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Research Article

Molecular dynamic of omega-3 compounds as an anti-obesity agent into GPR-120 receptor

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Abstract

Obesity is a cause of comorbid diseases such as type 2 diabetes mellitus, dyslipidemia, hypertension which is based on low-level chronic inflammation. The GPR-120 receptor plays a role in insulin sensitization which is related to diabetes mellitus which is a comorbid obesity. Omega-3 fatty acids are believed to possess anti-inflammatory properties, hence potentially serving as a preventive measure against obesity-related comorbidities. The aim of this study is to do a stability analysis of the binding affinity between nine specific chemicals derived from omega-3 and the active site of the human GPR120 receptor using molecular dynamics simulations. Docking analysis was performed using Discovery Studio Visualizer, AutoDock Tools 1.5.6, and molecular dynamic simulation with AMBER 16. In this study, we used neurotensin 8–13 as a natural ligand to bind with the neurotensin receptor. Based on the neurotensin receptor docking results, the ΔG values for the following compounds are close to the values for neurotensin 8–13 -6.41 kcal/mol; docosahexaenoic acid -8.96 kcal/mol; eicosapentaenoic acid -7.41 kcal/mol; and heneicosapentaenoic acid -6.34 kcal/mol. Neurotensin 8–13 forms hydrogen bonds with TYR146, ARG213, and PHE344 of the neurotensin receptor, whereas docosahexaenoic acid forms hydrogen bonds with TYR146. Meanwhile, the average RMSD fluctuations for each system, namely docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, were 0.672, 0.437, and 0.650, respectively. The SASA of the neurotensin receptor-ligand complex showed similar fluctuations, with the average values for docosahexaenoic acid, eicosapentaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, and heneicosapentaenoic acid, and heneicosapentaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, eicosapentaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, and heneicosapentaenoic acid, and heneicosapentaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, and heneicosapentaenoi

Keywords

comorbidity, fatty acids, GPR120, obesity, Omega-3

Introduction

Obesity is a highly prevalent global health issue. The condition under consideration is defined by the presence of an excessive amount of adipose tissue, accompanied by an elevated quantity and enlarged size of white adipocytes, and a body mass index (BMI) equal to or greater than 30 kg/m^2 (Salam 2023). In the present era, obesity has emerged as a global health issue of significant concern. Obesity is considered a significant risk factor for the development of various health conditions, including heart disease, stroke, diabetes mellitus, osteoarthritis (OA), and

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hypertension (Mohamed et al. 2014). There are a multitude of potential interventions for the treatment of obesity, including but not limited to weight control strategies, pharmaceutical interventions, and surgical procedures. Various dietary interventions, including the ketogenic diet, low-carbohydrate diet, high-protein diet, high-fat diet, and low-energy diets, are employed in the management of obesity. These interventions are implemented alongside recognized behavior-change approaches and social support, typically on a short-term basis (Huei et al. 2020). Despite the presence of several adverse effects, that have the potential to diminish one's quality of life. Given these circumstances, the utilization of natural substances emerges as the most feasible solution (Morgan et al. 2017).

Omega-3, an indispensable nutrient, has demonstrated efficacy in facilitating weight loss through its capacity to reduce the buildup of adipose tissue. Omega-3 fatty acids assume a crucial function in the regulation of lipid metabolism and serve as sensors with anti-inflammatory properties (Calder 2018). This is the preventive mechanism for obesity. The relationship between comorbidity and its impact on insulin resistance, a known contributor to obesity-associated metabolic illnesses, is not yet fully understood. However, there have been reports suggesting that comorbidity may ameliorate insulin resistance by interacting with proteins such as the peroxisome proliferator-activated receptor PPARy and GPR120 (Song et al. 2017). The GPR120 receptor is responsible for recognizing and binding to long-chain fatty acids. It is found in various locations within the body, including small intestine endocrine cells, L cells, and adipose tissue. It has been shown that turning on GPR120 makes the incretin hormone GLP-1 come out more quickly. This has been linked to good effects on anti-metabolic syndrome. Additionally, the GPR120 receptor has been implicated in the regulation of lipid metabolism (Psimadas et al. 2012; Halder et al. 2013).

