Contents lists available at IOCS

Science Midwifery

journal homepage: www.midwifery.iocspublisher.org

Activity predication of rhodomyrtus tomentosa (Aiton) hassk against ace1 inhibitors

Samsul Hadi[1], Kunti nastiti[2]

[1, 1]Department Pharmacy, Universitas Lambung Mangkurat, Banjarbaru, Kalimantan Selatan
[2]Department Pharmacy, Universitas Sari Mulia, Banjarmasin, Kalimantan Selatan

ARTICLE INFO

Article history:

Received May 31, 2023
Revised Jun 3, 2023
Accepted Jun 21, 2023

Keywords:

ACE
Tomentosa
Tomentosine

ABSTRACT

ACE is a peptidyl-dipeptidase enzyme that catalyzes the conversion of substrates from angiotensin I to angiotensin II. These changes cause constriction of blood vessels so that blood pressure increases (hypertension), so This study aims to find compounds that have the potential to reduce blood pressure through the pathway of ACE1 enzyme inhibition. The method used is docking, the material used is a compound contained from Rhodomyrtus tomentosa and. The ACE1 protein was obtained from RCSB with the code 1UZF. The equipment used was an online pass webserver, PLNTS software and discovery studio. This research was started by redocking the native ligand to determine the coordinates and radius, followed by validating the docking results. The results of the early stage screening obtained 4 compounds with a threshold value above 0.3, these four compounds were continued with the docking test. The docking scores obtained were Afrormosin (-59.620); Pedunculagin (-45.205); Tomentosine (-70.986); Desgalloylstachyurin (-54.374). The conclusion obtained is that the Tomentosine compound binds most easily to ACE1

Corresponding Author:

Samsul Hadi,
Department pharmacy,
Universitas Lambung Mangkurat,
Jl. Ahmad Yani Km 36, Banjarbaru, 70714, Kalimantan Selatan, Indonesia
Email: samsul.hadi@ulm.ac.id

INTRODUCTION

ACE is a *peptidyl-dipeptidase enzyme* that catalyzes the conversion of substrates from angiotensin I to angiotensin II. These changes cause narrowing of the blood vessels so that blood pressure increases (hypertension). The widely used ACE inhibitor compounds include captopril and elanapril (Khirzin et al., 2015) . *Angiotensin-converting enzyme* (ACE) inhibitors or angiotensin-converting enzyme inhibitors are a group of drugs used to treat hypertension, heart failure, and chronic kidney failure (Korzeniowska et al., 2017) . this medicine make blood vessel walls relax so that blood pressure can decrease (Silvariño et al., 2019) . ACE inhibitory activity has 2 mechanisms, namely competitive and non-competitive. Competitive inhibitors are able to enter into the ACE protein molecule and interact with the active site of the enzyme, while non-competitive inhibitors work by joining the ACE enzyme molecule and forming a dead-end complex, regardless of whether the substrate molecule binds or not (Zhang et al., 2020) . Angiotensin-converting enzyme

tests are used to detect and monitor the development of sarcoidosis. Sarcoidosis is an inflammatory disease characterized by the presence of granulomas in the organs and tissues under the skin. In patients with sarcoidosis, the cells around the granulomata will continue to secrete ACE so that the concentration of this enzyme will increase in the blood. The ACE test is needed if a person shows symptoms of sarcoidosis such as granulomas, shortness of breath or cough (Pongpanich et al., 2018) .

The angiotensin-converting enzyme (ACE) inhibitor class drugs work by inhibiting *the converting enzyme, peptidyl dipeptidase which hydrolyzes angiotensin* I to angiotensin II and inactivates bradykinin (a potent vasodilator) . in the form of octapeptides by ACE inhibitors (Whelton et al., 2018) . ACE causes the degradation of bradykinin into an inactive peptide. ACE inhibitors have a role in blocking the degradation of bradykinin, so that bradykinin levels increase and contribute as a blood vessel vasodilator (Messerli et al., 2018) . This vasodilation will reduce peripheral vessel pressure, preload and afterload on the heart so that blood pressure can be lowered (Riyadi, 2018) . The chain of the entire renin system to become angiotensin II is known as the Renin Angiotensin Aldosterone System (RAAS). This system plays an important role in the pathogenesis of hypertension. The RAAS is a complex hormonal system that plays a role in controlling the cardiovascular system, kidneys, adrenal glands, and blood pressure regulation (Williams et al., 2018) . Based on this description, alternative compounds from natural ingredients are needed that can help overcome blood pressure through the angiotensin inhibition pathway. One of the natural ingredients that has the potential to help lower blood pressure is R. tomentosa.

