Jurnal Biodjati 9(1):80-89, May 2024

e-ISSN : 2541-4208
p-ISSN : 2548-1606

JURNAL BIODJATI

http://journal.uinsgd.ac.id/index.php/biodjati

In Silico Study: ACE Inhibitory Activity as a Marine Animal Fatty Acid Antihypertensive Candidate

Maharani Dyah Arumsari[1], A. Misbakhus Sururi[2], Excelino Hendrata[3], Rahmadian Kahfi Zulfa Kamila[4], Dhea Mutiara Fernanda Wibowo[5], Luluatul Fajriyah[6], Dwi Anggorowati Rahayu*[7]

Received: September 21, 2023
Revise from: October 30, 2023
Accepted: February 06, 2024

DOI: 10.15575/biodjati.v9i1.29899

[1,2,3,4,5]Department of Chemistry, Faculty of Mathematics and Natural Sciences, State University of Surabaya, Ketintang, Sub. Gayungan, Surabaya City, East Java-60231.[6,7]Department of Biology, Faculty of Mathematics and Natural Sciences, State University of Surabaya, Ketintang, Sub. Gayungan, Surabaya City, East Java-60231.

e-mail:

[1]*maharanidyah.21068@mhs.unesa.ac.id*
[2]*ahmadmisbakhus.19040@mhs.unesa.ac.id*
[3]*excelino.22046@mhs.unesa.ac.id*
[4]*rahmadiankahfi.21003@mhs.unesa.ac.id*
[5]*dheamutiara.21016@mhs.unesa.ac.id*
[6]*luluatulfajriyah.22018@mhs.unesa.ac.id*
[7*]*dwirahayu@unesa.ac.id*

Corresponding author

Abstract. *Marine life has much potential for development, especially in the medical field. Its main content is fatty acids, where fatty acids have potential as antihypertensive agents. This research aims to determine the potential of the primary fatty acids in marine biota as antihypertensive agents through an in-silico approach using molecular docking. This study uses the Angiotensin Converting Enzyme (ACE) receptor as the target protein and fatty acid ligands (myristic acid, pentadecanoic acid, eicosapentaenoic acid, linoleic acid, vaccenic acid, 11-eicosenoic acid, palmitic acid), and the control drug captopril for comparison. The initial stages of the research include protein and ligand preparation, followed by molecular docking and visualization. Potential compounds were then analyzed using Lipinski drug-likeness and PASSOnline. The research results show that eicosapentaenoic acid and linoleic acid have the potential as ACE inhibitors with binding affinity values lower than the drug control, namely -6.6 and -6.0. PASSOnline predictions indicate that both had a high probability of being vasodilator agents. Therefore, these two fatty acids had the potential as antihypertensive agents. Further research is needed through in vitro and in vivo testing to utilize marine biota in the medical world.*

Keywords: *in silico, fatty acid, hypertension, vasodilator agent, antihypertension*

Citation
Arumsari, M. D., Sururi, A. M., Hendrata, E., Kamila, R. K., Wibowo, D.M., Fajriyah, L., & Rahayu, D. A. (2024). In Silico Study: ACE Inhibitory Activity as a Marine Animal Fatty Acid Antihypertensive Candidate . *Jurnal Biodjati*, 9(1),80-89.