To date, the precise mechanism underlying the impact of omega-3, particularly in relation to lipid and glucose metabolism in individuals with obesity, remains an area that warrants more investigation. The existing body of published systematic studies has yielded inconclusive findings on the efficacy of omega-3 supplementation in the context of obesity. The findings from studies conducted on both experimental animals and humans have yielded inconsistent results. As a result, the precise mechanism by which omega-3 fatty acids impact obesity remains uncertain. However, the administration of omega-3 supplementation has promise in mitigating the development of comorbidities associated with obesity. The presence of chronic, subclinical inflammation has been recognized as a significant contributing factor in the pathogenesis of metabolic syndrome in individuals who are obese. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), crucial constituents of omega-3, possess the ability to regulate insulin sensitivity and glucose utilization

in adipocytes (Huang et al. 2019). This pertains to the capacity of the substance to induce GPR 120 activation. Omega-3 fatty acids have the potential to serve as a viable alternative for supplementation, offering a safe and efficacious means of reducing obesity.

Materials and methods

Materials

The hardware included a PC running Windows 7 Home 64-bit operating system, Intel Core (TM) i5- 3337U CPU 1.80GHz, NVIDIA Ge Force GTS 710M Graphic Card and 4 GB CPU memory (RAM). Analysis was performed with the following software: Discovery Studio Visualizer, AutoDock Tools 1.5.6 and Molecular dynamic simulation with AMBER 16.

The neurotensin receptor crystal structure (PDB code 4GRV), obtained from the Protein Data Bank online database (http://www.rcsb.org/pdb), at a resolution of 2.80 Å. Data and structures of Neurotensin 8–13 and compounds from omega-3 fatty acids were obtained from the binding database (https://www.pubchem.org). A total of 9 test compounds (test ligands) were obtained from research journals. The structures are shown in Table 1.

Preparation of ligand structure

Test ligand structures of the 9 compounds from omega-3 fatty acids and natural ligand are shown in Table 1. Compounds from omega-3 fatty acids and natural ligand were made into two-dimensional (2D) structures that were then converted into three-dimensional (3D) structures using ChemDraw 8.0.

Table 1. Two-dimensional structures of Neurotensin 8–13 and compounds from omega-3 fatty acids.



Preparation of protein receptor

The crystal structure of the neurotensin receptor crystal structure (PDB code 4GRV) was obtained from the PDB database (http/www/pdbbeta.rscb.org/pdb) with 2.80 Å resolution. Neurotensin 8–13 is a natural ligand of the neurotensin receptor. The crystal structure of the neurotensin receptor used is neurotensin 8–13 and other residues. Neurotensin is a 13 amino acid neuropeptide that plays a role in the regulation of lutein hormone and prolactin release and also has interactions with the dopaminergic system. Plasma neurotensin levels in the intestine increase after fat digestion, we used neurotensin positions 8–13 in the neurotensin receptor crystal structure as positions for all docking analyses.

Validation of the molecular docking method

Validation of the molecular docking method is performed by redocking a neurotensin 8–13 to a target protein that has been removed from the neurotensin receptor using the AutoDock Tools 1.5.6 program. The method is deemed successful if the root-mean-square deviation (RMSD) value returned is < 2 Å (Ramírez and Caballero 2018).

Docking simulation of the Neurotensin 8–13 and Test Ligands (compounds from omega-3 fatty acids)

The 3D structure of the Neurotensin 8–13 and Test Ligands were created and optimized using Chem3D Ultra 8.0. Structural optimization was carried out on the 3D structure of the reference and test ligands using the MM2 semi-empirical computational method. Calculations were carried out with geometry optimization on the minimum energy of the 3D structure of the compound to be used.

The structure of the neurotensin receptor (4GRV), neurotensin 8–13 and test ligands in the pdb format were converted into pdbqt format using the AutoDock Tools 1.5.6 program. The docking method was performed by tethering each ligand to neurotensin receptors using the tether coordinates (Grid Center) x = 40, y = 40, z = 40 Å and the Grid Box size coordinates x = 90.024, y = -11.196, and z = 68.538 Å. Each ligand was in a stable condition and interacted with biomacromolecules in a rigid condition.

Docking results were assessed for binding energy and chemical interactions such as hydrogen bonds, hydrophobic interactions and bond distances. These were visualized using the Discovery Studio Visualizer program. Discovery Studio is a comprehensive software suite for analyzing and modeling molecular structures, sequences, and other data of relevance to life science researchers. The product includes functionality for viewing and editing data along with tools for performing basic data analysis.

