and learning.

ACh is hydrolytically degraded by the enzyme Acetylcholinesterase (AChE). Acetylcholinesterase is the main enzyme required to break down the neurotransmitter acetylcholine. The

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hydrolysis of acetylcholine to acetic acid and choline by acetylcholinesterase is necessary for a healthy brain. In addition, BuChE is the sister enzyme of AChE, and inhibition of both enzymes is one approach to treating AD [6-8].

The second hypothesis is that amyloid plaques play a role in explaining the mechanism of AD, where β-amyloid peptides drive a pathological cascade that leads to neuronal death. Amyloid fibrils accumulate in the brain cells and central nervous system of Alzheimer's patients, contributing to the symptoms of dementia [7, 9]. Experimental results show that tau protein and Aβ synergize to form toxic plaques at the synapse [10].

Until now, there has been no effective treatment for AD [4]. Therefore, research to reveal the mechanism and treatment of Alzheimer's is still ongoing. One of them is through the approach of exploring natural material compounds [11-13]. Ciplukan (*Physalis angulata*) is included in the Solanaceae family, including 120 species [14]. Ciplukan is an herbal plant rich in carotenoids, flavonoids, phenolics, and phytosterols [15, 16].

Research on the bioactivity of extracts of Ciplukan plant parts has been conducted, including immunostimulant [17], antitumor [18], anti-inflammatory [19], antimalarial [20], anti-metastasis [21], antibacterial, and antioxidant [22, 23]. The molecular docking method is used in designing treatment against anti-Alzheimer as an initial selection stage from many substrates to predict the interaction between molecules, namely between a test compound and biological receptors. In this study, a molecular docking study was conducted on compounds in ciplukan fruit extract (*Physalis angulata L*) using receptor AChE for anti-Alzheimer

Methods

Phytochemical Screening

Characterization of the content of ciplukan fruit extract (Physalis angulata) was obtained based on the research results by De Oliveira et al. [11] and Pillai et al. [23]. The presence of alkaloids, glycosides, flavonoids, tannins, and phenolics is then tethered to the target receptor.

Receptor Preparation

The required AChE receptors were downloaded from the PDB Protein Data Bank (https://www.rcsb.org/) with PDB IDs: 4EY7. Water molecules not required from native ligands should be separated using Molegro Molecular Viewer software.

Validation of Docking Method

The redocking method validates of the docking method with the help of native ligands found in cytochrome AChE receptors using AutoDock Tools software. Grid box parameters were adjusted to achieve an RMSD value < 2 so that it can be used to tether ligand compounds to receptors. The docking validation results were compared with the ligand position in the original structure contained in the crystal structure.

Ligand Preparation

Ligand compounds were drawn using ChemDraw software and saved in .cdx format (named ligand.cdx). The Lipinski test was conducted using the MarvinSketch application, and the pharmacokinetic test was performed through the PreAdmet website (https://preadmet.webservice.bmdrc.org/). The ligand compounds were protonated, and their conformation was determined using MarvinSketch, followed by depreciation. The ligand conformer with the lowest potential energy value was selected. Protonation was carried out at pH 7.4, and the addition of hydrogen atoms was performed using the Autodocktools application.

Molecular Docking

Molecular docking for ligands and target receptors was performed using AutoDock Tools software. The binding sites were defined as follows: center x = -13.988, center y = -43.906, and center z = 27.109, with a box size of 40x40x40. The results obtained from the docking process are amino acid residues, hydrogen bonds, predicted inhibition constants, free bond energy, and inhibition constant values of each ligand. The interaction between ligand and target receptor was visualized and analyzed using Biovia Discovery Studio.

Result and Discussion

Phytochemical Screening

Phytochemical screening was carried out initially from ciplukan fruit (*Physalis angulata L*) based on the research results of De Oliveira et al. [11] and Pillai et al. [23] which are attached in Table 1, proving that this plant contains the largest

compound structure in alkaloids, glycosides, flavonoids, tannins, and phenolics.

Ligand Screening

In this study, ligand screening results are determined, including the Lipinski test to see the feasibility of drugs in oral preparations, pharmacokinetics to see the description of metabolic processes, and toxicity to see the safety of ligands as shown in Table 1.