R. tomentosa is a shrub that can be found throughout Southeast Asian countries, including Indonesia. This plant grows wild and abundant in the tropics, especially in humid areas, and can be found in the Indian Ocean Islands, throughout South and Southeast Asia, China, Taiwan, Australia, and the South Pacific Ocean (Sang & Ngo, 2019) . In general, the leaves, roots and fruit of the Karamunting plant are used as traditional medicine in Malaysia, India and Indonesia to treat various types of ailments such as diarrhea, dysentery, leucorrhoea, hemorrhoids, toothache, stomach ache, flatulence, leg pain and blood pressure. high (Abd Hamid et al., 2017) . The part of the plant that is used to treat high blood pressure is a purple fruit (Idris et al., 2022) . Based on this description, research is needed to find out potential compounds in treating blood pressure from R. tomentosa.

RESEARCH METHOD

Tools and materials

The equipment used in this research is PLANT software(Korb et al., 2009), discovery studio(Systèmes, 2020), Yasara (Krieger & Vriend, 2014), chemaxon (ChemAxon, 2016), online PASS webserver (Lagunin et al., 2000). The materials used in this study were ten compounds contained in R. Tomentosa

Screening

ACE1 inhibitor screening started with activity prediction using PASSonline. The second step was docking of the ACE1 protein. The ACE1 protein was obtained from RCSB with the code 1UZF. The next step is to remove ligands that are not related to interactions. Docking coordinate validation using native ligand. Preparation of the compounds contained in R. tomentosa using chemaxon. The docking of compounds from R. tomentosa uses the coordinates obtained from the native ligand.

Data analysis

The compound analysis method was carried out in two stages, the first with PASSonline with a score of 0> 3, the second stage by looking at the lowest docking score

RESULTS AND DISCUSSIONS

ACE inhibitor class drugs can lower blood pressure by preventing the enzymatic conversion of *angiotensin* (AT) *I* to *angiotensin II*. AT II is an active hormone of the Renin-Angiotensin-Aldosterone (RAAS) system (O'Gara et al., 2013) . AT II binds to AT receptors located in the kidney, vessel wall and heart, triggering several biological mechanisms, in particular a strong vasoconstrictive effect with increased blood pressure and aldosterone release. *Angiotensin converting enzyme* (ACE) which can be used as monotherapy in essential hypertension and renovascular hypertension include captopril, enalapril, and lisinopril (James et al., 2014) . In chronic heart failure, in addition to diuretics or digoxin, these drugs can improve symptoms (shortness of breath, fatigue, etc.) and limit morbidity and mortality (Rosano et al., 2018) . It is also useful after a heart infarction, including captopril and ramipril (Page, 2014) . Another indication is diabetic kidney disease, including captopril. *Angiotensin Convertong Enzyme* (ACE) can produce a dry, tickling cough that is tedious and persists throughout medication. The cause may be bradykinin and prostaglandins in the airways and lungs which are also broken down by ACE, but as a result of their inhibition accumulate there (Ponikowski et al., 2016) . One way to treat hypertension is to use drugs or medicinal plants that function as ACE inhibitors (Angiotensin I Converting Enzyme), because ACE is known to play an important role in the formation of angiotensin II which is one of the causes of hypertension (Williams, 2016) . Angiotensin II causes blood vessels to constrict, which can raise blood pressure (Yancy et al., 2017) . ACE inhibitors allow blood vessels to widen and allow more blood to flow to the heart, thereby lowering blood pressure (Sorodoc et al., 2010) . The mechanism of ACE inhibitors is an important target in managing blood pressure, so this screening study was carried out. Compound screening was carried out using PASSonline and docking. The samples used in this study were compounds contained in R. tomentosa.

