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High-Pressure Extraction, GC-MS Analysis, and In Silico Antihypertensive Activity of *Physalis angulata* L. from South Sulawesi

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Abstract

Hypertension is a medical disease condition by an elevation in systolic blood pressure above 140 mmHg and diastolic blood pressure over 90 mmHg. The Renin Angiotensin Aldosterone System (RAAS) is a complex endogenous system in which RAAS controls the levels of sodium, potassium, and blood volume. One of the plants that has an antihypertensive effect is *Physalis angulata* L. or known as the ground berry. The high-pressure extraction method has several benefits, including its cost-effectiveness, shorter extraction durations, decreased reliance on hazardous solvents, and higher yields compared to traditional extraction methods, accomplished by those using classical extraction. The study is to examine the impact of High-Pressure Extraction (HPE) on the percentage yield of the extract and determine the component by GC-MS analysis. Also, the investigation will utilize the Molecular Docking approach to identify the compound's potential as antihypertensive agents and provide insights about the compound's physiochemical, pharmacokinetic, and toxicological aspects. The percent yield shows that extraction using the HPE method with a pressure of 600 MPa obtained the highest yield of 40.238%. Analysis of GC-MS showed hexadecanoic acid, ethyl esters, and 9.12,15-Octadecatrienoic acid (Z, Z, Z) - appearing at each HPE pressure. 6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one has the highest binding affinity value -7.1 Kcal/mol to 3BKK protein angiotensin-converting enzyme (ACE) and Bis(2-ethylhexyl) phthalate has a highest bonding affinities value -7.0 Kcal/mol to 4ZUD protein angiotensin receptor blocker (ARB). The absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis suggests compounds from GC-MS analysis have better properties compared to standard drugs Captopril (ACE) and Valsartan (ARB) as antihypertensive.

Keywords: *Physalis angulata L.; High Pressure Extraction; In Silico; Antihypertensive; GC-MS*

1. Introduction

Hypertension is a medical disease condition by an elevation in systolic blood pressure above 140 mmHg and diastolic blood pressure over 90 mmHg. The risk factors for hypertension can be categorized into two groups. The first is unalterable risk factors, which include age, gender, and heredity. The second category comprises of variable risk factors, including obesity, smoking, sedentary lifestyle, high salt consumption, dyslipidemia, excessive alcohol use, and stress [1].

The Renin Angiotensin Aldosterone System (RAAS) is a complex endogenous system in which RAAS controls the levels of sodium, potassium, and blood volume. As a result, this system impacts the constriction of blood vessels and the activity of the sympathetic nervous system, making it the most significant factor in regulating blood pressure for maintaining homeostasis [2].

Within the RAAS, renin facilitates the transformation of angiotensinogen into angiotensin I in the bloodstream. The angiotensin-converting enzyme (ACE) initiates the transformation of angiotensin I into angiotensin II. Subsequently, angiotensin II will bind to its specific receptors, namely the AT1 and AT2 receptors. Angiotensin II induces constriction of small arteries, leading to an elevation in arterial blood pressure. Furthermore, it stimulates the reabsorption of sodium ions (Na+) and water from the kidney tubules, resulting in a rise in blood pressure [2], [3].

ACE inhibitor drugs such as captopril, lisinopril, and ramipril are the initial treatment for hypertension. An ACE inhibitor inhibits the process of converting angiotensin I into angiotensin II. Furthermore, ACE inhibitors additionally inhibit the degradation of bradykinin, resulting in the frequently observed adverse effect of a dry cough in people using ACE inhibitors [2]. Another class of medications used to treat hypertension are angiotensin receptor blockers (ARBs), which inhibit the

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angiotensin receptors responsible for the effects of angiotensin II. This medicine may cause hyperkalemia in patients suffering from chronic renal disease or kidney failure [2], [4].

Indonesians commonly use herbal plants as a substitute for hypertension medicine. *Physalis angulata* L., commonly referred to as the ground berry plant, is a plant that exhibits antihypertensive properties. A study conducted in 2019 demonstrated that rats, when administered *P. angulata* plant juice after being stimulated with NaCl, saw a significant decrease of 42.21% in their blood pressure. A study conducted in 2023 demonstrated that pregnant women with hypertension observed a reduction in blood pressure following the consumption of *P. angulata* water infusion [5].