The physicochemical properties of a ligand when crossing cell membranes in the body is tested using Lipinski [24]. Lipinski has established rules in selecting compounds as orally active agents expressed in Lipinski's rules: the molecular weight of the compound is less than 500 Da, the hydrogen bond donor should not exceed 5, the hydrogen bond acceptor should not exceed 10, the octanol-water partition coefficient (log P) value is not greater than 5, and the molar refraction value should be in the range of 40-130 [25].

The log P value expresses the fat/water solubility coefficient in the range of 0.4-5.0. Molecules with molecular weight above 500 Da cannot penetrate the cell membrane by diffusion. The higher the log P value, the more hydrophobic the molecule is. If the log P is too high, the molecule will be retained longer in the lipid bilayer and spread more widely in the body, making it toxic. Log P values that are too negative cannot pass through the membrane's lipid bilayer.

The number of hydrogen bond donors and acceptors can affect the hydrogen bonding capacity. The higher the hydrogen bonding capacity, the more energy required for absorption. More hydrogen bond donors and acceptors on the ligand make it easier to bind to water molecules or receptor targets through hydrogen bonding. However, with fewer hydrogen bond donors, detaching the ligand from the water molecule or receptor target will make absorption easier. Lipinski's rule provides insight into the solubility of compounds in cell membranes through passive diffusion.

The pharmacokinetic profile showed that all compounds were well absorbed by the large and small intestine, with some compounds unable to bind strongly to blood plasma proteins. This can reduce the compound's bioavailability, where the compound is lost during the distribution process and does not reach the target organ or where the receptor is located.

Docking Validation

The validation process as the basis of assessment using Root-Mean-Square Deviation (RMSD) value to evaluate the quality of protein-ligand interaction, with a value below 2 Å is considered as a solution with high docking accuracy. The table shows the RMSD value of 1.90, which indicates the theoretical value between the ligand and protein that has validity and meets the criteria. A simulation of the reattachment of native ligand compound molecules at receptors can be seen in Figure 1.

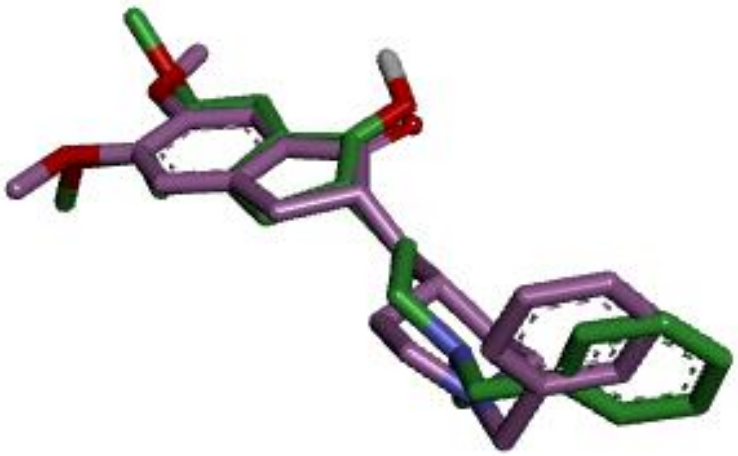

Figure 1. Simulation of Reattachment of Native Ligand Compound Molecules at Receptors

Docking Results, Analysis and Visualization

The molecular tethering analysis started with evaluating the free energy of binding (ΔG) at each receptor as displayed in Table 2. A low value of ΔG indicates a more significant interaction between the receptor and ligand for anti-Alzheimer Disease ability.

Macromolecules that bind to the test ligand will generate a series of conformations ordered by the best or lowest ΔG value. The conformations are obtained from 100 conformations in the interaction between the cytochrome receptor and the ligand. The test results showed that three compounds topped the list based on ΔG values, namely Sinapic, *p*-cumarate, and syiringic.

The results of the molecular tethering process show that there are six compounds derived from cipulkan fruit that have high binding affinity ability and have the potential to inhibit AChE receptors (PDB ID: 4EY7) as shown in Table 2.

The free energy value (ΔG) is comparable to the value of the inhibition constant (IC). The inhibition constant describes the concentration required to inhibit free radicals. The lower the IC value, the stronger the bond between the ligand and the receptor [26]. Table. 2 shows that all test ligand compounds have higher inhibitory values than the native ligand (Donepezil).

In Table 3, analysis was performed to evaluate the bonds and interactions that occur between the amino acids and the test ligands. The study focused on hydrogen bonding as it has more strength than Van Der Waals interactions (both aromatic and hydrophobic) [27]. Hydrogen bonding refers to the interaction between an atom with a pair of free electrons and a hydrogen atom bound to another electronegative atom, such as N, O, S, or F [28]. A two-dimensional visualization of the interaction between the test ligand and the AChE receptor can be seen in the following Figure 2.