The successful compounds from R.tomentosa were obtained from the KNAPSack database. From the database obtained 10 compounds. These ten compounds were then screened with PASSonline, the selected compounds had a score of 0.3. Choosing a score above 0.3 means that compounds are predicted by computation to have activity based on structural similarities, but there is no evidence of in vitro or in vivo studies. The results of the PASSonline screening can be seen in Table 1. From this selection, four compounds were obtained that have the potential to lower blood pressure, these compounds are Afrormosin, Pedunculagin, Tomentosin, 5'-Desgalloylstachyurin. So that these four compounds were screened at an advanced stage using docking to see the ease of carrying out the reaction, because the docking score was getting minus, indicating an easy reaction to occur.

Table 1. Compound screening based on PASSonline

compound	Pa	Pi
Afrormosin	0.407	0.037
Pedunculagin	0.380	0.174
Tomentosine	0.303	0.144
Lupeol	-	-
Rhodomyrtone	-	-
5'-Desgalloylstachyurin	0.399	0.057
Rhodomyrtosone A	-	-
Rhodomyrtosone B	-	-
Rhodomyrtosone C	-	-
Rhodomyrtosone D	-	-

The docking of the four selected compounds was used to see the stability of the interaction between the ligand and the ACE1 protein. This increasingly negative docking score was obtained because the ligand occupies the location of the binding cite and catalytic cite of the ACE1 protein.

However, before testing the four ligands, a redocking of the native ligand was first carried out to determine the coordinates and radius of the binding cite. In this study, the native ligand coordinates were X:41.3709, Y:34.5804, Z: 43.8915 and the radius obtained was 9.92955. From the redocking results of the superimpose complex ligand-protein values, an RMSD value of 1.71 Å is obtained, so that the coordinates and radius used meet the validation requirements of the docking method because they are below 2 Å, so the coordinates and radius used can be used for docking test

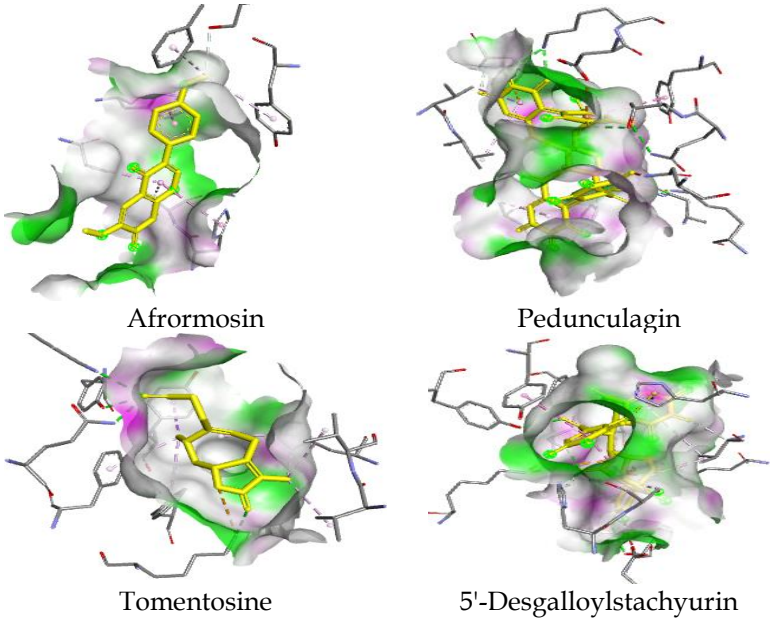

Figure 1. Three Dimensional Structure

The yellow color is a compound from R. Tomentosa, the pink color is a hydrogen donor and the green color is a hydrogen acceptor when hydrogen bonds occurs on samples. This 3D structure describes the interaction between the compound and the amino acid residues of the ACE1 enzyme.