High Pressure Extraction (HPE) is a modern method of extraction that does not involve the use of heat and utilizes fluids, mostly water, to transmit extremely high pressures (100-1000 MPa) to extract substances [6]. The HPE technique is highly advantageous for extracting natural materials due to its economic properties and shorter extraction times. This method saves a significant amount of energy and reduces the need for toxic solvents, resulting in lower residues of the solvent in the extracted material [7] the yields produced from this extraction process are significantly greater than those accomplished by those using classical extraction [8].

The study is to examine the implications of HPE on the percentage yield of the extract and determine the component by GC-MS analysis. The investigation utilize the Molecular Docking approach to identify the compounds and assess their binding affinity, as well as their potential as antihypertensive agents. Additionally, this approach will provide insights into the physiochemical, pharmacokinetic, and toxicological aspects of the compounds.

Table 1: Summary of data obtained from least-squares fit of Eq. (20) to k_m vs E_i plots for three selected systems

Redox moiety	Diluent	Method	k_0 (s^{-1})	$E_i^{0'}$ V vs SSCE	γ	fwhm (V)[a]
R1	D1	ILIT	3.4×10^4	0.495	95	-
		CV	3.3×10^4	0.474	100	0.103
R2	D2	ILIT	6.0×10^4	0.340	24	-
		CV	6.1×10^4	0.346	24	0.112
R3	D3	ILIT	3.2×10^6	0.328	12.0	-
		CV	3.2×10^6	0.324	12.1	0.121

[a]Full-

2. Experimental

2.1 Sample Preparation

The samples of *Physalis angulata* L. plant were collected from the Pinrang Province in South Sulawesi. Samples were gathered and organized. Afterward, the drying process is carried out by utilizing an oven. The simplisia of *P. angulata* plants is obtained through the process of dry disorting, grinding, and sieving.

2.2 High-Pressure Extraction Method

The extraction was conducted using a high-pressure extraction method. The Simplisia powder is placed in a solvent called Reserved Osmosis (RO). The extraction process was conducted under high-pressure conditions, specifically at pressures of 200, 400, and 600 MPa, for 15 minutes. The liquid extraction underwent filtration and later freeze-drying until it transformed into a dry extract. The yield percentage was then calculated.

2.3 Infusion Extraction Method

The extraction process was conducted using an infusion pot at a temperature of 55°C for a duration of 15 minutes. Subsequently, the mixture underwent filtration and evaporation processes until it transformed into a dense extract.

2.4 Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

Sample preparation was carried out with 100 mL of sample, then 100 mL of methanol: chloroform (1:1) was added. Extraction was then carried out using Ultrasonics at a temperature of 55°C for 30 minutes. Then the sample was centrifugated and the supernatant part was taken. Derivatization of the sample was carried out by adding DMF dialkyl acetal reagent, then the sample was heated at 100°C, then the sample was injected into the GC-MS. The chromatogram data was analyzed using the NIST 17 and Wiley 9 libraries.

2.5 Software and Materials In Silico Analysis

The study utilized the following applications: Chem3D (Version 15.0), Chimera (Version 1.17.3), AutoDock Vina, Pymol (version 3.0), and Discovery Studio 2021. The target proteins utilized are the three-dimensional structures of Angiotensin Converting Enzyme (ACE) identified by the Protein Data Bank (PDB) with the ID: 3BKK [9] and Angiotensin Receptor (AT1) (PDB ID: 4ZUD) [10] which obtained from https://www.rcsb.org/. The ligands were obtained from the results of GC-

MS analysis data of *P. angulata* plant extracts. The 3D structure of the compound was obtained from https://pubchem.ncbi.nlm.nih.gov/.

2.6 Protein Preparation

Chimera (Version 1.17.3) was used to get rid of any water molecules, chains, or natural ligands that were still in the 3BKK and 4ZUD target proteins. Validation was performed using AutoDock Vina and Pymol (Version 3.0), with redocking of the natural ligand and target protein.

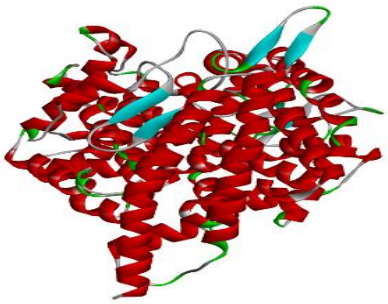

Fig. 1. 3BKK Protein (ACE)

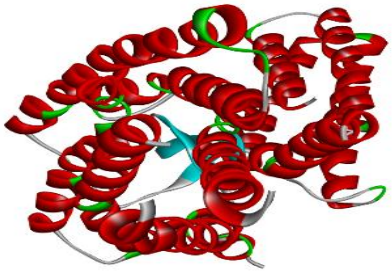

Fig. 2. 4ZUD Protein (ARB)

2.7 Ligand Preparation

This study utilized chemical compounds obtained from the gas chromatography-mass spectrometry (GC-MS) examination of *P. angulata* plants as ligands. Captopril and Valsartan served as reference drugs in this investigation. The chemicals that were downloaded were subsequently transformed from sdf format to pdb format using Chem3D (Version 15.0). Next, the compound is optimized using Chimera (Version 1.17.3).