Jurnal Biodjati 9(1):80-89, May 2024

JURNAL BIODJATI

http://journal.uinsgd.ac.id/index.php/biodjati

INTRODUCTION

Hypertension is one of the leading causes of premature death worldwide, with 10.8 million deaths attributed to hypertension and a predicted 1.3 billion adults aged 30-79 worldwide suffering from hypertension, and a burden of 235 million years of life lost or lived with a disability. Mostly (two-thirds) in low and middle-income countries (WHO, 2023). Hypertension in Indonesia continues to rise from 25.8% in 2013 to 34.1% in 2018 (Kemenkes, 2019). Hypertension is often called the silent killer because it is frequently unnoticed by patients and only diagnosed after complications arise (Kemenkes, 2019). Hypertension is defined as systolic blood pressure≥ 140 mmHg and diastolic blood pressure≥ 90 mmHg after repeated clinic and home examinations (Unger et al., 2020). Primary risks such as coronary heart disease, stroke, kidney complications, heart problems, eye issues, and other vital organ complications increase as the condition progresses (Kurniawan & Sulaiman, 2019). The mechanism of hypertension occurs through the formation of angiotensin II from Angiotensin I by Angiotensin Converting Enzyme (ACE), where angiotensin II has an impact on blood vessel constriction (Cutrell et al., 2023; Ezzahraoui et al., 2023). Another contributing factor to hypertension is lipid oxidation, leading to artery blockages or atherosclerosis (Arrosyadi et al., 2016). Hypertension is a degenerative disease; typically, people use chemical medications to manage it (Wang et al., 2021; Wicaksono et al., 2021). However, prolonged use of chemical drugs can lead to adverse side effects, including increased bradykinin plasma levels, angioedema, agranulocytosis, proteinuria, hyperkalemia, taste changes, teratogenesis, postural hypotension, acute kidney failure, and leukopenia (Wang et al., 2021). Therefore, alternative, preferably natural, options are needed.

A less-explored but effective natural alternative for hypertension is fatty acids. Fatty acids are beneficial as antihypertensive agents by releasing antioxidants and oxidizing nitrate (NO) (Zhang et al., 2020). Monounsaturated fatty acids can also reduce low-density lipoprotein (LDL) cholesterol levels, thus lowering blood pressure. Long-chain PUFA, including omega-3 and omega-6, are essential fatty acids that the body cannot produce. Consuming these fatty acids at a rate of 3 grams per day for six weeks can reduce blood pressure in hypertensive patients by five mmHg (Sari et al., 2017). Omega-3 intake can lower blood pressure through its vasodilator effects and prevent platelet aggregation (Djuricic & Calder, 2021). Fatty acids can be obtained from marine biota, including shellfish. This foundational study describes the potential of fatty acids in marine biota as antihypertensive agents using an in-silico approach. The in silico study is an approach to predict the interaction of drug compounds with target proteins, both enzymes and receptors, in a computational study (Brogi et al., 2020). It serves as an initial exploration of the utilization of marine biota, particularly its fatty acid content, which has been rarely explored.

MATERIALS AND METHODS

This study uses an in-silico approach with molecular docking, aided by the RCSB webserver (rcsb.org), ScfBio (scfbio-iitd.res.in), Way2Drug (way2drug.com/passonline), and PubChem (pubchem.ncbi.nlm.nih.gov). Meanwhile, the software includes PyRx 0.8, PyMOL 2.5.5, and Discovery Studio 2021 Client.

Protein Preparation:

The receptor protein used in this study is Angiotensin-Converting Enzyme (ACE), which plays a role in the production of angiotensin 2, a substance that narrows blood vessels, leading to high blood pressure. The X-ray structure of the ACE protein (PDB ID: 1O86) was obtained from rcsb (rcsb.org) and then prepared using Discovery Studio to obtain the active site position and remove water molecules, chains, and unnecessary molecules. The sterilized protein was input as a macromolecule in the PyRx pro-

gram (Sururi et al., 2023; Trott & Olson, 2010).

Ligand Preparation:

The ligands used in this study were fatty acids commonly found in marine animals, particularly shellfish, including myristic acid, pentadecanoic acid, eicosapentaenoic acid, linoleic acid, vaccenic acid, 11-eicosenoic acid, and palmitic acid (Kumar Sethukali & Darshaka Jayasena, 2022). Additionally, the control drug captopril was used. The 3D structures of the compounds were obtained from PubChem (pubchem.ncbi.nlm.nih.gov) and then minimized using OpenBabel to obtain optimized and flexible structures, resulting in minimum energy (Pradeepkiran et al., 2016; Sururi et al., 2022). Compounds that have produced minimum energy are then input as ligands, and the minimized compound structures are input as ligands in PyRx (Trott & Olson, 2010).

Molecular docking and Visualization:

Molecular docking simulations were conducted using Vina Wizard within the PyRx program to determine the binding affinity values between the ligand and receptor. Subsequently, the binding affinity values were selected based on the control comparison. Potential compounds were those with binding affinity values lower than captopril. The conformers of potential compounds were then interacted with using PyMOL and visualized using Discovery Studio to determine the position and types of interactions formed (Nugroho et al., 2023).

