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Original Article

IN SILICO STUDY OF EUCALYPTOL FROM *EUCALYPTUS GLOBULUS* LABILL. AGAINST ANGIOTENSIN-CONVERTING ENZYME AS AN ANTIHYPERTENSIVE IN COVID-19 COMORBID

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ABSTRACT

Objective: This study aimed to determine the best compound from the 62 compounds of *Eucalyptus globulus* Labill. as an antihypertensive based on its interaction with angiotensin-converting enzyme (ACE) using the *in silico* study.

Methods: The study was carried out *in silico* through molecular docking simulations, analysis of potential compounds using Lipinski's rule, and ligand-based ADMET prediction on 62 compounds of the *E. globulus*.

Results: It was found that eucalyptol (1,8-cineole) had the best interaction with the ACE as indicated by a bond energy value (ΔG) of -6.40 kcal/mol with an inhibition constant of 20.82 μM, and interacted with key amino acid residues in captopril, namely HIS513, HIS353, TYR523, and ALA354. Eucalyptol also had good physicochemical properties by fulfilling Lipinski's rule and had the best ADMET profile compared to other compounds.

Conclusion: Eucalyptol was the best antihypertensive against ACE based on amino acid residue interaction, physicochemical properties, and ADMET profile.

Keywords: ACE, ADMET, Antihypertensive, Eucalyptol, *Eucalyptus globulus* labill

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a viral infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and attacks the human respiratory system. The first case of COVID-19 was discovered in Wuhan, China at the end of the year 2019 and rapidly spread worldwide [1]. The spread of COVID-19 cases to various countries, with a rapid increase in the number of events, led WHO to declare COVID-19 a pandemic on March 11, 2020. Data on confirmed cases of COVID-19 in the world continued to increase in 2021 and there is no sign of a downward trend in the number of cases [2]. This pandemic decrease in 2022.

Based on the results of several studies that have been conducted show that factors such as age>65 y, being male, and having comorbid diseases are independent risk factors for increasing the severity of the disease and death from COVID-19. The results of clinical and epidemiological data analysis of COVID-19 show that 20-51% of COVID-19 patients have at least one comorbidity, such as hypertension (21.1%), cardiovascular disease (8.4%), diabetes (9.7%), and respiratory tract disease (1.5%) [3]. Research by Ejaz H, *et al.* [4] found the mortality rate of patients with confirmed COVID-19 who had comorbidities in China, namely hypertension (9.5%), diabetes (7.4%), chronic obstructive pulmonary disease (COPD, 7.0%), cardiovascular disease (7.3%), liver disease (2.4%), obesity (13%), kidney disease (0.7%), and malignancy (2.0%). Other data from Italy found a mortality rate of COVID-19 infection with comorbid hypertension (73.8%), diabetes (35.5%), COPD (13.7%), cardiovascular disease (42.5%), liver disease (3.7%), obesity (8.5%), kidney disease (20.2%), and malignancy (5.0%). It can be concluded that one of the most common comorbid diseases suffered by confirmed COVID-19 patients is hypertension and also one of the comorbidities with the highest mortality rate. Among genetic reasons, the angiotensin II enzyme, which is produced as a result of the abnormal function of the renin-angiotensin system, is reported as a major cause of hypertension. Angiotensin Converting Enzyme (ACE) is considered to play an important role in controlling hypertension. Therefore, ACE can be a potential therapeutic target in regulating the conversion of angiotensin I to angiotensin II and ultimately controlling hypertension [5].

Eucalyptol is an important component of the *Eucalyptus globulus* Labill and a study demonstrating that intravenous administration of eucalyptol significantly reduced blood pressure in awake and anesthetized rats. Measurements with isolated rat aortas showed that eucalyptol has a vasodilating effect, suggesting that the blood pressure-lowering effect may result from a decrease in peripheral vascular resistance due to the direct relaxation of vascular smooth muscle [6]. Animal studies have shown that renin-angiotensin-aldosterone system (RAAS) inhibitors increase the expression of ACE2 in cardiac tissue [7], leading to concerns that hypertension may increase the interaction of the virus with host cells and worsen COVID-19. Hypertension is almost double the severity and mortality of COVID-19 [8, 9]. This study was conducted to determine the best compounds that have potential as antihypertensives from the 62 compounds in *E. globulus*. The activity was determined using *in silico* study based on the interaction of the 62 compounds with ACE and ADMET prediction. This study was important to do because hypertension increases the severity and mortality in COVID-19 patients.