2.8 Validation of Molecular Docking Methods

Validation is performed through the process of redocking, which involves docking the native ligand again into the target protein after removing the original ligand. The validation parameter used is the root mean square deviation (RMSD) value, which is less than 2 Å. [10].

2.9 Molecular Docking Process

Chimera (Version 15.0) was used to perform molecular docking of the chemicals analyzed by GC-MS with their target proteins. The molecular docking process was performed using AutoDock Vina with a grid box size for protein 3BKK set as center_x = 45.88; center_y = 44.29; center_z = 45.38; size_x = 8.00; size_y = 11.82; size_z = 14.46. And for the 4ZUD protein, center_x = -41.37, center_y = 63.11, center_z = 28.59, size_x = 11.86, size_y = 9.83, and size_z = 10.61. The binding affinity values of the docking results were recorded, and the structure of the docking results on each ligand was visualized to determine the interaction between the protein and its ligand [11].

2.10 Drug-Likeness and Prediciton ADMET

The SwissADME online tool available at http://www.swissadme.ch/ it was applied to predict many physicochemical characteristics, including the molecular weight, Log P value, the number of hydrogen bond acceptors, the number of hydrogen bond donors, and polar surface activity value.. The pKCSM online tool is the technique employed to forecast pharmacokinetic parameters, involving the process of absorption, distribution, metabolism, and excretion., as well as drug toxicity. https://biosig.lab.uq.edu.au/pkcsm/ [12], the data is then collected and checked.

3. Result and Discussion

3.1 Percent Extraction Yield

High-pressure extraction (HPE) works by applying pressure to the plant cells, which damages their cell walls and internal structures, causing a reduction in the resistance of mass transfer within the cell internally so that the cell is pushed out. Bioactive components that can be extracted through this method include vitamins, alkaloids, saponins, flavonoids, and pigments [8]. The percent yield results in the four methods show that extraction using the HPE method with a pressure of 600 MPa obtained the highest yield of 40.238%, and the lowest yield of 10.72% was obtained by extraction with the infusion method.

Table 2: Percent Yield Results of High Pressure Extraction (HPE) and Infusa extraction methods

Methods	Pressure (MPa)	Initial Weight (g)	Final Weight (g)	Yield (%)
HPE	200	50	10.937	21.874
HPE	400	50	15.838	31.676
HPE	600	50	20.119	40.238
Infusion	-	10	1.072	10.72

According to Sun *et al* (2016) explain that pressure can increase the extraction results of a sample because high pressure can increase solubility, this is based on the theory of mass transfer that the mass transfer rate = pressure/mass transfer resistance. The more solvent that enters the cell, the more compounds can penetrate the cell membrane under high pressure [22].

The use of high-pressure extraction offers a significant benefit in terms of achieving a higher yield compared to traditional extraction methods. [8], so that the results obtained in this study are appropriate.

3.2 GC-MS Analysis Results

The results of GC-MS analysis showed that the results of extract analysis using the HPE method with a pressure of 200 MPa contained six compounds, the HPE method with a pressure of 400 MPa contained nine compounds, and the HPE method with a pressure of 600 MPa contained eight compounds. While the results of extract analysis using the infusa method contained three compounds.

Based on the table above, the n-Hexadecanoic Acid compound is found in the extraction of HPE pressure 200, 400, 600, and infusion methods. According to Jalan & Al-Rufaye (2023), n-Hexadecanoic acid, which is a fatty acid found in leaf extracts of *P. angulata* plants [13]. Other compounds found in the analysis results with HPE extraction pressures of 200, 400, and 600 are hexadecanoic acid ethyl ester, and 9,12,15-octadecatrienoic acid, ethyl ester, (Z,Z,Z)-. Based on research that identifies the compound content of *P. angulata* leaves, the contain compounds such as octadecatrienoic acid ethyl ester [14]. These fatty acids have been use for antimicrobial, hypercholesterolemia, dermatogenic, anti-inflammatory, and anti-tumor [15]. Fatty acids possess the capability to function as antihypertensive agents through their potential effects by reducing blood pressure through their vasodilatory actions and inhibiting platelet aggregation. Fatty acids such as linoleic acid can enhance blood vessel dilatation by promoting vasodilation [16]. Polyunsaturated Fatty Acids (PUFAs) such as linoleic acid and α-linolenic acid could increased nitric oxide generation leading to vasodilation of arteriole [23]. PUFAs could also inhibit the activity of ACE by decreasing angiotensin II formation and suppressed the TGF expression which could prevent the primary hypertension [25]. In gestational hypertension and pre-eclampsia, fatty acids are