Based on the docing score, four potential compounds were obtained as ACE1 inhibitors. The docking score is Afrormosin (-59.620); Pedunculagin (-45.205); Tomentosine (-70.986) and Desgalloylstachyurin (-54.374). The docking scores when compared with natite ligands are Afrormosin (81.94%); Pedunculagin (62.51%); Tomentosine (97.32%); Desgalloylstachyurin (75.21%). So based on the docking score obtained, the tomentosine compound has the potential to be developed into an angiotensin inhibitor. This is supported by the GLN281:NE2 amino acid residue; :LYS511:NZ; :TYR520:OH; :TYR520:OH; :HIS513:CE1; and HIS383:NE2 which are involved in the interaction between compounds from caramunting to the Angiotensin-converting enzyme. This is supported by research that has been conducted by other researchers. Research has been conducted on Afrormosin, Tomentosine, pedunculagin and 5'-Desgalloylstachyurin which affect AKT/ERK and MAPK signals by inhibiting p38/JNK (Kim et al., 2022) . Besides that, this compound inhibits fMLP or PMA-induced neutrophil degranulation, myeloperoxidase activity, TNF-α secretion and reactive oxygen species (ROS) (de Araújo Lopes et al., 2013).

Several compounds of natural origin have been investigated for their potential as ACE1 inhibitors. Some examples include: Quercetin: Quercetin is a flavonoid found in various fruits and vegetables such as apples, onions and green tea. Research has shown that quercetin has ACE1

inhibitory activity which can help lower blood pressure. (Larson et al., 2012). Grape seed extract: Grape seed extract contains compounds such as proanthocyanidins, which have been shown to have an ACE1 inhibitory effect. Several in vitro and animal studies have shown that grape seed extract may help lower blood pressure (Sugamoto et al., 2022). Olive leaf extract: Olive leaf extract contains a number of phenolic compounds, including oleuropein, which have potential as ACE1 inhibitors. Some research shows that olive leaf extract can help reduce blood pressure (Ghasemi et al., 2018). Green tea extract: Green tea contains catechins, one of which is epigallocatechin gallate (EGCG), which has ACE1 inhibitory properties. Several studies have shown that consumption of green tea can help lower blood pressure.(Joseph et al., 2022).

Table 2. Docking score and type interaction

compound	score	Hydrogen interactions		electrostatic	Hydrophobic
		Donors - receptors	Distance	residue	residue
native	-72,632	:GLN281:NE2 - :non1:O1	2.74352	-	HIS353
		:LYS511:NZ - :non1:O2	3.09297		HIS 383
		:TYR520:OH - :non1:O1	2.89986		HS 513
		:TYR520:OH - :non1:O2	2.90088		TYR523
		:HIS513:CE1 - :non1:O2	3.24624		PHE527
		:non1:C5 - :HIS383:NE2	3.4308		
		:non1:S1 - :HIS383	4.07369		
Afrormosin	-59,620	:UNK1:C17 - :SER526:OG	3.36186	-	
Pedunculagin	-45,205	:GLN281:NE2 - :UNK1:O22	2.83393	LYS511	VAL379
		:THR282:OG1 - :UNK1:O21	2.76082	ASP415	PHE457
		:ALA354:N - :UNK1:O15	2.37733	ASP453	ALA354
		:LYS454:NZ - :UNK1:O13	2.85457		VAL380
		:LYS454:NZ - :UNK1:O20	2.88499		
		:LYS511:NZ - :UNK1:O9	2.60677		
		:HIS353:CE1 - :UNK1:O4	2.61018		
		:ASP415:CA - :UNK1:O19	3.7297		
		:HIS513:CE1 - :UNK1:O5	2.60217		
Tomentosine	-70,986	:GLN281:NE2 - :UNK1:O3	2.76957	LYS454	TYR523, VAL379
		:LYS454:NZ - :UNK1:O2	2.95764		VAL380, HIS383
		:LYS511:NZ - :UNK1:O3	2.95828		PHE457, PHE527
		:TYR520:OH - :UNK1:O3	2.84516		
Desgalloylstachyurin	-54,374	:THR166:OG1 - :UNK1:O10	3.1056	LYS511	HIS383, TYR523
		:ASN277:ND2 - :UNK1:O7	2.51775	PHE457	ALA354, VAL380
		:GLN281:NE2 - :UNK1:O3	2.60101	HIS383	
		:GLN281:NE2 - :UNK1:O11	3.28521		
		:THR282:OG1 - :UNK1:O4	2.98891		
		:TYR520:OH - :UNK1:O13	2.79361		
		:UNK1:O4 - :GLU376:OE2	2.53268		
		:UNK1:O5 - :ASP453:OD1	2.88871		
		:HIS353:CE1 - :UNK1:O11	3.63134		
		:VAL380:CA - :UNK1:O21	2.64883		