Druglikeness Lipinski and PASS Online Predictions:

Potential compounds were then analyzed for drug-likeness using Lipinski parameters, commonly called Lipinski's rule of five (Ro5). The analysis was performed using ScfBio (scfbio-iitd.res.in) with the following criteria: molecular weight < 500 Da; hydrogen bond donors < 10; hydrogen bond acceptors < 5; lipophilicity < 5; and molar refractivity 80-120 (Jayaram et al., 2012; Lipinski, 2004; Lipinski et al., 2001). PASS Online predictions were conducted to assess the likelihood of activity (Pa) and inactivity (Pi) against specific bioactivities. PASSOnline predictions were made using the Way2Drug server (way2drug.com/passonline) (way2drug.com/passonline) (Lagunin et al., 2000).

RESULTS AND DISCUSSION

Fatty acids are compounds derived from carboxylic acids with aliphatic chains divided into saturated and unsaturated fatty acids. Fatty acids are a major component of lipids (up to 70% by weight) in some species, such as microalgae (Chen et al., 2012). However, in some other organisms, they are not found in their standalone form but rather exist in three main classes of esters: triglycerides, phospholipids, and cholesterol esters. In any form, fatty acids are an essential food source as fuel for animals and important structural components for cells. Fatty acids have the potential to act as antihypertensive agents by lowering blood pressure through their vasodilator effects and preventing platelet aggregation (Djuricic & Calder, 2021). Based on similar research, one of the fatty acids, namely linolenic acid, has been shown to increase blood vessel dilation due to nonspecific vasodilators (Lee et al., 2019). Fatty acids contained in basil seeds have also been identified as an alternative option for inhibiting ACE (Kheeree et al., 2020).

This research aims to determine the potential of fatty acids as candidate antihypertensive agents, particularly in the preliminary exploration of using fatty acids in marine biota, especially shellfish. This study employs the molecular docking method with the Angiotensin Converting Enzyme (ACE) protein. ACE plays a role in hypertension by converting Angiotensin I into Angiotensin II, which affects blood vessels, causing them to narrow(Cutrell et al., 2023; Helmer et al., 2018). The ligand structures used in this research can be seen in Figure 1, including myristic acid, pentadecanoic acid,

Jurnal Biodjati 9(1):80-89, May 2024

JURNAL BIODJATI

http://journal.uinsgd.ac.id/index.php/biodjati

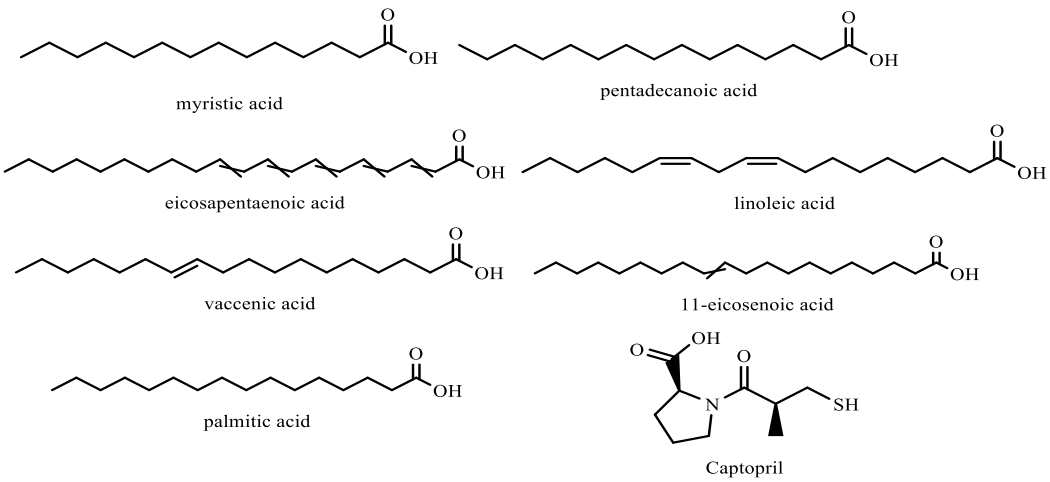

Figure 1. Structure of Ligand (Fatty Acid) and Control Drug (Captopril)

including myristic acid, pentadecanoic acid, eicosapentaenoic acid, linoleic acid, vaccenic acid, 11-eicosenoic acid, palmitic acid, and the control drug captopril.