proposed to protect the uterine blood vessels via their anti-inflammatory effects, thus might lowering the onset of gestational hypertension [24]. So, the compound from GC-MS highly had a chance as an antihypertensive agent.

Table 3: Comparative results of GC-MS analysis profiles on *P.angulata* using high-pressure extraction of 200, 400, 600 Mpa, and Infusa method.

Compounds Name	Methods			
	HPE 200 Mpa (%)	HPE 400 Mpa (%)	HPE 600 Mpa (%)	Infusion
4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl-	2.73	-	-	2.79
6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one	1.58	-	-	2.10
n-Hexadecanoic acid	7.87	20.49	20.74	1.72
Hexadecanoic acid, ethyl ester	1.46	5.91	8.37	-
2-HEXADECEN-1-OL, 3,7,11,15-TETRAMETHYL-, [R-[R*,R*-(E)]]-	1.65	4.43	-	-
9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z)-	4.89	11.64	15.14	-
9,12-Octadecadienoic acid (Z,Z)-	-	5.99	4.02	-
9,12,15-Octadecatrienoic acid, (Z,Z,Z)-	-	20.32	14.71	-
Linoleic acid ethyl ester	-	5.95	7.49	-
Bis(2-ethylhexyl) phthalate	-	1.03	1.01	-
Octadecanoic acid, ethyl ester	-	-	1.65	-

3.3 In Silico Analysis Results

The results of *in silico* validation with redocking on native ligand target protein and ACE and ARB target proteins obtained RMSD values of 0.0 Å and 0.127 Å. RMSD value on this redocking has been valid because the value is below 2 Å. [10]. The interaction visualization results of the docked native ligand and the actual native ligand can be seen in Figure 3 and 4.

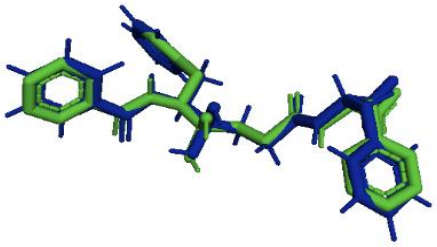

Fig. 3. Validation results of native ligand of 3BKK protein (ACE)

Fig. 4. Validation results of native ligand of 4ZUD protein (ARB)

Table 4: Comparative results of *in silico* analysis

	3BKK		4ZUD	
	Binding affinity (kcal/mol)	Hydrogen Bond Interaction	Binding affinity (kcal/mol)	Hydrogen Bond Interaction
Native Ligan	-10.5	ALA 356 GLN 281 GLU 411 HIS 383 HIS 353 TYR 523	-8.9	ARG 167
Control	-5.5	ALA 356 HIS 387	-7.7	ARG 167
4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl-	-5.1	HIS 383 TYR 523	-4.8	ARG 167
6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one	-7.1	LYS 511 TYR 520	-6.9	ARG 167
n-Hexadecanoic acid	-5.7	GLU 411	-5.8	ARG 167
Hexadecanoic acid, ethyl ester	-5.3	-	-5.5	-
2-HEXADECEN-1-OL, 3,7,11,15-TETRAMETHYL-, [R-[R*,R*-(E)]]-	-6.0	-	-6.7	-
9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z)-	-6.0	ALA 356	-5.7	-
9,12-Octadecadienoic acid (Z,Z)-	-5.7	GLN 281 LYS 511 TYR 520	-6.0	TYR 292
9,12,15-Octadecatrienoic acid, (Z,Z,Z)-	-6.2	ARG 522 TYR 523	-6.2	ARG 167 SER 105 SER 109
Linoleic acid ethyl ester	-6.0	-	-6.1	ARG 167
Bis(2-ethylhexyl) phthalate	-6.8	ARG 522 HIS 387	-7.0	ARG 167
Octadecanoic acid, ethyl ester	-5.4	ARG 522	-6.1	ARG 167