MATERIALS AND METHODS

Materials

The software in this study was hardware in the form of personal laptops with Intel(R) Core(TM) i5-8250U processor specifications @ 1.60GHz 1.80 GHz and RAM 4GB and software, such as BIOVIA Discovery Studio 2017® [10], AutoDock Tools® [11], ChemDraw, Chem 3D, and PreADMET 2.0 [12].

The materials were ACE, which was downloaded via the Protein Data Bank (https://www.rcsb.org/) with the PDB code 2XY9 and the three-dimensional structure of 62 compounds of *E. globulus* prepared with the Chem 3D program.

Methods

This research was conducted *in silico* on the structure of the isolated compound from *E. globulus* against ACE (PDB ID: 2XY9) with the following stages, i. e, selection of test compounds using Lipinski's rule of five analysis, prediction of ADME, the toxicity of test compounds of *E. globulus*, and pharmacophore modeling.

RESULTS AND DISCUSSION

ACE with the PDB ID: 2XY9 was downloaded via the Protein Data Bank [13], and then prepared using the BIOVIA Discovery Studio

2017 software, which was set to view quality for publication. Then the water molecules in the structure were removed to simplify energy calculations when the simulation was carried out. The presence of water molecules in the structure causes the program to be unable to place the ligands correctly [14]. The native ligand inhibitor of the ACE is (2S)-3-(4-hydroxyphenyl)-2-[[(2R)-2-[[hydroxy[(1R)2phenyl 1phenylmethoxycarbonyl aminoethyl] phosphoryl] methyl]-3-(3-phenyl-1,2-oxazol-5-yl) propanoyl] amino] propanoic acid was separated from the receptor structure. The structure of the ACE and native ligand can be seen in fig. 1.

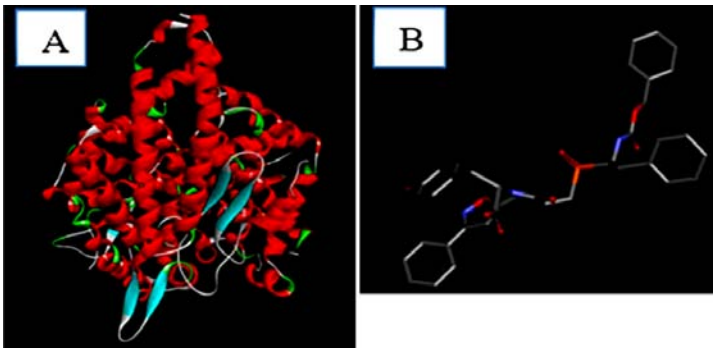

Fig. 1: Structure of ACE (A) and native ligand (B) which had been separated from ACE

Lipinski's rule is a rule for the physicochemical properties of a ligand so that the hydrophobic/hydrophilic character of a compound through the cell membrane for passive diffusion can be determined. Lipinski's rule can help in observing the permeability of a drug to the lipid bilayer of the target body. Lipinski's rule consists of four points, namely (1) molecular weight<500 Da; (2) Log P (partition coefficient)<5; (3) number of hydrogen bond donors<5; (4) the number of hydrogen bond acceptors is less than 10 [15].

If the test compound has a molecular weight>500 Da, it will be difficult for the compound to penetrate the cell membrane. A Log P value that is greater than 5 also indicates that the compound will be increasingly lipophilic which causes the compound to bind tightly to the membrane, making it difficult to recognize the target protein and is toxic. Donor hydrogen bonds in a compound will partition in solvents that have strong hydrogen bonds (such as water). Meanwhile, hydrogen bond acceptors affect permeability because they have more ability to interact well in solvents that have strong hydrogen bonds, such as water [16]. About 62 compounds were docked and the results are presented in table 1 following Lipinski's Rule of Five. All the test compounds met the requirements and could be used as oral drug candidates and could be further investigated for their pharmacokinetic and toxicity profiles (table 1).