Molecular docking tests were conducted to determine the activity of fatty acids when they interact with the active site of the ACE receptor, assessing their potential inhibitory effects by binding ligands to the ACE receptor's active site, thereby forming complexes (Agu et al., 2023). The results were complex stability values (binding affinity), where lower values indicate greater stability. The binding affinity of fatty acids was then compared to the control drug captopril to identify potential compounds (Awaluddin et al., 2023). The results of the molecular docking analysis were presented in Table 1, indicating that all seven fatty acids as ligands exhibit inhibitory activity on the ACE receptor, as evidenced by their negative binding affinity values. Based on this data, it is known that there are two potential compounds, namely eicosapentaenoic acid (-6.6 kcal / mol) and linoleic acid (-6.0 kcal / mol), which have better activity potential as antihypertensive agents because they have more negative binding affinity value than captopril control. The lower the binding affinity value, the more stable the complex is formed. The more stable a complex is, the better its inhibitory activity (Kulkarni et al., 2023).

The results of molecular docking tests related to fatty acids, especially eicosapentaenoic acid, and linoleic acid, which have been carried out are in line with the results of research by Kim et al., who found that fatty acids derived from the lipid extract of Semisulcospira coreana were involved in inhibiting ACE activity. In previous research, the effect of fatty acids on ACE has been studied, and it has been concluded that they have antihypertensive activity or can inhibit ACE. The ability of fatty acids to inhibit ACE activity is related to high concentrations of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) such as EPA, DHA, ARA, GLA (gamma-linolenic acid), and LA (linoleic acid) (Kim et al., 2015). Similar observations regarding in silico studies of fatty acids were obtained cis-4,7,10,13,16,19-docosahexaenoic acid (docosahexaenoic acid, DHA), cis-5,8,11,14,17-eicosapentaenoic acid (eicosapentaenoic acid, EPA) and cis-5, 8,11,14-eicosatetraenoic acid (arachidonic acid) are the top three fatty acid active ingredients for ACE inhibition (Pekkoh et al., 2022).

The conformer structures resulting

Table 1. Molecular Docking Result Analysis of Fatty Acid and ACE Receptor

Ligand Compound	Binding Affinity (kcal/mol)
Captopril (control)	-5.6
Myristic acid	-5.3
Pentadecanoic acid	-5.3
Eicosapentaenoic acid	**-6.6**
Linoleic acid	**-6.0**
Vaccenic acid	-5.5
11-eicosenoic acid	-5.5
Palmitic acid	-5.2

from docking were then interacted with using PyMOL and visualized using Discovery Studio to determine the positions and types of interactions formed. The visualization results presented in Figure 2 indicate that both potential compounds form hydrogen and hydrophobic bonds. Hydrogen bonds are strong bonds that form due to interactions between hydrogen atoms (H) and highly electronegative atoms (fluorine, oxygen, and nitrogen) (Głowacki et al., 2013; Kharisma et al., 2021). Hydrogen bonds are often a focal point in developing new drug compounds. Meanwhile, hydrophobic bonds form due to hydrophobic group interactions between ligands and receptors (Cheng et al., 2020). The results show that eicosapentaenoic acid forms hydrogen bonds at the Tyr 523l position while forming hydrophobic bonds at the His 353, His 383, His 513, Tyr 523, Phe 457, and Val 380 positions. In linoleic acid, only hydrophobic bonds form at the Val 380, His 383, His 353, Ala 254, Val 379, Phe 527, Phe 457, and Tyr 523 positions. This result explains their binding affinity values; the more favorable interactions that form, the more stable the complex becomes, resulting in lower binding affinity values (Pires et al., 2018). Both potential compounds share a common position with the control drug captopril, specifically at the Val 380 position. The similarity in amino acid residue positions supports the inhibitory activity of these fatty acids as antihypertensive agents (Nugroho et al., 2023). The similarity in inhibition positions indicates that fatty acids will inhibit the receptor at the same position as the control drug, which can be used to validate the docking results and support the findings obtained.