The 3BKK (ACE) protein has a native ligand, KAF, which has a binding affinity value of -10.5 Kcal/mol. 4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl- has the lowest binding affinity value of -7.1 Kcal/mol to 3BKK protein when compared to other GC-MS compounds. 6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (-7.1 Kcal/mol), n-Hexadecanoic acid (-5.7 Kcal/mol), 2-HEXADECEN-1-OL, 3,7,11,15-TETRAMETHYL-, [R-[R*,R*-(E)]]- (-6. 0 Kcal/mol), 9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z)- (6.0 Kcal/mol), 9,12-Octadecadienoic acid (Z,Z)- (-5. 7 Kcal/mol), 9,12,15-Octadecatrienoic acid, (Z,Z,Z)- (-6.2 Kcal/mol), Linoleic acid ethyl ester (-6.0 Kcal/mol) and Bis(2-ethylhexyl) phthalate (-6.8 Kcal/mol) had smaller binding affinity values compared to the control compound captopril (-5.5 Kcal/mol). The lower the bond energy value, the more stable a compound will be in order to bind to a receptor [17].

The native ligand of the 3BKK protein, KAF, forms six hydrogen bond interactions with specific amino acid residues in Table 3. These amino acid residues are ALA 356, GLN 281, GLU 411, HIS 383, HIS 353, and TYR 523. The control compound, Captopril, exhibits a hydrogen bond interaction identical to that of the native ligand, ALA 356. The compounds identified through GC-MS analysis that exhibit the same hydrogen bond interactions as the native ligands are 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- (HIS 383 and TYR 523), n-Hexadecanoic acid (GLU 411), 9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z)- (ALA 356), 9,12-Octadecadienoic acid (Z,Z)- (GLN 281), and 9,12,15-Octadecatrienoic acid, (Z,Z,Z)- (TYR 523).

The hydrogen bond interactions observed in the compounds from GC-MS indicate that they possess similar hydrogen bond interactions at active sites as the native ligands and control compounds. The *P. angulata* plant exhibits promising properties as an anti-hypertensive agent and demonstrates efficacy in inhibiting ACE proteins. The 4ZUD (ARB) protein possesses a natural ligand, OLM, with a binding affinity of -8.9 Kcal/mol. The control compound, Valsartan, exhibits a binding affinity value of -7.7 Kcal/mol. The binding affinity value of Bis(2-ethylhexyl) phthalate is nearly equivalent to the control compound value of -7.0 Kcal/mol. Table 3 shows that the 4ZUD protein's native ligand, OLM, and the control

molecule both have a hydrogen bond interaction with ARG 167. The compounds identified using GC-MS analysis, which exhibit hydrogen bond interactions similar to those of the native ligands and control compounds, are listed in Table 3. These compounds specifically form hydrogen bonds at the active site ARG 167. So, the *P. angulata* plant also has the potential to work with ARB proteins.

3.4 Drug-Likeness and Prediction ADMET

Prediction of the physicochemical properties of 6-Hydroxy-4,4,7a-trimethyl-5,6,7,7atetrahydrobenzofu-ran2(4H)-one (compound A) and Bis(2-ethylhexyl) phthalate (compound B) when crossing the cell membrane can be done by looking at *Lipinski's rule of five*. Based on *Lipinski's rule of five*, there are five rules, such as the molecular weight of the compound ≤ 500 Da, a partition coefficient (logP) value < 5, The maximum number of hydrogen bond donors is 5, the maximum amount of hydrogen bond acceptors is 10, and the molar refractivity varies between 40 to 130. [18] . The prediction results for physicochemical properties can be seen in Table 4. Compounds A and B have a molecular weight of less than 500 Da, whereas compounds with a molecular weight ≤ 500 Da can easily penetrate the cell wall. [19]. Compound A has a logP value of less than five, while compound B has a value of more than five, so compound B does not meet the requirements of *Lipinski's rule of five*. The logP value quantifies how well the substance dissolves in a liquid membrane [11], As the log P value increases, the ability of a substance to cross the cell membrane decreases. The compound will exhibit a high affinity for the cell membrane, resulting in a challenging identification of the target enzyme. In addition, due to its great affinity for the cell membrane, it can exhibit toxicity as it becomes more challenging to eliminate [20]. Compounds A and B have less than five hydrogen bond donors and fewer than ten hydrogen bond acceptors. As the value increases, the amount of energy needed for the absorption process also increases [11]. Compounds A and B have molar refractivity values that are still in the range of 40–130. According to the results, compound A meets all the requirements of *Lipinski's rule of five*.