Table 1: Parameters of lipinski's rule of *E. globulus* compounds

No	Compounds	Molecular weight	Log P	Hydrogen bond		Notes
				Donor	Acceptor	
1	Captopril	217.29	0.45	1	3	Adequate
2	1,8-Cineole (eucalyptol)	154.25	2.45	0	1	Adequate
3	1,7,7-Trimethylbicyclo[2,2,1]hept-5-en-ol	152.23	2.3	1	1	Adequate
4	2-Phenylaethyl Isovalerate	206.28	3.13	0	2	Adequate
5	2,6-Dimethylocta-1,5,7-trien-3-ol	152.23	2.49	1	1	Adequate
6	3,7-Dimethyl-2,6-octadien-1-ol	154.29	2.59	1	1	Adequate
7	Alloaromadendrene	204.35	5.65	0	0	Adequate
8	α-Cadinol	222.37	3.67	1	1	Adequate
9	α-Gurjunene	204.35	5.65	0	0	Adequate
10	Aromadendrene	204.35	5.65	0	0	Adequate
11	Hydroxy Phenyl Acetic Acid	168.15	0.61	3	4	Adequate
12	Ellagic Acid	302.19	0.41	4	8	Adequate
13	Gallic Acid	170.12	-0.16	4	5	Adequate
14	Caffeic Acid	180.16	0.70	3	4	Adequate
15	Quinic Acid	192.17	-2.14	5	6	Adequate
16	Protocatectic Acid	154.12	0.4	3	4	Adequate
17	β-Panasinsene	204.35	5.65	0	0	Adequate
18	Camphene	136.23	4.29	0	0	Adequate
19	Carvyl Acetate	194.27	2.56	0	2	Adequate
20	cis-β-Ocimene	136.23	3.56	0	0	Adequate
21	Citronellol	156.27	2.70	1	1	Adequate
22	Cyclohexanol 2-methylene-5-(1-methyl ethenyl	152.23	2.20	1	1	Adequate
23	Dehydro Aromadendrene	202.34	4.63	0	0	Adequate
24	Epiglobulol	222.37	3.81	1	1	Adequate
25	Eriodictyol	288.25	0.16	4	6	Adequate
26	Eudesma-4(14), 7(11)-dien	204.35	4.63	0	0	Adequate
27	Eudesmol	224.38	3.81	1	1	Adequate
28	Exo-2-Hydroxycineole	170.25	1.52	1	2	Adequate
29	Fenchols	154.25	2.45	1	1	Adequate
30	Geranyl Acetate	196.29	2.95	0	2	Adequate
31	Globulol	222.37	3.81	1	1	Adequate
32	Isobornyl Formate	182.26	2.48	0	2	Adequate
33	Isoledeni	204.35	5.65	0	0	Adequate

No	Compounds	Molecular weight	Log P	Hydrogen bond		Notes
				Donor	Acceptor	
34	Isolongifolene	204.35	5.65	0	0	Adequate
35	Isopulegol Acetate	196.29	2.65	0	2	Adequate
36	Isoramnetin	316.26	-0.31	4	7	Adequate
37	Jensenone	266.25	-0.42	3	6	Adequate
38	Kaempferol	286.24	-0.03	4	6	Adequate
39	Catechins	290.27	0.24	5	6	Adequate
40	Kubenol	222.37	3.67	1	1	Adequate
41	Quercetin	302.24	-0.56	5	7	Adequate
42	Ledene	204.35	5.65	0	0	Adequate
43	Ledol	222.37	3.81	1	1	Adequate
44	Limonene	136.23	3.27	0	0	Adequate
45	Luteolin	286.24	-0.03	4	6	Adequate
46	Methyl Gallate	184.15	0.18	3	5	Adequate
47	Naringenin	272.25	0.71	3	5	Adequate
48	Nerolidol	222.37	3.86	1	1	Adequate
49	Pinocarveol	152.23	2.3	1	1	Adequate
50	Sabinene	136.23	4.29	0	0	Adequate
51	Spathulenol	220.35	3.67	1	1	Adequate
52	Taxifoline	304.25	-0.64	5	7	Adequate
53	Terpinen-4-ol	154.25	2.3	1	1	Adequate
54	Terpinolene	136.23	3.27	0	0	Adequate
55	Trans-Carveol	152.23	2.2	1	1	Adequate
56	α-guaiene	204.35	4.63	0	0	Adequate
57	α-Pinene	136.23	4.29	0	0	Adequate
58	α-terpineol	196.29	2.65	0	2	Adequate
59	α-terpineol acetate	154.25	2.3	1	1	Adequate
60	β-gurjunen	204.35	5.65	0	0	Adequate
61	β-pinene	136.23	4.29	0	0	Adequate
62	γ-terpinene	136.23	3.27	0	0	Adequate