Molecular dynamic (MD) simulation

MD simulations to determine the ligand with the lowest binding energy at the neurotensin receptor (Bowers 1989). Ligand and topology parameters were determined using ACPYPE (Essmann et al. 1995). To calculate the electrostatic force at a certain distance, the Ewald particle mesh method is used (Sousa Da Silva and Vranken 2012). Enter Cl- and Na+ ions to neutralize the system. The solution is constructed using the TIP3P water cube model (Mark and Nilsson 2001). The minimization process, 310 K heating, temperature acclimatization, and pressure acclimatization are all part of the simulation setup steps. A 2 fs time step MD stage is produced in 100 ns. By estimating the binding free energy by using the MM-PBSA method, solvent accessible surface area (SASA), and RMSD root mean squared (RMSF) fluctuations from the docking, a post-MD simulation analysis was completed.

Results and discussion

Preparation of protein receptor

The neurotensin receptor binds to natural ligands with chemical bonds. Natural ligands that interact with the neurotensin receptors (4GRV), namely neurotensin 8–13, were separated using Discovery Studio Visualizer software. The structure of the neurotensin receptor and neurotensin 8–13 are depicted in Fig. 1.

Besides the Neurotensin receptor, exploration of the docking process requires a ligand. Ligand selection used in the process of tethering the target protein is based on initial screening results according to Lipinski's Rule of Five. Ligands that are considered to have binding potential can enter the cell membrane to be absorbed by the body if they meet the following criteria: (1) molecular weight < 500 g/ mol; (2) < 5 proton donor groups for hydrogen bonds; (3) < 10 proton acceptor groups for hydrogen bonds; and (4) a logarithmic value of the partition coefficient in water and 1-octanol < 5 (Lipinski et al. 2012). The neurotensin receptor (4GRV) forms a hydrogen bond of 2.14, 2.36 and 2.16 Å with neurotensin 8-13. The -NH2 and -CO group in neurotensin 8-13 forms a hydrogen bond with TYR146, ARG213, and PHE344 of the neurotensin receptor with a binding energy of -6.41 kcal/mol. A smaller ΔG value indicates that the bonds are more balanced. Based on Lipinski's criteria, compounds from omega-3 fatty acids are predicted to have good bioavailability in the body. Bioavailability is the ability of a drug to be absorbed and circulated in the body (Veber et al. 2002).

Validation of molecular docking method

Analysis of the bonds formed between neurotensin 8–13 and the neurotensin receptor (4GRV) was performed using Discovery Studio Visualizer software. The analysis results of the bonds formed are shown in Table 2.



Figure 1. A. Neurotensin receptor (4GRV) and B. Overlay of the docked pose of Neurotensin 8–13 with the co-crystallized ligand 4GRV.



Figure 2. A. Visualization of interactions between Neurotensin 8–13 and receptors (4GRV) and **B.** Visualization of molecular docking between the receptor 4GRV and natural ligand.

Table 2. Validation results for the molecular docking method.

Protein	Compound	Binding energy (kcal/mol)	RMSD	Hydrogen bond distance (Å)	Amino acids that bind	Nearest residues
4GRV	Neurotensin 8–13	-6.41	0.31	2.14; 2.36; 2.16	TYR146; ARG213; PHE344	VAL224

Note: RMSD, root-mean-square deviation.

The molecular docking method is validated by redocking neurotensin 8–13 to the target protein. In this study, we redocked the neurotensin 8–13 to the neurotensin receptor (4GRV) at a resolution of 2.80 Å. The redocking results had an RMSD value of 0.31 Å and a bond energy of -6.41 kcal/mol. According to (Ramírez and Caballero 2018), an RMSD \leq 3Å and a bond energy similar to what we obtained with the redocking results indicates that the interaction between the ligand and the receptor is at a low energy condition; thus, the molecule will be more stable. Hydrogen bonds that form between TYR146, ARG213, and PHE344 and the functional group of neurotensin 8–13 showed a value of 2.14, 2.36, and 2.16 Å. Interactions that occur with VAL224 are predicted to play an important role in the neurotensin receptor ligand binding domain.

Docking simulation of the Neurotensin 8–13 and Test Ligands (compounds from omega-3 fatty acids

Docking simulation of neurotensin 8–13 and Test Ligands (compounds from omega-3 fatty acids) was performed with the AutoDock Tools 1.5.6 program. The same coordinate settings at the site of the interaction between Neurotensin 8–13 and the neurotensin receptor (4GRV) were used for the docking simulation. This analysis was performed for binding energy. There was a hydrogen bond between the test/reference ligand and the neurotensin receptor. Docking simulation results are shown in Table 3.