Table 5: Lipinski's parameters of compound A and B

Lipinski's Parameters	Compounds		Standard
	6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (Compound A)	Bis(2-ethylhexyl) phthalate (Compound B)	
Molecular Weight	196.246	390.564	≤ 500 Dalton
iLogP	1.4092	6.433	< 5
H-bond acceptors	3	4	≤ 10
H-bond donors	1	0	≤ 5
Molar Refractivity	52.51	116.30	40-130

ADMET prediction is performed to forecast the absorption pattern through the gastrointestinal tract, distribution within the bloodstream towards the therapeutic target, and metabolism within the liver to produce active metabolites for subsequent elimination through certain organs. The ADMET prediction results can be seen in Table 5. Compounds A and B exhibit a relatively high absorption rate. A compound is considered to have a favorable absorption rate if it exceeds 80%, while it is considered to have a poor absorption rate if it falls below 30% [12]. Caco-2, also known as human colon adenocarcinoma, serves as an indicator for the movement of drugs across the epithelial cells of colon adenocarcinoma [20]. The predicted value of Caco-2 is categorized into three groups: ≤0.500, indicating low permeability; <2.50, indicating medium permeability; and ≥2.50, indicating high permeability [21]. Compounds A and B exhibit Caco-2 values below 2.50, indicating that they possess medium permeability. VDss or Volume Distribution Steady State, refers to the quantity of an active drug that can be evenly distributed throughout the human body. Compounds A and B have low VDss values. A compound is said to have a low VDss if the value is <-0.15 log L/kg and a high value if it is >0.45 log L/kg [17]. But when compared to the standard drugs, the VDss values of both compounds have higher values. The blood-brain barrier serves as a predictive measure to assess a compound's capacity to enter the region of the brain protected by the blood-brain barrier. Compound B has a Log BB value of more than 0.3, so it can be predicted that the compound possess the capability to pass through the blood-brain barrier. A compound is said to be able to penetrate the blood-brain barrier well if it has a Log BB value greater than 0.3, and cannot be distributed properly if the value is less than -1 [12]. Both compounds A and B are not metabolized by the enzyme CYP2D6. However, compound A is metabolized by the enzyme CYP3A4. None of the substances exhibited inhibitory activity against CYP1A2, CYP2D6, and CYP3A4. Compound B exhibited inhibitory activity against CYP2C19 while compound A did not. Total clearance is the combined amount of clearance from the liver and clearance from the kidneys [12]. Compound A exhibits a total clearance of 1.042, while Compound B demonstrates a total clearance of 1.898. The elimination of a chemical

accelerates in correlation to its higher total clearance value [17]. Both compounds exhibited no hepatotoxicity. Compounds A and B are non-mutagenic. Amex toxicity refers to the assessment of whether a substance has the potential to cause genetic mutations or cancer. Both compounds have skin sensitization properties. Skin sensitization refers to an exaggerated immune response that can be caused by chemicals that penetrate the outermost barrier of the skin, which is called the stratum corneum [11].

Table 6: ADMET Properties

	Properties	6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (Compound A)	Bis(2-ethylhexyl) phthalate (Compound B)	Captopril	Valsartan	Unit
Absorbtion	Intestinal Absorbtion (%)	95.935%	92.45%	79.769%	45.544%	% Absorbed
	Caco-2 permeability	1.239	1.408	1.179	-0.17	(log Papp in 10^{-6} cm/s)
Distribution	VDss	0.117	0.36	-0.939	-0.887	(log L/kg)
	Blood-Brain Barrier	-0.189	-0.175	-0.229	-1.545	(Log BB)
Metabolism	CYP2D6 Substrate	No	No	No	No	Yes/No
	CYP3A4 Substrate	No	Yes	No	No	Yes/No
	CYP1A2 Inhibitor	No	No	No	No	Yes/No
	CYP2C19 Inhibitor	No	Yes	No	No	Yes/No
	CYP2D6 Inhibitor	No	No	No	No	Yes/No
	CYP3A4 Inhibitor	No	No	No	No	Yes/No
Excretion	Total Clearance	1.042	1.898	0.306	0.62	log ml/min/kg
Toxicity	Hepatotoxicity	No	No	No	Yes	Yes/No
	Oral Rat Acute Toxicity (LD50)	1.94	1.451	1.654	2.643	mol/kg
	AMES Toxicity	No	No	No	No	Yes/No
	Skin Sensitisation	No	No	No	No	Yes/No

4. Conclusions

This research focuses on the effect of high-pressure extraction on yield results. The yield results obtained using the high-pressure extraction method are much greater than those obtained using conventional methods. GC-MS results of extracts with three different pressures showed Hexadecanoic acid, ethyl ester and 9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z)- appeared at each extraction pressure. *In silico* results show 6-Hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one has the highest binding affinity value of -7.1 Kcal/mol to protein 3BKK (ACE) and Bis(2-ethylhexyl) phthalate has the highest binding affinity value of -7.0 Kcal/mol to protein 4ZUD (ARB). ADMET analysis showed that compounds from GC-MS analysis have a better properties compared to the standard drugs, Captopril (ACE) and Valsartan (ARB), as antihypertensives.