In carrying out molecular docking, validation was required by re-docking ACE with the native ligand that had been separated previously using the Autodock 4.2 program. The Root Mean Square Deviation (RMSD) value was used as a method validation parameter, where this value indicated a deviation from the measurement results when measurements were carried out repeatedly. The RMSD value of molecular docking indicated the deviation of the bond pose that occurs in the test ligand compared to the reference bond pose (download from PDB). The lower the RMSD value, the better the model was docked to the target structure [17, 18]. Fig. 2 showed that the RMSD value was 1.74 Å with a grid box size of 50 x 50 x 50 and coordinates x, y, and z (15,070,-2,582,-22,842). This implied that the molecular docking method carried out met the qualifications and showed the good quality of bond pose reproduction.

Fig. 2: Conformation overlay of native ligand validation result (blue) with natural ligan crystallography result (green)

In addition, the validation results also analyzed the active site of the amino acid residue of the protein that binds to the native ligand. Fig. 3 showed that the amino acid residues responsible for the binding of native ligands at the ACE binding sites were HIS513, GLU411, GLN281, HIS383, GLU384, HIS353, LYS511, HIS387, PHE457, TYR520, TYR523, ASP415, and VAL380. HIS513, GLU411, and GLN281 form hydrogen bond interactions. HIS383, GLU384, HIS353, LYS511, HIS387, PHE457, TYR520, TYR523, ASP415, and VAL380 form hydrophobic interactions. These amino acid residues are the amino acid residues that form the active site of ACE, so the existence of interactions with these amino acids is important when determining the antihypertensive activity of a compound [7].

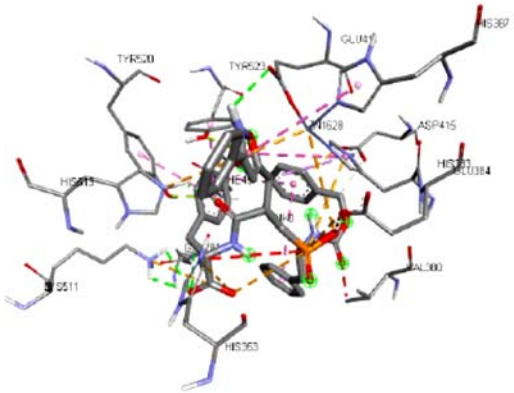

Fig. 3: Interaction between native ligand and ACE

There were three parameters considered to determine the affinity of the test compound for the receptor, namely the bond energy (ΔG), the inhibition constant (Ki), and the interaction with amino acid residues. Bond energy indicates the affinity between eucalyptol and the enzyme, the smaller the bond energy obtained, the more stable the bond formed [19]. The ΔG value was directly proportional to the Ki value, the Ki value gave an idea of the ability of a compound to inhibit an enzyme. The smaller the Ki value, the compound had pharmacological capabilities in smaller doses [20]. Eucalyptol had a bond energy value (ΔG) of-6.40 kcal/mol with an inhibition constant of 20.82 μM. Interaction with amino acid residues indicated the presence of hydrogen bonds with HIS513 and HIS353 and hydrophobic interactions with the same amino acid residues of HIS383 and TYR523 as the native ligand. The functional groups of eucalyptol and captopril have similar hydrophobic interactions and hydrogen bonds to ACE amino acid residues. In addition, both have similar binding energies and inhibition constants (table 2). Based on the bond energy value, it showed that the eucalyptol had potential activity as an antihypertensive because it has an affinity and forms hydrogen bonds with the ACE. Overall, the molecular docking parameters of plant compounds of *E. globulus* can be seen in table 2. The visualization of molecular docking of captopril and tested compounds showed hydrogen bond and hydrophobic interaction between amino acid residues and the tested compounds.