Based on the table, some compounds form the highest number of hydrogen bonds, namely 1-dehydrohydrocortisone forming 3 hydrogen bonds. This number exceeds the hydrogen bonds formed in the original ligand (Donepezil). It is important to note that the number of hydrogen bonds formed can affect the free energy value of the ligand compound when it binds to the receptor. In docking simulations, hydrogen bonds have a more significant influence than hydrophobic interactions in determining the resulting free energy value.

Visualization results show that the test ligand occupies the same binding site as the native ligand, with the dominant interaction being Van der Waals interaction with similarity at amino acid residue Gly448 and hydrophobic interaction (π-π stacked) at amino acid residues Tyr337, Tyr341, and Phe338. Based on the results of molecular tethering studies, the compounds 1-dehydrohydrocortisone and Ergost-5-en-3-ol are predicted to inhibit the hydrolysis process of the AChE enzyme. Other benefits in some literature for Ergost-5-en-3-ol (3 beta), known as cholesterol-lowering and anticancer [29] while hydrocortisone (HC) is proven to inhibit neuroinflammation and oxidative stress [30].

Table 1. Lipinsky Pharmacokinetic, Toxicity Test Results from Phytochemicals Physalis angulate

No	Compound	Lipinsky					Pharmacokinetic		
		Molecular weight	Proton Donor	Proton Aceptor	Log P	Refracto molar	$CaCO_2$	HIA	PBB
		<500 g/mol	<5	<10	<5	40-130			
1	Gallic	170.11	4	5	0.72	39.25	14.50	54.11	47.91
2	Protocatechuic	154.12	3	4	1.02	37.26	18.70	75.00	16.74
3	*p*-hydroxybenzoic	138.12	2	3	1.33	35.3	20.44	88.21	5.72
4	Vanilic	168.14	2	4	1.17	41.76	19.96	85.43	37.53
5	Caffeic	180.15	3	4	1.53	47.02	21.10	82.41	26.55
6	Syringic	198.17	2	5	1.01	48.22	18.80	82.08	57.64
7	*p*-coumaric	164.15	2	3	1.83	45.04	21.11	92.12	45.87
8	Ferullic	194.18	2	4	1.67	51.5	21.14	90.63	39.35

9	Sinapic	224.21	2	5	1.52	57.97	19.96	88.57	39.64
10	Lauric acid	200.31	1	2	4.48	58.68	23.41	97.00	100
11	Methyl palmitate	270.45	0	1	6.4	81.85	45.83	100	100
12	Palmitic acid	256.42	1	2	6.26	77.08	27.52	98.29	100
13	Methyl, linoleate	294.47	0	1	6.57	93.29	47.11	100	100
14	Linoleic acid	280.44	1	2	6.42	88.52	30.35	98.37	100
15	1,2-Benzenedicarboxylic acid	376.52	0	2	7.58	110.01	47.10	97.81	100
16	Trihydroxy-16α,17α-Propyl methylene dioxy pregna-1,4-diene-3,20-dione(1dehydrohydrocortisone)	360.444	3	5	1.27	98.49	17.72	88.00	69.87
17	5-(7a-Isopropenyl-4,5-dimethyl-octahydroinden-4-yl)-3-methyl pent-2-enal	288.46	0	1	5.32	91	28.04	100	100
18	Acetic acid, 13-hydroxy-4,4,6a,6b,8a,11,11,14 Boctamethyldocosahydropicen -3-ylester	486.76	1	2	6.95	141.8	50.82	100	100
19	1-Pyrrolidinebutanoic acid	535.69	1	6	4.2	146.75	41.30	97.60	88.069
20	Cholest-5-ene-16,22-dione,3 ,26-dihydroxy-, 3-acetate,(20S,25R)	472.65	1	4	4.35	132.95	227.257	96.930	93.091
21	Ergost-5-en-3-ol	400.68	1	1	7.4	125.17	51.40	100	100
22	Lupenyl acetate	468.75	0	1	7.89	140.06	51.03	100	100
23	Alpha-tocopherol	430.70	1	2	10.51	135.37	29.11	97.83	100

Table 2. Docking Result of The Test Compound from Ciplukan Fruit on Ache Receptor