CONCLUSION

Based on the screening of ACE1 inhibitors from the R. tomentosa compound, four compounds were obtained that have the potential to reduce blood pressure. Of the four compounds, further screening was carried out to see their interactions. It was found that Tomentosine is the most easily binds to ACE1. Because this research is limited to research using the insilico model, namely using a computer, it is necessary to do further research using in vitro and in vivo studies in experimental

animals in the laboratory. By conducting research in the laboratory, these compounds have the potential to treat blood pressure in the form of standardized herbal medicines in the future

ACKNOWLEDGEMENTS

The researcher would like to thank the University of Gastric Mangkurat for providing this research opportunity.

References

Abd Hamid, H., Mutazah, R., Yusoff, M. M., Abd Karim, N. A., & Abdull Razis, A. F. (2017). Comparative analysis of antioxidant and antiproliferative activities of Rhodomyrtus tomentosa extracts prepared with various solvents. *Food and Chemical Toxicology*, *108*, 451–457. https://doi.org/https://doi.org/10.1016/j.fct.2016.10.004

ChemAxon. (2016). ChemAxon - Software Solutions and Services for Chemistry and Biology. In *MarvinSketch, Version 16.10.31*. https://chemaxon.com/

de Araújo Lopes, A., Magalhães, T. R., de Andrade Uchôa, D. E., Silveira, E. R., Azzolini, A. E. C. S., Kabeya, L. M., Lucisano-Valim, Y. M., Vasconcelos, S. M. M., de Barros Viana, G. S., & Leal, L. K. A. M. (2013). Afrormosin, an Isoflavonoid from Amburana cearensis A. C. Smith, Modulates the Inflammatory Response of Stimulated Human Neutrophils. *Basic & Clinical Pharmacology & Toxicology*, *113*(6), 363–369. https://doi.org/10.1111/bcpt.12106

Ghasemi, S., Koohi, D. E., Emmamzadehhashemi, M. S. B., Khamas, S. S., Moazen, M., Hashemi, A. K., Amin, G., Golfakhrabadi, F., Yousefi, Z., & Yousefbeyk, F. (2018). Investigation of phenolic compounds and antioxidant activity of leaves extracts from seventeen cultivars of Iranian olive (Olea europaea L.). *Journal of Food Science and Technology*, *55*(11), 4600–4607. https://doi.org/10.1007/s13197-018-3398-1

Idris, M., Sukandar, E. R., Purnomo, A. S., Martak, F., & Fatmawati, S. (2022). Antidiabetic, cytotoxic and antioxidant activities of Rhodomyrtus tomentosa leaf extracts. *RSC Advances*, *12*(39), 25697–25710. https://doi.org/10.1039/D2RA03944C

James, P. A., Oparil, S., Carter, B. L., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., Lackland, D. T., LeFevre, M. L., MacKenzie, T. D., Ogedegbe, O., Smith, S. C. J., Svetkey, L. P., Taler, S. J., Townsend, R. R., Wright, J. T. J., Narva, A. S., & Ortiz, E. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*, *311*(5), 507–520. https://doi.org/10.1001/jama.2013.284427

Joseph, J., Karthika, T., Das, V. R. A., & Raj, V. S. (2022). The use of Pseudotyped Coronaviruses for the Screening of Entry Inhibitors: Green Tea Extract Inhibits the Entry of SARS-CoV-1, MERSCoV, and SARS-CoV-2 by Blocking Receptor-spike Interaction. *Current Pharmaceutical Biotechnology*, *23*(8), 1118–1129. https://doi.org/10.2174/1389201022666210810111716

Khirzin, H., Sukarno, S., Yuliana, N., Fawzya, Y., & Chasanah, E. (2015). The Activity of Angiotensin Converting Enzyme (ACE) Inhibitor and Collagen Peptide Antioxidant from Gama Sea Cucumber (Stichopus variegatus). *Jurnal Pascapanen Dan Bioteknologi Kelautan Dan Perikanan*, *10*, 27–35. https://doi.org/10.15578/jpbkp.v10i1.242