Table 2: Molecular docking of tested compounds of *E. globulus* to ACE

No	Compounds	ΔG (kcal/mol)	Inhibition constant (μM)	Amino acid interaction	
				Hydrogen bond	Hydrophobic interaction
1	Captopril	-6.49	17.37	HIS513, HIS353, GLN128, LYS511, TYR520	ALA354, PHE457, TYR523
2	1,8-Cineole (eucalyptol)	-6.4	20.82	HIS513, HIS353	HIS383, ALA354, TYR523
3	1,7,7-Trimethylbicyclo[2,2,1]hept-5-en-ol	-4.25	773.67	ALA129	ALA89, MET86, LEU132
4	2-Phenylaethyl Isovalerate	-5.64	72.96	ASN85	LEU82, ALA129, LEU132, MET86
5	2,6-Dimethylocta-1,5,7-trien-3-ol	4.84	282.25	ALA129	ALA89, MET86, LEU132
6	3,7-Dimethyl-2,6-octadien-1-ol	-4.58	437.69	MET86	LEU132, LEU82, LYS137
7	Alloaromadendrene	-4.50	501.67		MET86, ALA129, ALA89, LEU132
8	α-Cadinol	-5.38	113.76	-	L YS137, MET86, LEU82
9	α-Gurjunene	-4.76	325.19		MET86, ALA129, LEU82, LEU132
10	Aromadendrene	-4.50	501.95	-	MET86, ALA129, ALA89, LEU82, LEU132
11	Hydroxy Phenyl Acetic Acid	-4.35	645	LEU82, GLU133	MET86, LEU13
12	Ellagic Acid	-4.78	312.87	ASN85, ASN136, ASN90	MET86, ALA129, ALA89, LEU132, GLU133
13	Gallic Acid	-4.64	399.47	HIS513, GLU411, GLN281, LYS511, TYR520	-
14	Caffeic Acid	-5.10	183.70	GLN83, LYS79, GLU133, ASN136	LEU82, MET86
15	Quinic Acid	-4.38	614.56	GLU133	LEU82
16	Protocatectic Acid	-4.26	752.60	LYS79, GLU133	LEU82, MET86
17	β-Panasinsene	-4.80	300.56	-	MET86, ALA129, ALA89, LEU82, LEU132
18	Camphene	-4.34	657.43	-	MET86, ALA89, LEU82, LEU132
19	Carvyl Acetate	-5.75	60.75	HIS513, HIS353	HIS383, TYR523, TYR520, PHE457, PHE527
20	cis-β-Ocimene	-4.70	358.28	-	MET86, LYS79, ALA89, LEU82, LEU132
21	Citronellol	-4.64	396.23	ALA129	ALA89, LEU132, LEU82, LYS137, MET86
22	Cyclohexanol 2-methylene-5-(1-methyl ethenyl	-4.16	886.37	-	MET86, LYS79, ALA89, LEU132
23	Dehydro Aromadendrene	-5.56	84.42	-	ALA129, LEU132
24	Epiglobulol	-4.64	394.41	MET86	ALA129, ALA89, LEU82, LEU132
25	Eriodictyol	-5.55	85.16	MET86, GLU133	ALA89, LEU82, LEU132
26	Eudesma-4(14), 7(11)-dien	-4.14	924.53	-	MET86, LEU82, LEU132
27	Eudesmol	-4.73	340.49	ALA129	MET86, LEU82, LEU132
28	Exo-2-Hydroxycineole	-4.28	718.39	ALA129	MET86, LEU132
29	Fenchols	-4.18	861.90	GLU133	MET86, LEU82, LEU132
30	Geranyl Acetate	-5.39	111.76	-	MET86, ALA129, ALA89, LEU132, GLU133
31	Globulol	-4.26	748.28	-	MET86, ALA129, ALA89, LEU132
32	Isobornyl Formate	-4.00	1160	ASN136	MET86, ALA129, ALA89, LEU132
33	Isoledeni	-4.40	596.96	-	MET86, ALA129, LEU132
34	Isolongifolene	-4.58	438.02	-	MET86, ALA129, LEU132
35	Isopulegol Acetate	-5.04	201.02	-	MET86, ALA129, LEU82, LEU132
36	Isoramnetin	-4.87	267.04	LEU132, ASN136	MET86, ALA129, LEU82, GLU133
37	Jensenone	-4.07	1040	ASN85, ASN136, GLU133	MET86, LEU82, LEU132
38	Kaempferol	-5.40	109.74	HIS513, GLU411, GLN281, LYS511, TYR520	HIS383, HIS353, TYR523
39	Catechins	-5.36	116.96	ALA129, MET86, ASN90, GLU133	-
40	Kubenol	-6.11	33.27	TYR523, HIS353	HIS387, HIS383, HIS513, TYR520, ALA354, VAL380
41	Quercetin	-4.71	351.37	ASN136	MET86, ALA129, LEU82, LEU132, GLU133
42	Ledene	-4.46	537.16	-	MET86, LEU132, LEU82, LYS137
43	Ledol	-5.43	103.90	MET86	ALA129, ALA89, LEU132
44	Limonene	-4.88	265.28	-	MET86, ALA129, LEU82, LEU132
45	Luteolin	-5.03	205.06	ASN136, LYS137	MET86, LEU82, GLU133
46	Methyl Gallate	-5.09	186.16	ALA129	MET86, ALA89, LEU132, GLU133
47	Naringenin	-5.38	112.92	ASN136, LYS137	MET86, LEU82, GLU133, LYS79, GLN83
48	Nerolidol	-5.31	127.26	LEU82	ALA89, LEU132, ALA89, LYS137, MET86
49	Pinocarveol	-4.25	773.16	LEU127	MET86, ALA129, ALA125, ALA89, LEU93, LEU132
50	Sabinene	-5.07	193.58	-	LEU132, LEU82, LYS137, MET86
51	Spathulenol	-4.13	945.83	MET86	ALA129, ALA89, LEU132
52	Taxifoline	-5.68	68.47	TYR520, HIS513, GLU384, ALA356	TYR523
53	Terpinen-4-ol	5.31	129	-	MET86, LEU82, LEU132
54	Terpinolene	-4.81	296.73	-	MET86, ALA129, LEU82, LEU132
55	Trans-Carveol	-4.48	515.81	-	MET86, ALA89, LEU132
56	α-guaiene	-4.79	306.70	-	MET86, ALA129,
57	α-Pinene	-4.53	477.52	-	MET86, LEU82, LEU132
58	α-terpineol	-5.57	82.79	GLN128, LYS511, TYR520	HIS513, HIS353, HIS383, PHE457, PHE557, TYR523
59	α-terpineol acetate	-5.44	102.64	-	LYS79, MET86, LEU82
60	β-gurjunen	-4.92	246.94	-	MET86, ALA129, LEU82, LEU132
61	β-pinene	-4.53	445.92	-	MET86, ALA129, ALA89, LEU132
62	γ-terpinene	-4.50	502.34	GLU133	MET86, ALA129, LEU82, LEU132