5. Conflicts of interest

There are no conflicts to declare”

6. Acknowledgments

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7. References and Bibliography

[1] Kemenkes RI. "Pedoman Teknis Penemuan dan Tatalaksana Hipertensi". Jakarta. Direktorat Pengendalian Penyakakit Tidak Menular. KEMENKES RI. 2013.

[2] DiPiro, Joseph T. PharmD F. "Pharmacotherapy: A Pathophysiologic Approach 11th Edition". Dipiro. 2020.

[3] H. J. Qureshi and N. Hamid, "Review Article Renin-Angiotensin Aldosterone System (Raas)". *Journal of Akhtar Saeed Medical & Dental College*. Vol. 2, no. 4. 2020. doi: 10.1042/CS20100.

[4] Wells, B. G., DiPiro, J. T., Schwinghammer, T. L., & DiPiro, C. V. "*Pharmacotherapy Handbook Tenth Edition*". McGraw-Hill. 2017.

[5] E. Pujiati & Ambarwati. "Antihypertensive Effect of Ciplukan (*Physalis angulata* L): A Literature Review Efek Antihipertensi Ciplukan (*Physalis angulata L*): A Literature Review." Menara *Journal of Health Science* [Online]. Available: https://jurnal.iakmikudus.org/index.php/mjh

[6] A. K. Balakrishna, M. Abdul Wazed, and M. Farid, "A review on the effect of high pressure processing (HPP) on gelatinization and infusion of nutrients," *Molecules*, vol. 25, no. 10. MDPI AG, May 01, 2020. doi: 10.3390/molecules25102369.

[7] J. Li, M. Pettinato, R. Campardelli, I. De Marco, and P. Perego, "High-Pressure Technologies for the Recovery of Bioactive Molecules from Agro-Industrial Waste," *Applied Sciences (Switzerland)*, vol. 12, no. 7. MDPI, Apr. 01, 2022. doi: 10.3390/app12073642.

[8] S. A. Khan, R. Aslam, and H. A. Makroo, "High pressure extraction and its application in the extraction of bio-active compounds: A review," *Journal of Food Process Engineering*, vol. 42, no. 1. Blackwell Publishing Inc., Feb. 01, 2019. doi: 10.1111/jfpe.12896.

[9] Y. Bare, D. R. Sari, Y. T. Rachmad, S. S. N. D. Tiring, A. H. Rophi, and F. A. D. Nugraha, "Prediction Potential Chlorogenic Acid As Inhibitor Ace (In Silico Study)," *Bioscience*, vol. 3, no. 2, p. 197, Oct. 2019, doi: 10.24036/0201932105856-0-00.

[10] D. Budiarto, B. Wijianto, and H. Ih, "Indonesian Journal of Chemical Research Study of Anthocyanin Molecule Blocking as Anti-Hypertensive through the Pathway of the Renin-Angiotensin-Aldosterone System (RAAS)," *J. Chem. Res*, vol. 11, no. 1, pp. 49–58, 2023, doi: 10.30598//ijcr.

[11] F. A. Muslikh, R. R. Samudra, B. Ma'arif, Z. S. Ulhaq, S. Hardjono, and M. Agil, "In Silico Molecular Docking and ADMET Analysis for Drug Development of Phytoestrogens Compound with Its Evaluation of Neurodegenerative Diseases," *Borneo Journal of Pharmacy*, vol. 5, no. 4, pp. 357–366, Nov. 2022, doi: 10.33084/bjop.v5i4.3801.

[12] [12]. Dwi, D. K., Sasongkowati, R., & Haryanto, E. "Studi In Silico Sifat Farmakokinetik, Toksisitas, Dan Aktivitas Imunomodulator Brazilein Kayu Secang Terhadap Enzim 3-Chymotrypsin-Like Cysteine Protease Coronavirus". *Journal of Indonesian Medical Laboratory and Science*. Vol. 1, no. 1. 2020. doi: https://doi.org/10.53699/joimedlabs.v1i1.14

[13] Jalab, A. Z., & AL-RUFAYE, Z. T. A. "Chemical composition and antioxidant activity of Physalis angulata AH-ZE," World *Journal of Advanced Research and Reviews*, vol. 19, no. 2, pp. 1072–1077, Aug. 2023, doi: 10.30574/wjarr.2023.19.2.1610.