No.	Ligand	Energy Binding (Kkal/mol)	inhibition constant (μM)
1	*p*-hidroksi benzoat	-4.27	738.5
2	Syiringic	-4.69	363.36
3	*p*-kumarat	-4.94	238.41
4	Sinapic	-5.76	92.02
5	Ergost-5-en-3-ol, acetate,(3β,24R)-	-12.85	383.74
6	Trihydroxy-16α,17α-Propyl methylene dioxy pregna-1,4-diene-3,20-dione (1-dehydrohydrocortisone)	-10.23	31.56 nM
7	Native (Donepezil)	-9.67	43.70 nM

Table 3. Interaction Results Between Test Ligand and Native Ligand

Compound	Interactions				
	Hydrogen Bond	Hydrophobic	Electrostatic	Unfavorable	Van Der Waal
1-dehydrohydrocorti-sone	Glu^{202} Tyr^{133} Tyr^{124} Phe^{295}	Tyr^{341} Trp^{86} Tyr^{337} Phe^{338}	Lys^{213}		Val^{294} Phe^{297} Trp^{286} Asp^{74} Gly^{122} Gly^{120} Leu^{130} Ile^{451} Gly^{448} His^{447} Gly^{121}
Ergost-5-en-3-ol,	Phe^{295}	Ile^{243}	Tyr^{337} Tyr^{341} Trp^{86} Phe^{297} His^{447} Phe^{338}		Trp^{236} Ala^{204} Glu^{202} Gly^{121} Ser^{203} Tyr^{124} Trp^{286} Arg^{296} Gly^{448}
Native	Arg^{296} Ser^{293}	Tyr^{341} Phe^{338} Trp^{86} Tyr^{337} Trp^{286}			Gly^{342} Glu^{292} Leu^{289} Val^{294} Phe^{297} Asp^{74} Phe^{295} Tyr^{124} Gly^{448} His^{447}

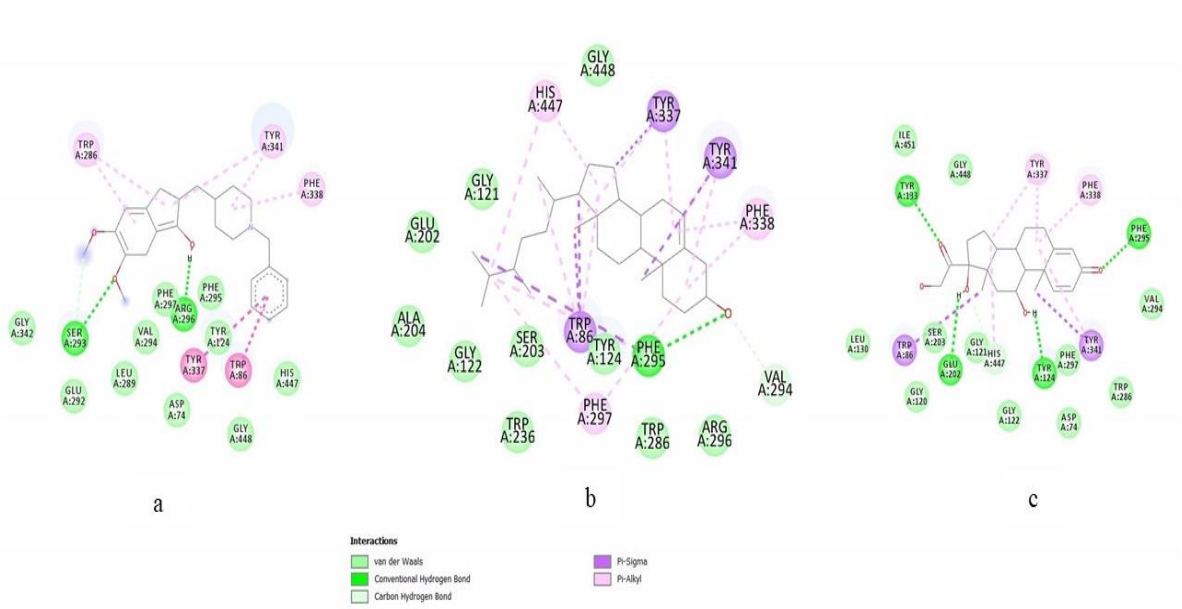

Figure 2. Visualization of Dioxy Compounds (A) and Ergos (B) With Ache Receptor Native Ligand (C)

Conclusion

Based on the research that has been done, it can be concluded that the compounds Ergost-5-en-3-ol and 1-dehydrohydrocortisone in Ciplukan (Physalis angulata) show potential as drug candidates with anti-Alzheimer Diese mechanism of AChE enzyme inhibition. Further exploration of the active compounds contained in ciplukan fruit and comparing them with other plant parts is needed.