The potential compounds were then analyzed for drug-likeness profiles using Lipinski's rule of five (Ro5), which includes parameters such as molecular weight, lipophilicity, hydrogen bond donor numbers, hydrogen bond acceptors numbers, and molar refractivity. Lipinski's rule of five is a set of rules that predict the potential of a compound when used as an orally administered drug. These rules are often used to select compounds for drug development. The molecular weight (MW) parameter should be less than 500 Dalton, the number of hydrogen bond donors (HBD) should be less than 5, the number of hydrogen bond acceptors should be less than 10, lipophilicity should be less than 5, and molar refractivity should be in the range of 80-130 (Lipinski, 2004; Lipinski et al., 2001). A compound is considered to have the potential as a drug

compound if it meets at least three of these rules. Lipinski's drug-likeness analysis results were presented in Table 2, indicating that both compounds meet Lipinski's criteria and have the potential as drug compounds because they satisfy four parameters, including molecular weight, hydrogen bond donors, hydrogen bond acceptors, and molar refractivity, but do not meet lipophilicity parameters. Therefore, both fatty acids have the potential to be oral drugs due to their favorable Lipinski profile. This profile represents how a compound is distributed in the body when consumed orally.

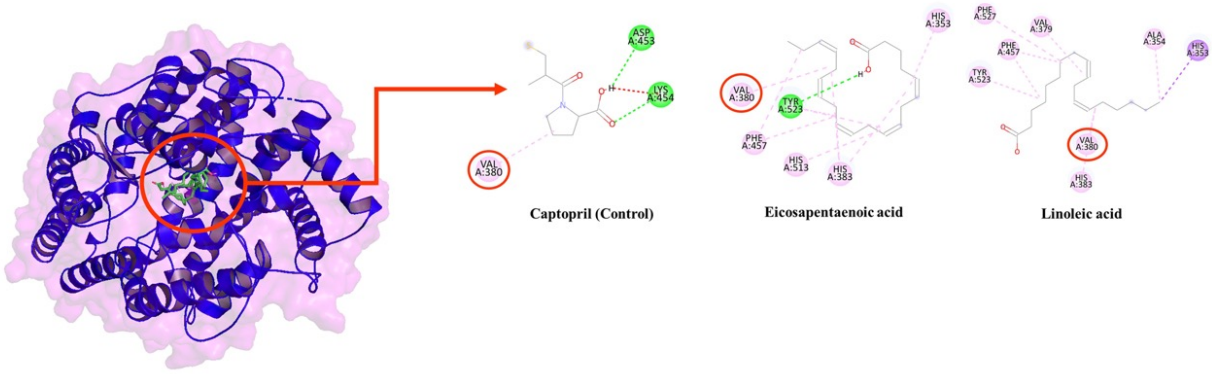

Figure. 2. Visualization 2D and 3D ACE-Ligand

The potential compounds were then analyzed for the probability of their activity as antihypertensive agents through PASS Online prediction, considering the values of the active probability (Pa) and the inactive probability (Pi). The Pa value is the possibility that a compound has significant biological activity, while the Pi value is the opposite. If a compound has a Pa value greater than the Pi value, it indicates that the compound has the potential to have biological activity (Andhiarto & Praditapuspa, 2022). A Pa value greater than 0.7 is categorized as high probability, while a Pa value greater than 0.3 is categorized as moderate probability (Rahmaningsih & Pujiastutik, 2019; Sururi et al., 2022). The analysis results in Table 3 eicosapentaenoic acid has a Pa> 0.3 in vasodilators, peripheral and vasodilators, apart from that, it has Pa<0.3 in vasodilators, coronary. While linoleic acid has Pa> 0.7 in vasodilators, peripheral and has Pa> 0.3 in vasodilators and vasodilators, coronary. The evaluation results using a web server in Table 3 show that the highest probability value is found in linoleic acid as a peripheral vasodilator agent, vasodilator, and vasodilator, coronary rather than eicosapentaenoic acid. However, because both have a probability value of Pa > Pi, these two compounds have the potential to act as vasodilator agents, which play a role in widening blood vessels. If it is above 0.3, then all three have medium probability, when the probability value is above 0.7, they have a high bioactive probability (Rahmaningsih & Pujiastutik, 2019; Sururi et al., 2024). This result supports the findings from molecular docking that both fatty acids have the potential as antihypertensive agents.