Visualization of the docking interactions that occur between docosahexaenoic acid and receptors (4GRV) to the neurotensin receptor (4GRV) are shown in Fig. 3. Compound docosahexaenoic has the best binding energy to the neurotensin receptor compared to other compounds.

Docking is a process of tethering interactions between ligands and proteins; it allows one to predict the position and orientation of ligands when bound to protein receptors (Abdurrahman et al. 2021). The docking process produces ΔG , which is the stability parameter of the



Figure 3. A. Visualization of interactions between docosahexaenoic acid and receptors (GPR120 (4GRV)) and **B.** Visualization of molecular docking between the receptor GPR120 (4GRV) and docosahexaenoic acid.

Compound	Binding	Hydrogen	Hydrogen	Nearest	
-	energy	bond	bonds	amino acid	
	(kcal/mol)	distance (Å)		residue(s)	
alpha-linolenic acid	-7.0	1.91; 2.89;	ARG149;	VAL224	
		1.99; 1.91	TYR251;		
			ARG327;		
			ARG328		
Docosahexaenoic acid	-8.96	2.15; 2.15;	TYR351;	PHE344;	
		2.18; 2.30;	ARG149;	TRY347;	
		2.00	TYR146;	HIS348;	
			ARG327;	TRP339	
			ARG328		
Docosapentaenoic acid	-7.08	1.69; 2.08	ARG327;	PHE128;	
			ARG328	PHE344;	
				TRY347;	
				TRP339	
Eicosapentaenoic acid	-7.41	1.71; 2.03;	ARG327;	HIS132;	
		2.56	ARG149;	HIS348	
			TYR351		
Eicosatetraenoic acid	-7.63	1.95; 1.78	ARG149;	PHE128;	
			ARG328	HIS348	
Eicosatrienoic acid	-7.24	2.55; 1.96;	ARG327;	-	
		1.96	TYR146;		
			TYR351		
heneicosapentaenoic acid	-7.69	2.03; 2.06	ARG327;	TRP339	
			ARG328		
hexadecatrienoic acid	-7.18	1.99; 2.01	ARG327;	TRP339	
			ARG328		
stearidonic acid	-7.17	1.96; 2.09	TYR351;	PHE331;	
			ARG149	TRP339	

 Table 3. Docking simulation results.

conformation between the ligand and the neurotensin receptor. In this study, we used neurotensin 8–13 as natural ligands bind with neurotensin receptor. Based on the neurotensin receptor docking results, the ΔG values for the following compounds are close to the value for neurotensin 8–13 (-6.41 kcal/mol; Table 2): docosahexaenoic acid -8.96 kcal/mol, eicosapentaenoic acid -7.41 kcal/mol, and heneicosapentaenoic acid -6.34 kcal/mol. Therefore, compounds from omega-3 fatty acids of neurotensin 8–13 and the neurotensin receptor occurs at TYR146, ARG213, and PHE344, with the other closest amino acid residues being VAL224. Docosahexaenoic acid has lower binding energy than neurotensin 8–13. This can be caused by the

presence of proximal amino acids of docosahexaenoic acid that are also found in the neurotensin 8-13. Factors that cause the binding energy for test compounds to be higher than neurotensin 8-13 are different amino acid residues forming a hydrogen bond with the neurotensin receptor. Neurotensin 8-13 form hydrogen bonds with TYR146, ARG213, and PHE344 of the neurotensin receptor, whereas docosahexaenoic acid forms hydrogen bonds with TYR146. Interactions between neurotensin 8-13 at TYR146, ARG213, and PHE344, including the -NH2 side chain with the -CO functional group, provide hydrogen bonds that are in the mooring region of 2.14, 2.36, and 2.16 Å. Additional hydrophobic interactions play a role in determining ligand stability with the neurotensin receptor. Hydrophobic interactions, which repel liquid, are more likely to group together in the globular structure of proteins (Abdurrahman et al. 2023). This study fits with previous research that shows that GPR120 has promising agonistic activity when it interacts with certain amino acid residues, such as ARG327 and TYR146. The fact that Eicosapentaenoic acid, docosahexaenoic acid, and eicosatetraenoic acid have binding energies of -9.4, -8.72, and -8.15 kcal/mol shows that they have a lot of potential as agonists. In comparison, the neurotensin ligand exhibits a lower binding energy of -6.31 kcal/mol. All compounds satisfy the absorption and distribution criteria, indicating that the chosen compounds possess the capacity to mitigate obesity by targeting PPARy and GPR120 (Megawati et al. 2021). The formation of hydrophobic bonds can minimize interactions with nonpolar residues in water. This interaction is strengthened by the composition of surrounding functional groups that play a role in the interaction of the reference ligand, more specifically, the basic -NH and -CO groups, which contain the amino acids PHE344. However, the hydrophobic interactions of the natural ligands and neurotensin 8-13 involve the residues VAL224. Hydrophobic interactions of docosahexaenoic acid involve the residues PHE344 and TRP339. Residues involved in hydrophobic interactions are nonpolar amino acids, which form clusters towards the center of proteins.