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References

1. Jamir K, Ganguly R, Seshagirirao K (2020) ZCPG, a cysteine protease from *Zingiber montanum* rhizome exhibits enhanced anti-inflammatory and acetylcholinesterase inhibition potential. Int J Biol Macromol. 163:2429-2438. https://doi.org/10.1016/j.ijbiomac.2020.09.097.
2. Pievani M, De Haan W, Wu T, Seeley WW, Frisoni GB (2011) Functional network disruption in the degenerative dementias. Lancet Neurol. 10:829-843. https://doi.org/10.1016/S1474-4422(11)70158-2.
3. Beshir SA, Aadithsoorya AM, Parveen A, Goh SSL, Hussain N, Menon VB (2022) Aducanumab therapy to treat Alzheimer's disease: A narrative review. Int J Alzheimers Dis. 2022:1-10. https://doi.org/10.1155/2022/9343514.
4. Guo T, Zhang D, Zeng Y, Huang TY, Xu H, Zhao Y (2020) Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol Neurodegener. 15:40. https://doi.org/10.1186/s13024-020-00391-7.
5. Peterson AC, Li CR (2018) Noradrenergic dysfunction in Alzheimer's and Parkinson's diseases—An overview of imaging studies. Front Aging Neurosci. 10:127. https://doi.org/10.3389/fnagi.2018.00127.
6. Giacobini E (1998) Cholinergic foundations of Alzheimer's disease therapy. J Physiol-Paris. 92:283-287. https://doi.org/10.1016/S0928-4257(98)80034-X.
7. Ferreira FL, Rodrigues VG, Silva FC, Matildes BLG, Takahashi JA, Silva GDF, Duarte LP, Oliveira DM, Filho SAV (2017) *Maytenus distichophylla* and *Salacia crassifolia*: Source of products with potential acetylcholinesterase inhibition. Rev Bras Farmacogn. 27:471-474. https://doi.org/10.1016/j.bjp.2016.12.006.
8. Nordberg A, Ballard C, Bullock R, Darreh-Shori T, Somogyi M (2013) A review of butyrylcholinesterase as a therapeutic target in the treatment of Alzheimer's disease. Prim Care Companion CNS Disord. 15. https://doi.org/10.4088/PCC.12r01412.
9. Pasandideh S, Arasteh A (2021) Evaluation of antioxidant and inhibitory properties of *Citrus aurantium* L. on the acetylcholinesterase activity and the production of amyloid nano-bio fibrils. Int J Biol Macromol. 182:366-372. https://doi.org/10.1016/j.ijbiomac.2021.04.043.
10. Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu G-Q, Mucke L (2007) Reducing endogenous tau ameliorates amyloid ß-induced deficits in an Alzheimer's disease mouse model. Science. 316:750-754.