Kim, H., Han, M., Shin, S.-A., An, J., Ahn, M.-J., Lee, J. H., Park, H. H., & Lee, C. S. (2022). Afrormosin exerts an anticancer effect via MAPK and AKT signaling pathways in B16F10 cells. *Applied Biological Chemistry*, *65*(1), 71. https://doi.org/10.1186/s13765-022-00743-5

Korb, O., Stützle, T., & Exner, T. E. (2009). Empirical scoring functions for advanced Protein-Ligand docking with PLANTS. *Journal of Chemical Information and Modeling*, *49*(1), 84–96. https://doi.org/10.1021/ci800298z

Korzeniowska, K., Cielewiczi, A., Pawlaczyk, M., Motowidlo, K., Andrys-Wawrzyniak, I., & Jablecka, A. (2017). ANGIOEDEMA AFTER ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. *Acta Poloniae Pharmaceutica*, *74*(3), 983–986.

Krieger, E., & Vriend, G. (2014). YASARA View—molecular graphics for all devices—from smartphones to workstations. *Bioinformatics*, *30*(20), 2981–2982. https://doi.org/10.1093/bioinformatics/btu426

Lagunin, A., Stepanchikova, A., Filimonov, D., & Poroikov, V. (2000). PASS: prediction of activity spectra for biologically active substances. *Bioinformatics (Oxford, England)*, *16*(8), 747–748. https://doi.org/10.1093/bioinformatics/16.8.747

Larson, A. J., Symons, J. D., & Jalili, T. (2012). Therapeutic potential of quercetin to decrease blood pressure:

review of efficacy and mechanisms. *Advances in Nutrition (Bethesda, Md.)*, *3*(1), 39–46. https://doi.org/10.3945/an.111.001271

Messerli, F. H., Bangalore, S., Bavishi, C., & Rimoldi, S. F. (2018). Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? *Journal of the American College of Cardiology*, *71*(13), 1474–1482. https://doi.org/10.1016/j.jacc.2018.01.058

O'Gara, P. T., Kushner, F. G., Ascheim, D. D., Casey, D. E. J., Chung, M. K., de Lemos, J. A., Ettinger, S. M., Fang, J. C., Fesmire, F. M., Franklin, B. A., Granger, C. B., Krumholz, H. M., Linderbaum, J. A., Morrow, D. A., Newby, L. K., Ornato, J. P., Ou, N., Radford, M. J., Tamis-Holland, J. E., … Yancy, C. W. (2013). 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, *127*(4), e362-425. https://doi.org/10.1161/CIR.0b013e3182742cf6

Page, M. R. (2014). The JNC 8 hypertension guidelines: an in-depth guide. In *The American journal of managed care* (Vol. 20, Issue 1 Spec No., p. E8).

Pongpanich, P., Pitakpaiboonkul, P., Takkavatakarn, K., Praditpornsilpa, K., Eiam-Ong, S., & Susantitaphong, P. (2018). The benefits of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers combined with calcium channel blockers on metabolic, renal, and cardiovascular outcomes in hypertensive patients: a meta-analysis. *International Urology and Nephrology*, *50*(12), 2261–2278. https://doi.org/10.1007/s11255-018-1991-x

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., González-Juanatey, J. R., Harjola, V.-P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., … van der Meer, P. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution o. *European Heart Journal*, *37*(27), 2129–2200. https://doi.org/10.1093/eurheartj/ehw128

Riyadi, P. (2018). Peptida Bioaktif Untuk Penurunan Tekanan Darah Dari Hidrolisa Limbah Perikanan : Kajian Pustaka Bioactive Peptide For Lowering Pressure Blood From Fisheris By-Product : A Review. *Jurnal Pengolahan Dan Bioteknologi Hasil Perikanan*, *7*(1), 1–6.