The tested compound must contain at least one amino acid residue that were the same as the native ligand amino acid residues so that it could be concluded that the tested compound has the potential to bind to ACE. The tested compounds that interact with important

amino acid residues on the ACE active site, with captopril as the comparator drug, were 1,8-cineole, carvyl acetate, kaempferol, cubenol, taxifolin, and alpha-terpineol. Meanwhile, other compounds did not interact with important amino acid residues on the ACE active site because they bind to the other side, in contrast to captopril. Captopril interacted at the hydroxyl group with HIS513, HIS353, GLN128, LYS511, and TYR520, forming hydrogen bonds and forming hydrophobic interactions with ALA354, PHE457, and TYR523. Eucalyptol has the same 4 amino acid residues as captopril, namely HIS513, HIS353, TYR523, and ALA354. The carvyl acetate has the same 5 amino acid residues as captopril, namely TYR523, HIS353, HIS513, TYR520, and PHE457.

Among all the compounds, alpha-terpineol, carvyl acetate, and kaempferol had more bonds with the same amino acid residues as captopril, but these two compounds had bond energy affinity values and inhibition constants that were much different from captopril. Whereas 1,8-cineole (eucalyptol) and cubenol, which had almost the same binding energy affinity and inhibition constant values as captopril had interactions with amino acid residues that were similar to captopril. The toxicity profile of the 1,8-cineole based on AMES and TD_{50} tests showed that the compound was not mutagenic and not carcinogenic. The bond that occurs between eucalyptol and the ACE receptor can cause a decrease in blood pressure [21, 22].

Molecular docking of the eucalyptol (1,8-cineole) was carried out using Autodock 4.2 program, with the coordinates of the interaction site being set the same as the coordinates of the native ligand on the ACE. The visualization of the molecular docking process between eucalyptol and ACE can be seen in fig. 4.