[14] Awaludin, Yulma, and Kartina, "Identification of Secondary Metabolites from Ethanol Extract of Ciplukan (Physalis angulate) Leaves and Toxicity Test on Post-Larvae of Tiger Shrimp (Penaeus monodon)," *Jurnal Ilmiah Perikanan dan Kelautan*, vol. 11, no. 2, pp. 92–99, Nov. 2019, doi: 10.20473/jipk.v11i2.13162.

[15] N. Usaizan, N. A. P. Abdullah, S. H. Ahmad, and G. Saleh, "Preliminary Phytochemical Screening and GC-MS Analysis of Ethanol Extract of Physalis Minima L. (Solanaceae)," *Journal of Advanced Agricultural Technologies*, vol. 1, no. 2, 2014, doi: 10.12720/joaat.1.2.100-103.

[16] Arumsari, M. D., Sururi, A. M., Hendrata, E., Kamila, R. K. Z., Wibowo, D. M. F., Fajriyah, L., & Rahayu, D. A. "In Silico Study: ACE Inhibitory Activity as a Marine Animal Fatty Acid Antihypertensive Candidate". *Jurnal Biodjati*, vol. 9, no. 1, pp. 80–89. May. 2024, doi: 10.15575/biodjati.v9i1.29899.

[17] J. K. Islam, A. Tilaqza, M. Herbani, and H. Articel, "Studi In silico Potensi Anti Hipertensi dan Prediksi Profil Farmakokinetika Daun Jati Belanda (Guazuma ulmifolia. Lamk)," 2021, doi: 10.33474/jki.v1.

[18] C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," *Advanced Drug Delivery Reviews*, vol. 64, no. SUPPL. pp. 4–17, Dec. 2012. doi: 10.1016/j.addr.2012.09.019.

[19] R. Hasan, R. Herowati, and G. P. Widodo, "In Silico Analysis Of Antidiabetic Activity And Admet Prediction Of Potential Compounds From Luffa Acutangula". *Proceedings of The International Conference on Health Technology*. Vol. 1. 2022. Available: https://karya.brin.go.id/id/eprint/22777

[20] Wulandari, R. P., Gabriel, K., Nurdin, H. A., Pakhrul, D. H. F., Harits, S. S., Prameswari, N., & Aulifa, D. L. "Indonesian Journal of Chemical Science In Silico Study of Secondary Metabolite Compounds in Parsley (*Petroselinum crispum*) as a Drug Terapy for Blood Cancer (Myeloproliferative Neoplasm (MPN)) targeting JAK-2," 2023. *Indonesian Journal of Chemical Science*. Vol 12, no. 2. 2023. doi: 10.15294/ijcs.v12i2.69942

[21] R. B. Van Breemen and Y. Li, "Caco-2 cell permeability assays to measure drug absorption," *Expert Opinion on Drug Metabolism and Toxicology*, vol. 1, no. 2. pp. 175–185, Aug. 2005. doi: 10.1517/17425255.1.2.175.

[22] Sun, P., Wang, Y., & Tang, W. The Pressure Enhances the Extraction Yield of Total Triterpenoidpropis from Ganoderma Lucidum. *MATEC Web of Conferences*. Vol. 67. 2016. doi: https://doi.org/10.1051/01003

[23] Brosolo, G., Da Porto, A., Marcante, S., Picci, A., Capilupi, F., Capilupi, P., & Sechi, L. A. Omega-3 fatty acids in arterial hypertension: is there any good news?. *International journal of molecular sciences.* Vol. 24, no. 11. 2023. doi: https://doi.org/10.3390/ijms24119520

[24] Ma, Z., & He, W. Fatty acids and pregnancy-induced hypertension: a Mendelian randomization study. *Lipids in Health and Disease*. Vol. 22, no. 1. 2023. doi: https://doi.org/10.1186/s12944-023-01889-x
[25] Pekkoh, J., Phinyo, K., Thurakit, T., Lomakool, S., Duangjan, K., Ruangrit, K., & Srinuanpan, S. Lipid profile, antioxidant and antihypertensive activity, and computational molecular docking of diatom fatty acids as ACE inhibitors. *Antioxidants*. Vol. 11, no. 2. 2022. doi: https://doi.org/10.3390/antiox11020186