Rosano, G. M. C., Tamargo, J., Kjeldsen, K. P., Lainscak, M., Agewall, S., Anker, S. D., Ceconi, C., Coats, A. J. S., Drexel, H., Filippatos, G., Kaski, J. C., Lund, L., Niessner, A., Ponikowski, P., Savarese, G., Schmidt, T. A., Seferovic, P., Wassmann, S., Walther, T., & Lewis, B. S. (2018). Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society . *European Heart Journal. Cardiovascular Pharmacotherapy*, *4*(3), 180–188. https://doi.org/10.1093/ehjcvp/pvy015

Sang, V. T., & Ngo, D.-H. (2019). The Health Beneficial Properties of Rhodomyrtus tomentosa as Potential Functional Food. *Biomolecules*, *9*, 76. https://doi.org/10.3390/biom9020076

Silvariño, R., Rios, P., Baldovinos, G., Chichet, M. A., Perg, N., Sola, L., Saona, G., De Souza, N., Lamadrid, V., & Gadola, L. (2019). Is Chronic Kidney Disease Progression Influenced by the Type of Renin-Angiotensin-System Blocker Used? *Nephron*, *143*(2), 100–107. https://doi.org/10.1159/000500925

Sorodoc, V., Sorodoc, L., Lionte, C., Gazzi, E., Jaba, I. M., & Mungiu, O. C. (2010). [Intentional poisoning with ACE inhibitors. Emergeny Hospital Iaşi]. *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi*, *114*(2), 359–362.

Sugamoto, K., Tanaka, Y. L., Saito, A., Goto, Y., Nakayama, T., Okabayashi, T., Kunitake, H., & Morishita, K. (2022). Highly polymerized proanthocyanidins (PAC) components from blueberry leaf and stem significantly inhibit SARS-CoV-2 infection via inhibition of ACE2 and viral 3CLpro enzymes. *Biochemical and Biophysical Research Communications*, *615*, 56–62. https://doi.org/10.1016/j.bbrc.2022.04.072

Systèmes, D. (2020). *Free Download: BIOVIA Discovery Studio Visualizer - Dassault Systèmes*. https://discover.3ds.com/discovery-studio-visualizer-download#_ga=2.4935860.685747970.1587999055-a5d1c1c0-3176-11e9-a86f-e302515d21c8

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E. J., Collins, K. J., Dennison Himmelfarb, C., DePalma, S. M., Gidding, S., Jamerson, K. A., Jones, D. W., MacLaughlin, E. J., Muntner, P., Ovbiagele, B., Smith, S. C. J., Spencer, C. C., Stafford, R. S., Taler, S. J., Thomas, R. J., Williams, K. A. S., … Wright, J. T. J. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical P. *Journal of the*

American College of Cardiology, *71*(19), e127–e248. https://doi.org/10.1016/j.jacc.2017.11.006

Widiasari, S. (2018). Mekanisme Inhibisi Angiotensin Converting Enzym Oleh Flavonoid Pada Hipertensi Inhibition Angiotensin Converting Enzym Mechanism By Flavonoid in Hypertension. *Collaborative Medical Journal*, *1*(2), 30–44. https://doi.org/http://jurnal.univrab.ac.id/index.php/cmj/article/view/474

Williams, B. (2016). Drug discovery in renin-angiotensin system intervention: past and future. *Therapeutic Advances in Cardiovascular Disease*, *10*(3), 118–125. https://doi.org/10.1177/1753944716642680

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D. L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S. E., Kreutz, R., Laurent, S., … Desormais, I. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European Heart Journal*, *39*(33), 3021–3104. https://doi.org/10.1093/eurheartj/ehy339

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E. J., Colvin, M. M., Drazner, M. H., Filippatos, G. S., Fonarow, G. C., Givertz, M. M., Hollenberg, S. M., Lindenfeld, J., Masoudi, F. A., McBride, P. E., Peterson, P. N., Stevenson, L. W., & Westlake, C. (2017). 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Ame. *Circulation*, *136*(6), e137–e161. https://doi.org/10.1161/CIR.0000000000000509

Zhang, Y., Ding, X., Hua, B., Liu, Q., Chen, H., Zhao, X.-Q., Li, W., & Li, H. (2020). Real-world use of ACEI/ARB in diabetic hypertensive patients before the initial diagnosis of obstructive coronary artery disease: patient characteristics and long-term follow-up outcome. *Journal of Translational Medicine*, *18*(1), 150. https://doi.org/10.1186/s12967-020-02314-y