Table 2. Molecular Docking Result Analysis of Fatty Acid and ACE Receptor

Potential Compound	Lipinski Parameter				
	MW[1]	HBD[2]	HBA[3]	Log P[4]	MR[5]
Eicosapentaenoic acid	302.0	1	2	5.99*	95.94
Linoleic acid	280.0	1	2	5.88*	86.99

Note: [1]MW= molecular weight (Da) <500 Da; [2]HBD= hydrogen bond donor < 5; [3]HBA= hydrogen bond acceptors < 10; [4]Log P= lipophilicity <5; [5]MR= molar refractivity= 40-130; *=not complying with rules

Table 3. PASS Online Result Analysis of Potential Compound as Antihypertensive

Potential Compound	PASS Result
Eicosapentaenoic acid	Vasodilator, peripheral
	Pa=0.694; Pi=0.010
	Vasodilator
	Pa=0.443; Pi=0.0219
	Vasodilator, coronary
	Pa=0.282; Pi=0.139
Linoleic acid	Vasodilator, peripheral
	Pa=0.734; Pi=0.007
	Vasodilator
	Pa=0.509; Pi=0.021
	Vasodilator, coronary
	Pa=0.316; Pi=0.106

CONCLUSION

Based on the research results, it can be concluded that fatty acids have the potential as ACE inhibitors, antihypertensive agents, and vasodilators. The potential compounds identified through molecular docking are eicosapentaenoic acid (-6.6 kcal/mol) and linoleic acid (-6.0 kcal/mol). These findings were supported by PASS Online predictions indicating a favorable likelihood as vasodilator agents indicated by Pa score. This foundational research needs further development through in vitro and in vivo testing to harness the significant potential of marine-derived fatty acids.

AUTHOR CONTRIBUTION

M.D.A, E.H. and A.M.S designed the research, collected and analyzed the data, M.D.A and R.K.Z prepare raw material and supervised all the study processes, D.M.F and L.F help correct the article, and D.A.R guide and correct the article.

ACKNOWLEDGMENTS

The authors would like to express our gratitude to Belmawa Dikti and Unesa for their support in funding the student research creativity program and to all parties who assisted in this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this research.

REFERENCES

Agu, P. C., Afiukwa, C. A., Orji, O. U., Ezeh, E. M., Ofoke, I. H., Ogbu, C. O., Ugwuja, E. I., & Aja, P. M. (2023). Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. *Scientific Reports*, 13(1), 13398.

Andhiarto, Y., & Praditapuspa, E. N. (2022). In Silico Analysis and ADMET Prediction of Flavonoid Compounds from *Syzigium cumini* var. album on α-Glucosidase Receptor for Searching Anti-Diabetic Drug Candidates. *Pharmacognosy Journal*, 14(6), 736–743.

Arrosyadi, U. L., Astutik, Y. D. P., Pradana, H. A., Islamianti, A. C., & Marfuah, S. (2016). *Aktivitas Antioksidan dan Efek Antihipertensi Kopi Rendah Kafein Berantioksidan (Komik Aksi) Sebagai Minuman Fungsional*. Jember: Fakultas Teknologi Pertanian, Universitas Jember.

Awaluddin, F., Batubara, I., & Tri Wahyudi, S. (2023). Virtual Screening of Natural Compounds Against Six Protein Receptors Coded by The SARS-CoV-2 Genome. *Molekul*; 18(1) (2023) DOI: 10.20884/1.Jm.2023.18.1.7884 .

Brogi, S., Ramalho, T. C., Kuca, K., Medina-Franco, J. L., & Valko, M. (2020). In silico methods for drug design and discovery. *In Frontiers in chemistry* (Vol. 8, p. 612). Frontiers Media SA.

Chen, L., Liu, T., Zhang, W., Chen, X., & Wang, J. (2012). Biodiesel production from algae oil high in free fatty acids by two-step catalytic conversion. *Bioresource Technology*, 111, 208–214.

Cheng, X., Shkel, I. A., O'Connor, K., & Record, M. T. (2020). Experimentally determined strengths of favorable and unfavorable interactions of amide atoms involved in protein self-assembly in water. *Proceedings of the National Academy of Sciences,* 117(44), 27339 LP – 27345. https://doi.org/10.1073/pnas.2012481117

Cutrell, S., Alhomoud, I. S., Mehta, A., Talasaz, A. H., Van Tassell, B., & Dixon, D. L. (2023). ACE-Inhibitors in Hypertension: A Historical Perspective and Current Insights. *Current Hypertension Reports*, 1–8.