Molecular dynamic simulation

The MD simulation was carried out using the chemical docosahexaenoic acid, eicosapentaenoic acid and heneicosapentaenoic acid, where the two test compounds had the same ΔG value. The RMSD and RMSF analysis of the receptor–ligand complex using GROMACS 2016 was carried out by measuring the stability of the RMSD and RMSF values in the system during the simulation (Fig. 4).



Figure 4. RMSD (a) and RMSF (b) value of docosahexaenoic acid (blue), eicosapentaenoic acid (maroon), and heneicosapentaenoic acid (green).

RMSD analysis was used to assess the stability of the complex over time, while RMSF analysis assessed the stability per amino acid.

Assessed the stability per amino acid. Docosahexaenoic acid, eicosapentaenoic acid and heneicosapentaenoic acid, with the best docking score of the metabolites, was simulated with MD and its complex stability which are neurotensin receptor blockers. Docosahexaenoic acid, eicosapentaenoic acid and heneicosapentaenoic acid in complex with the neurotensin receptor showed the same high fluctuations. Meanwhile, the average RMSD fluctuations for each system, namely Docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, were 0.672, 0.437 and 0.650, respectively. The average RMSD showed that (eicosapentaenoic acid) had the lowest fluctuation, which indicates that the ligand has reached a stable conformation that binds to the protein (Abdurrahman et al. 2022). This study aligns with other research that has demonstrated the stability of omega-3 molecules, including docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and heneicosapentaenoic acid (HPA), using the molecular dynamics modeling approach. Docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and heneicosapentaenoic acid (HPA) can be used as primary therapeutic agents to bind to PPAR- and GPR120 receptors in order to treat and prevent obesity (Musfiroh

et al. 2021, 2022). The amino acid fluctuations of the two receptor complex systems calculated by RMSF showed the same pattern in all regions. Residues 53, 93, 185, 215, 339, 1036, and 1048 on the neurotensin receptor showed higher fluctuations than the other residues. These residues are the amino acids responsible for the loop region in the protein structure.

SASA was analyzed for 100 ns of simulated MD trajectory, as shown in Fig. 5. The SASA of the neurotensin receptor–ligand complex on the graph for (Docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid) showed similar fluctuations; the average values for Docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid were 230.40, 229.89 and 230.20 nm², respectively. A low SASA value indicates an increasingly stable complex system (Ramírez and Caballero 2018). This analysis correlated with that of the RMSD value, which indicated that (eicosapentaenoic acid) had better stability at the neurotensin receptor.

To forecast the conformational changes in proteins that make them accessible to water molecules, the SASA was the result during simulations. Fig. 5 illustrates the results of this investigation, which demonstrated that eicosapentaenoic acid was more stable at the neurotensin m accessible to water molecules, the make them accessible to water molecules, the SASA was the result during simulations. Fig. 5 illustrates the results of this investigation, which demonstrated that eicosapentaenoic acid was more stable at the neurotensin.



Figure 5. SASA plot of docosahexaenoic acid (blue), eicosapentaenoic acid (maroon), and heneicosapentaenoic acid (green).

SASA was analyzed for 100 ns of simulated MD trajectory, as shown in Fig. 5. The SASA of the neurotensin receptor-ligand complex on the graph for (Docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid) showed similar fluctuations; the average values for Docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid were 230.40, 229.89 and 230.20 nm2, respectively. A low SASA value indicates an increasingly stable complex system [10]. This analysis correlated with that of the RMSD value, which indicated that (eicosapentaenoic acid) had better stability at the neurotensin receptor.