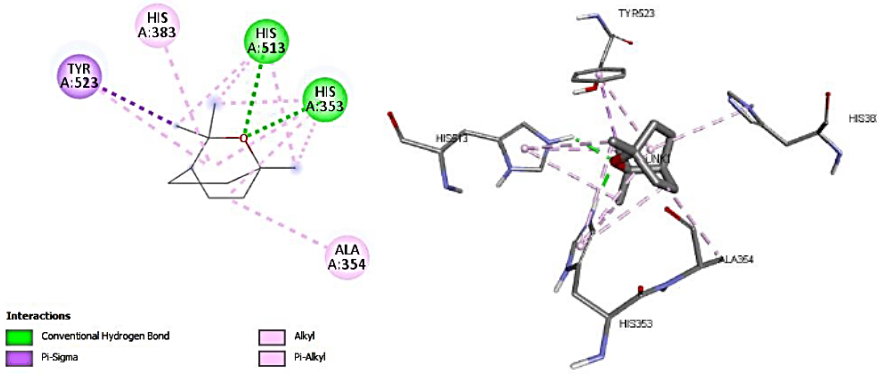

Fig. 4: Visualization of interaction between eucalyptol and ACE

Table 3: Prediction of absorption, distribution, and toxicity of several selected compounds of *E. globulus*

No	Compounds	Absorption		Distribution		Toxicity	
		HIA (%)	Caco2 (10^{-6} cm/s)	PPB (%)	BBB	Muta-genic	Carcino-genic
1	Captopril	75.898	1.171	31.89	-0.211	No	No
2	1,8-Cineole (eucalyptol)	96.533	1.388	89.09	0.368	No	No
3	1,7,7-Trimethylbicyclo[2,2,1]hept-5-en-ol	94.494	1.479	69.97	0.620	No	No
4	2-Phenylaethyl Isovalerate	95.454	1.731	91.75	0.403	No	No
5	2,6-Dimethylocta-1,5,7-trien-3-ol	93.418	1.493	52.33	0.611	No	Yes
6	3,7-Dimethyl-2,6-octadien-1-ol	92.788	1.49	88.87	0.606	No	No
7	Alloaromadendrene	95.302	1.395	90.95	0.822	No	No
8	α-Cadinol	92.983	1.528	95.97	0.607	No	No
9	α-Gurjunene	97.025	1.411	97.57	0.787	No	No
10	Aromadendrene	95.302	1.395	93.57	0.822	No	No
11	Hydroxy Phenyl Acetic Acid	76.099	0.341	37.81	-0.606	No	No
12	Ellagic Acid	82.893	0.270	78.23	-1.329	No	Yes
13	Gallic Acid	39.954	-0.102	53.49	-1.110	No	No
14	Caffeic Acid	68.465	0.264	87.71	-0.804	No	No
15	Quinic Acid	14.745	-0.368	11.48	-0.999	No	No
16	Protocatectic Acid	76.227	0.270	41.69	-0.780	No	No
17	β-Panasinsene	95.171	1.387	73.42	0.833	No	No
18	Camphene	95.525	1.398	67.76	0.796	No	No
19	Carvyl Acetate	96.966	1.841	67.19	0.532	No	No
20	cis-β-Ocimene	94.506	1.401	95.67	0.757	Yes	Yes
21	Citronellol	92.610	1.483	93.48	0.623	No	No
22	Cyclohexanol 2-methylene-5-(1-methyl ethenyl	94.690	1.499	48.97	0.565	No	Yes
23	Dehydro Aromadendrene	95.363	1.402	94.30	0.805	No	No
24	Epiglobulol	92.814	1.483	93.73	0.632	No	No
25	Eriodictyol	75.138	0.359	93.32	-0.947	Yes	No
26	Eudesma-4(14), 7(11)-dien	94.859	1.415	96.88	0.788	No	No
27	Eudesmol	93.303	1.503	96.49	0.632	No	No
28	Exo-2-Hydroxycineole	95.297	1.581	65.74	0.114	No	Yes
29	Fenchols	94.206	1.503	67.23	0.655	No	No
30	Geranyl Acetate	95.041	1.524	92.42	0.568	No	No
31	Globulol	92.814	1.483	96.12	0.632	No	No
32	Isobornyl Formate	95.409	1.771	58.29	0.573	No	Yes
33	Isoledeni	97.790	1.412	97.79	0.783	No	No
34	Isolongifolene	95.640	1.419	95.93	0.796	No	No
35	Isopulegol Acetate	95.692	1.597	56.24	0.523	No	No
36	Isoramnetin	88.672	0.027	96.24	-1.174	Yes	No