https://doi.org/10.1126/science.1141736.
11. De Oliveira AM, Malunga LN, Perussello CA, Beta T, Ribani RH (2020) Phenolic acids from fruits of *Physalis angulata* L. in two stages of maturation. South Afr J Bot. 131:448-453. https://doi.org/10.1016/j.sajb.2020.02.029.
12. He Z, Guo JL, McBride JD, Narasimhan S, Kim H, Changolkar L, Zhang B, Gathagan RJ, Yue C, Dengler C, Stieber A, Nitla M, Coulter DA, Abel T, Brunden KR, Trojanowski JQ, Lee VM-Y (2018) Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. Nat Med 24:29-38. https://doi.org/10.1038/nm.4443.
13. Ibrahim NH, Yahaya MF, Mohamed W, Teoh SL, Hui CK, Kumar J (2020) Pharmacotherapy of Alzheimer's disease: Seeking clarity in a time of uncertainty. Front Pharmacol. 11:261. https://doi.org/10.3389/fphar.2020.00261.
14. Ozaslan C, Farooq S, Onen H, Ozcan S, Bukun B, Gunal H (2017) Germination biology of two invasive Physalis species and implications for their management in arid and semi-arid regions. Sci Rep. 7:16960. https://doi.org/10.1038/s41598-017-17169-5.
15. Bertoncelli DJ, Oliveira MDC, Bolina CDO, Passos AID, Ariati AC, Ortolan AO (2016) Chemical characteristics of fruits of two species of Physalis under nitrogen fertilization. Afr J Agric Res. 11:1872-1878. https://doi.org/10.5897/AJAR2016.11031.
16. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA (2013) Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. Sleep. 36:1027-1032. https://doi.org/10.5665/sleep.2802.
17. Sisley GMM, Horna FYM, Isern FR, Aranda-Ventura J, Vallejo JV (2017) Actividad inmunoestimulante del extracto acuoso liofilizado de la planta entera de *Physalis angulata* L. en ratas *Albinas cepa* Holtzman. Rev Peru Med Exp Salud Pública. 2:38-46.
18. Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R (2006) AMPAR removal underlies Aβ-induced synaptic depression and dendritic spine loss. Neuron. 52:831-843. https://doi.org/10.1016/j.neuron.2006.10.035.
19. Rivera DE, Ocampo YC, Castro JP, Barrios L, Diaz F, Franco LA (2019) A screening of plants used in Colombian traditional medicine revealed the anti-inflammatory potential of *Physalis angulata* calyces. Saudi J Biol Sci. 26:1758-1766. https://doi.org/10.1016/j.sjbs.2018.05.030.
20. Lusakibanza M, Mesia G, Tona G, Karemere S, Lukuka A, Tits M, Angenot L, Frédérich M (2010) In vitro and in vivo antimalarial and cytotoxic activity of five plants used in Congolese traditional medicine. J Ethnopharmacol. 129:398-402. https://doi.org/10.1016/j.jep.2010.04.007.
21. Hseu Y-C, Chen S-C, Lin W-H, Hung D-Z, Lin M-K, Kuo Y-H, Wang M-T, Cho H-J, Wang L, Yang H-L (2011) *Toona sinensis* (leaf extracts) inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis in vascular endothelial cells. J Ethnopharmacol. 134:111-121. https://doi.org/10.1016/j.jep.2010.11.058.
22. Pietro RCLR, Kashima S, Sato DN, Januário AH, Franca SC (2000) In vitro antimycobacterial activities of *Physalis angulata* L. Phytomedicine. 7:335-338. https://doi.org/10.1016/S0944-7113(00)80052-5.
23. Pillai AKB, Chu JJH, Mariappan V, Jean-Pierre AR (2022) Platelets in the pathogenesis of flavivirus disease. Curr Opin Virol. 52:220-228. https://doi.org/10.1016/j.coviro.2021.12.007.
24. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2012) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 64:4-17. https://doi.org/10.1016/j.addr.2012.09.019.
25. Ortiz CLD, Completo GC, Nacario RC, Nellas RB (2019) Potential inhibitors of galactofuranosyltransferase 2 (GlfT2): Molecular docking, 3D-QSAR, and in silico ADMETox studies. Sci Rep. 9:17096. https://doi.org/10.1038/s41598-019-52764-8.
26. Puspita PJ, Liliyani NPP, Ambarsari L (2022) In silico analysis of active compounds of avocado fruit (*Persea americana* Mill.) as tyrosinase enzyme inhibitors. Curr Biochem. 9:73-87. https://doi.org/10.29244/cb.9.2.3.
27. Bulusu G, Desiraju GR (2020) Strong and weak hydrogen bonds in protein-ligand recognition. J Indian Inst Sci. 100:31-41. https://doi.org/10.1007/s41745-019-00141-9.
28. Mishra S, Suryaprakash N (2017) Intramolecular hydrogen bonding involving organic fluorine: NMR investigations corroborated by DFT-based theoretical calculations. Molecules. 22:423. https://doi.org/10.3390/molecules22030423.
29. Choi, J. M., Lee, E. O., Lee, H. J., Kim, K. H., Ahn, K. S., Shim, B. S., Kim, N. I., Song, M. C., Baek, N. I., & Kim, S. H. (2007). Identification of campesterol from Chrysanthemum coronarium L. and its antiangiogenic activities. Phytotherapy research : PTR, 21(10), 954–959. https://doi.org/10.1002/ptr.2189
30. Li, J., Chen, L., Liu, S., Sun, Y., & Zhen, L. (2013). Hydrocortisone Mitigates Alzheimer 's-Related Cognitive Decline through Modulating Oxidative Stress and Neuroinflammation. Inflammation in Psychiatry, 28, 20–32. https://doi.org/10.1159/000343965