Polar solvation energy has a positive value while van der Waals, electrostatic, and SASA energies have a negative value in both of these complex systems. The results

Table 4. MM-PBSA energy summary ligand-neurotensin receptor during 100 ns simulation.

Ligand	van der Waals energy	Electrostatic energy	Polar solvation energy	SASA energy (KJ/mol)	Total binding energy (KJ/mol)
	(KJ/mol)	(KJ/mol)	(KJ/mol)		
Docosahexaenoic acid	-197.15 +/- 16.24	-46.94 +/- 9.48	148.64 +/-15.46	-24.075 +/- 1.27	-119.53+/-16.20
Eicosapentaenoic acid	-169.71 +/- 17.07	-36.34 +/- 23.89	132.306 +/-30.29	-20.088 +/- 1.43	-93.83+/-16.61
Heneicosapentaenoic acid	-184.44 +/- 15.28	-46.94 +/- 11.49	131.710 +/- 15.27	-20.388 +/- 0.94	-120.07 +/-14.41

show that van der Waals, electrostatic, and SASA energy favor the binding while polar solvation energies oppose it in both complex systems. The total binding free energy of the ligands had varying values. Heneicosapentaenoic acid provided the lowest binding free energy -120.065 kJ/mol, while those for Docosahexaenoic acid, and eicosapentaenoic acid were -119.530, and -93.826 kJ/mol, respectively. The MM-PBSA analysis indicated that scopolin has better affinity for the neurotensin receptor. The binding free energy of the MD trajectories of the system complex was calculated using the MM-PBSA method for a timestep of 0–100 ns (Table 4).

Conclusion

Based on the docking results, the ΔG values for omega-3 compounds of docosahexaenoic acid, eicosapentaenoic acid, heneicosapentaenoic acid and neurotensin 8–13 as native ligand were -8.96 ; -7.41 ; -6.34 and -6.41kcal/mol, respectively. Neurotensin 8–13 forms hydrogen bonds

References

- Abdurrahman S, Ruslin R, Hasanah A, Mustarichie R (2021) Molecular docking studies and ADME-tox prediction of phytocompounds from *Merremia peltata* as a potential anti-alopecia treatment. Journal of Advanced Pharmaceutical Technology and Research 12(2): 132–39. https://doi.org/10.4103/japtr.JAPTR_222_20
- Abdurrahman S, Ruslin R, Hasanah AN, Mustarichie R, Ifaya M (2022) Active antialopecia Chemical identification of *Merremia peltata* leaves and computational study toward androgen receptor using molecular docking and molecular dynamic simulation. Scientific World Journal 2022: e1123047. https://doi.org/10.1155/2022/1123047
- Abdurrahman S, Ruslin R, Hasanah AN, Ifaya M, Mustarichie R (2023) Anti-alopecia activity of coumarin derivatives isolated from *Merremia peltata* leaves and computational study of their binding to androgen receptors using molecular docking and molecular dynamic simulation. Pharmaceuticals 16(5): 1–20. https://doi.org/10.3390/ph16050669
- Bowers LD (1989) High-performance liquid chromatography/mass spectrometry: State of the art for the drug analysis laboratory. Clinical Chemistry 35(7): 1282–1287. https://doi.org/10.1093/clinchem/35.7.1288
- Calder PC (2018) Very long-chain n-3 fatty acids and human health: Fact, fiction and the future. Proceedings of the Nutrition Society 77(1): 52–72. https://doi.org/10.1017/S0029665117003950
- Essmann U, Perera L, Berkowitz ML, Darden T, Lee H, Pedersen LG (1995) A smooth particle mesh Ewald method. The Journal of Chemical Physics 103(19): 8577–8593. https://doi.org/10.1063/1.470117
- Halder S, Kumar S, Sharma R (2013) The therapeutic potential of GPR120: A patent review. Expert Opinion on Therapeutic Patents 23(12): 1581–1590. https://doi.org/10.1517/13543776.2013.842977

with TYR146, ARG213, and PHE344 of the neurotensin receptor, whereas docosahexaenoic acid forms hydrogen bonds with TYR146. Meanwhile, the average RMSD fluctuations for each system, namely docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, were 0.672, 0.437, and 0.650, respectively. The SASA of the neurotensin receptor-ligand complex on the graph for docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, and heneicosapentaenoic acid, similar fluctuations. The average values for docosahexaenoic acid, eicosapentaenoic acid, and heneicosapentaenoic acid, were 230.40, 229.89, and 230.20 nm², respectively. This analysis correlated with that of the RMSD value, which indicated that eicosapentaenoic acid had better stability at the neurotensin receptor.