Djuricic, I., & Calder, P. C. (2021). Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: An update for 2021. *Nutrients*, 13(7), 2421.

Ezzahraoui, R., Salmi, N., El Ouartassi, H., Bourouhou, Z., & Cherti, M. (2023). ACE Inhibitors-Induced Skin Reaction: A Case Report. *Research and Analysis Journal*, 6(8), 1–3.

Głowacki, E. D., Irimia-Vladu, M., Bauer, S., & Sariciftci, N. S. (2013). Hydrogen-bonds in molecular solids – from biological systems to organic electronics. *Journal of Materials Chemistry B*, 1(31), 3742–3753. https://doi.org/10.1039/C3TB20193G

Helmer, A., Slater, N., & Smithgall, S. (2018). A review of ACE inhibitors and ARBs in black patients with hypertension. *Annals of Pharmacotherapy*, 52(11), 1143–1151.

Jayaram, B., Singh, T., Mukherjee, G., Mathur, A., Shekhar, S., & Shekhar, V. (2012). Sanjeevini: a freely accessible webserver for target directed lead molecule discovery. *BMC Bioinformatics*, 13(17), 1–13.

Kemenkes, R. I. (2019). Buku Pedoman Manajemen Penyakit Tidak Menular. Jakarta: Kementerian Kesehatan Republik Indonesia.

Kharisma, V., Widyananda, M., Nege, A., Naw, S., & Nugraha, A. (2021). Tea catechin as antiviral agent via apoptosis

agonist and triple inhibitor mechanism against HIV-1 infection: A bioinformatics approach. *Journal of Pharmacy & Pharmacognosy Research*, 9, 435–445.

Kheeree, N., Sangtanoo, P., Srimongkol, P., Saisavoey, T., Reamtong, O., Choowongkomon, K., & Karnchanatat, A. (2020). ACE inhibitory peptides derived from de-fatted lemon basil seeds: Optimization, purification, identification, structure–activity relationship and molecular docking analysis. *Food & Function*, 11(9), 8161–8178.

Kim, Y.-K., Kim, Y. A., Shin, S. B., Lee, T. S., & Yoon, H.-D. (2015). Angiotensin-I converting enzyme fatty acid inhibitory fractions from the Korean melania snail Semisulcospira coreana. *Food Science and Biotechnology*, 24, 681–688.

Kulkarni, S., Singh, Y., Biharee, A., Bhatia, N., Monga, V., & Thareja, S. (2023). Molecular docking, 3D-QSAR and simulation studies for identifying pharmacophoric features of indole derivatives as 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD5) inhibitors. *Journal of Biomolecular Structure and Dynamics*, 1–18.

Kumar Sethukali, A., & Darshaka Jayasena, D. (2022). Fatty Acid Profiles of Venus Clam (*Marcia opima*) and Blood Cockles (*Anadara granosa*) Harvested at Different Geographical Locations in the Northwest Coast of Sri Lanka. *Journal of Aquatic Food Product Technology*, 31(4), 311–320.

Kurniawan, I., & Sulaiman, S. (2019). Hubungan Olahraga, Stress dan Pola Makan dengan Tingkat Hipertensi di Posyandu Lansia di Kelurahan Sudirejo I Kecamatan Medan Kota. *Journal of Health Science and Physiotherapy*, 1(1), 10–17.

Lagunin, A., Stepanchikova, A., Filimonov, D., & Poroikov, V. (2000). PASS: prediction of activity spectra for biologically active substances. *Bioinformatics*, 16(8), 747–748.

Lee, S. H., Ok, S.-H., Kim, J.-Y., Subbarao, R. B., Bae, S. Il, Hwang, Y., Park, K.-E., Kim, J. W., & Sohn, J.-T. (2019). Linolenic acid attenuates the vasodilation induced by acetylcholine in isolated rat aortae. *Dose-Response*, 17(4), 1559325819894148.