No	Compounds	Absorption		Distribution		Toxicity	
		HIA (%)	Caco2 (10^{-6} cm/s)	PPB (%)	BBB	Muta-genic	Carcino-genic
37	Jensenone	62.699	0.304	95.93	-1.269	No	No
38	Kaempferol	80.064	0.195	97.86	-1.065	Yes	No
39	Catechins	66.773	-0.411	92.07	-1.005	Yes	No
40	Kubenol	94.369	1.604	95.93	0.616	No	No
41	Quercetin	75.347	-0.057	95.50	-1.339	No	No
42	Ledene	94.735	1.391	97.46	0.805	No	No
43	Ledol	92.814	1.483	95.27	0.632	No	No
44	Limonene	95.898	1.401	91.33	0.732	No	Yes
45	Luteolin	82.175	0.286	95.44	-1.145	Yes	No
46	Methyl Gallate	71.212	1.014	85.38	-1.030	No	No
47	Naringenin	90.009	1.108	93.76	-0.749	No	Yes
48	Nerolidol	91.673	1.498	92.52	0.655	No	No
49	Pinocarveol	94.942	1.081	39.20	0.735	No	No
50	Sabinene	94.343	1.378	69.45	0.833	No	No
51	Spathulenol	94.833	1.400	78.72	0.605	No	No
52	Taxifoline	58.999	-0.411	85.44	-1.046	Yes	No
53	Terpinen-4-ol	93.857	1.368	85.34	0.564	No	Yes
54	Terpinolene	95.60	1.404	95.55	0.695	No	Yes
55	Trans-Carveol	94.69	1.499	60.13	0.565	No	Yes
56	α-guaiene	95.273	1.416	95.06	0.753	No	Yes
57	α-Pinene	96.041	1.380	86.34	0.791	No	No
58	α-terpineol	96.405	1.488	91.59	0.429	No	No
59	α-terpineol acetate	94.183	1.489	89.88	0.305	No	Yes
60	β-gurjunen	97.12	1.409	93.25	0.821	No	No
61	β-pinene	94.607	1.373	64.33	0.812	No	No
62	γ-terpinene	96.219	1.414	93.74	0.754	No	Yes

Table 3 showed the ADMET analysis results for 62 compounds, only 2,6-dimethylocta-1,5,7-trien-3-ol, ellagic acid, cis-β-ocimene, cyclohexanol 2-methylene-5-(1-methyl ethenyl)-, exo-2-hydroxycineole, isobornyl formate, limonene, naringenin, terpinene-4-ol, terpinolene, trans-carveol, α-guaiene, α-terpineol acetate, and γ-terpinene were only 15 mutagenic compounds. Predictive results for HIA (%, Human Intestinal Absorption), Caco2 (10^{-6} cm/s) Caco-2 cell permeability assays to measure drug absorption, PPB (%) assays determine free drug concentration (fraction unbound) by evaluating affinity to plasma proteins, such as serum albumin, using plasma from treated animals, and BBB (blood-brain barrier) lets some substances, such as water, oxygen, carbon dioxide, and general anesthetics, pass into the brain. It also keeps out bacteria and other substances, such as many anticancer drugs that gave negative results of all tested compounds and gave reasonable predictions [12, 23, 24]. All the test compounds met the requirements and could be used as oral drug candidates and could be further investigated for their pharmacokinetic and toxicity profiles.

CONCLUSION

The eucalyptol has potential activity as an antihypertensive because it has an affinity with a bond energy value (ΔG) of -6.40 kcal/mol and an inhibition constant of 20.82 μM and has hydrogen bonding interactions with HIS513 and HIS353, and hydrophobic interactions with HIS383 and TYR523, so that they can inhibit ACE and can cause a decrease in blood pressure.

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AUTHORS CONTRIBUTIONS

Conceptualization: RM; methodology: SM, EP; investigation: EP; data curation: SM; NMS; writing of original draft preparation: SM; review and editing: NMS; supervision: RM. All authors have read and agreed to the published version of the article.

CONFLICT OF INTERESTS

Declared none

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