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- Huang F, del-Río-Navarro BE, Leija-Martinez J, Torres-Alcantara S, Ruiz-Bedolla E, Hernández-Cadena L, Barraza-Villarreal A, Romero-Nava R, Sanchéz-Muñoz F, Villafaña S, Marchat LA, Hong E (2019) Effect of omega-3 fatty acids supplementation combined with lifestyle intervention on adipokines and biomarkers of endothelial dysfunction in obese adolescents with hypertriglyceridemia. Journal of Nutritional Biochemistry 64: 162–169. https://doi.org/10.1016/j. jnutbio.2018.10.012
- Huei CS, Azlan A, Ismail A, Shafie NH, Sultana S (2020) Antioxidant and anti-obesity properties of local chilies varieties in Malaysia. Journal of Food Science and Technology 57(10): 3677–3687. https://doi. org/10.1007/s13197-020-04400-x
- Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2012) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews 64(Suppl.): 4–17. https://doi.org/10.1016/j. addr.2012.09.019
- Mark P, Nilsson L (2001) Structure and dynamics of the TIP3P, SPC, and SPC/E water models at 298 K. Journal of Physical Chemistry A 105(43): 9954–9960. https://doi.org/10.1021/jp003020w
- Megawati G, Herawati D, Musfiroh I (2021) Binding affinity of omega 3 fatty acid as an agonist PPAR-γ and GPR120 receptor for obesity using molecular docking and ADME prediction. European Journal of Molecular & Clinical Medicine 7(10): 1686–1695.
- Mohamed GA, Ibrahim SRM, Elkhayat ES, El Dine RS (2014) Natural anti-obesity agents. Bulletin of Faculty of Pharmacy, Cairo University 52(2): 269–284. https://doi.org/10.1016/j.bfopcu.2014.05.001

- Morgan PJ, Young MD, Lloyd AB, Wang ML, Eather N, Miller A, Murtagh EM, Barnes AT, Pagoto SL (2017) Involvement of fathers in pediatric obesity treatment and prevention trials: A systematic review. Pediatrics 139(2): e20162635. https://doi.org/10.1542/ peds.2016-2635
- Musfiroh I, Megawati G, Herawati DMD, Ifaya M (2022) Stability of omega-3 compounds complex with Ppar-γ receptor as an anti-obesity using molecular dynamic simulation. International Journal of Applied Pharmaceutics 14(Special Issue 5): 45–49. https://doi. org/10.22159/ijap.2022.v14s5.04
- Musfiroh I, Megawati G, Herawati DMD, Rusdin A (2021) 3D-pharmacophore modelling of omega-3 derivatives with peroxisome proliferator-activated receptor gamma as an anti-obesity agent. International Journal of Applied Pharmaceutics 13(Special Issue 4): 167–170. https://doi.org/10.22159/ijap.2021.v13s4.43851
- Psimadas D, Georgoulias P, Valotassiou V, Loudos G (2012) Molecular nanomedicine towards cancer. Journal of Pharmaceutical Sciences 101(7): 2271–2280. https://doi.org/10.1002/jps.23146

- Ramírez D, Caballero J (2018) Is it reliable to take the molecular docking top scoring position as the best solution without considering available structural data? Molecules 23(5): 1–17. https://doi.org/10.3390/ molecules23051038
- Salam Md M, Yousuf R, Salam Md W, Haque M (2023) Obesity and overweight: A global public health issue. Advances in Human Biology 13(1): 154–156.
- Song T, Yang Y, Zhou Y, Wei H, Peng J (2017) GPR120: A critical role in adipogenesis, inflammation, and energy metabolism in adipose tissue. Cellular and Molecular Life Sciences 74(15): 2723–2733. https:// doi.org/10.1007/s00018-017-2492-2
- Sousa Da Silva AW, Vranken WF (2012) ACPYPE AnteChamber PYthon parser interface. BMC Research Notes 5: 1–8. https://doi. org/10.1186/1756-0500-5-367
- Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD (2002) Molecular properties that influence the oral bioavailability of drug candidates. Journal of Medicinal Chemistry 45(12): 2615–2623. https://doi.org/10.1021/jm020017n