Lipinski, C. A. (2004). Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, 1(4), 337–341. https://doi.org/https://doi.org/10.1016/j.ddtec.2004.11.007

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings1PII of original article: S0169-409X(96)00423-1. The article was originally published in Advanced *Drug Delivery Reviews* 23 (1997) 3. Advanced Drug Delivery Reviews, 46(1), 3–26. https://doi.org/https://doi.org/10.1016/S0169-409X(00)00129-0

Nugroho, E. D., Ardiansyah, R., Kurniawan, N., Rahayu, A., & Sururi, A. M. (2023). An in-silico study on the chemical compounds from Macrophiothrix longipedia as antiviral compounds against covid-19. 16(4), 2380–2390.

Organization, W. H. (2023). Global report on hypertension: the race against a silent killer.

Pekkoh, J., Phinyo, K., Thurakit, T., Lomakool, S., Duangjan, K., Ruangrit, K., Pumas, C., Jiranusornkul, S., Yooin, W., & Cheirsilp, B. (2022). Lipid profile, antioxidant and antihypertensive activity, and computational molecular docking of diatom fatty acids as ACE inhibitors. *Antioxidants*, 11(2), 186.

Pires, D. E. V, Kaminskas, L. M., & Ascher,

D. B. (2018). Prediction and optimization of pharmacokinetic and toxicity properties of the ligand. In Computational drug discovery and design (pp. 271–284). *Springer*.

Pradeepkiran, J. A., Yellapu, N. K., & Matcha, B. (2016). Modeling, molecular docking, probing catalytic binding mode of acetyl-CoA malate synthase G in Brucella melitensis 16M. *Biochemistry and Biophysics Reports*. https://doi.org/10.1016/j.bbrep.2016.08.020

Rahmaningsih, S., & Pujiastutik, H. (2019). An in vitro and in silico evaluation of the antibacterial activity of the bioactive compounds in Majapahit (*Crescentia cujete* L.) fruit. *Veterinary World*, 12(12), 1959–1965. https://doi.org/10.14202/vetworld.2019.1959-1965

Sari, M. L., Probosari, E., & Wijayanti, H. S. (2017). Hubungan Asupan Asam Lemak Omega-3 Dan Omega-6 dengan Tekanan Darah Wanita Usia 30–50 Tahun. *Journal of Nutrition College*, 6(4), 313–318.

Sururi, A. M., Maharani, D. K., & Wati, F. A. (2023). Potensi Senyawa Eugenol dari Cengkeh (*Syzygium Aromaticum*) Sebagai Inhibitor Protease HIV-1 (PR). *Unesa Journal of Chemistry*, 12(1) (2023), 26–30.

Sururi, A. M., Raihan, M., Aisa, E. R., Safitri, F. N., & Constaty, I. C. (2022). Anti-Inflammatory Activity of Stem Bark Dichloromethane Fraction Syzygium samarangense Extract as COX-2 Inhibitor: A Bioinformatics Approach. *Jurnal Kimia Riset*, 7(2), 94–100. https://doi.org/10.20473/jkr.v7i2.39662

Sururi, A. M., Tukiran, T., Aisa, E. R., & Raihan, M. (2024). Identification of bioactive compounds and ADMET profile of stem bark of *Syzygium samarangense* and their potential as antibreast cancer and antiinflammatory. *Journal of Applied Pharmaceutical Science*, 14(2), 273–280.

Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry,* 31(2), 455–461.

Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., & Tomaszewski, M. (2020). 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension,* 75(6), 1334–1357.

Wang, Y., Li, Y., Ruan, S., Lu, F., Tian, W., & Ma, H. (2021). Antihypertensive effect of rapeseed peptides and their potential in improving the effectiveness of captopril. *Journal of the Science of Food and Agriculture*, 101(7), 3049–3055.

Wicaksono, A., Listyana, Y. I., Kesuma, A. A. M., & Fauziyah, H. N. N. (2021). Resiko Penggunaan Captopril terhadap Kejadian Batuk Kering pada Pasien Hipertensi. *Jurnal Pendidikan Tambusai*, 5(3), 11315–11322.

Zhang, S., Liu, Y., Wang, X., Tian, Z., Qi, D., Li, Y., & Jiang, H. (2020). Antihypertensive activity of oleanolic acid is mediated via downregulation of secretory phospholipase A2 and fatty acid synthase in spontaneously hypertensive rats. *International Journal of Molecular Medicine*, 46(6), 2019–2034.