Potential of the methanol extract from Cucumis melo var. cantalupensis as an antihypertensive agent possibly through the interference of glutathione S-transferase

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Research Article

Potential of the methanol extract from *Cucumis melo* var. *cantalupensis* as an antihypertensive agent possibly through the interference of glutathione S-transferase

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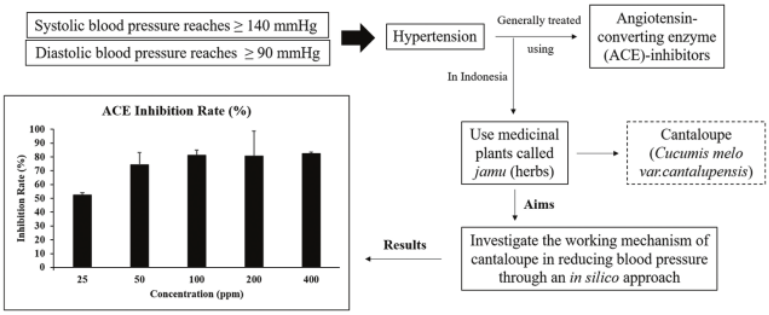
ABSTRACT

Background: Hypertension is a condition, in which a patient's systolic blood pressure reaches ≥140 mmHg and/or the diastolic blood pressure reaches ≥90 mmHg. The disease is generally treated using synthetic chemical drugs such as angiotensin-converting enzyme (ACE) inhibitors. In Indonesia, especially the island of Java, people often use medicinal plants called *Jamu* (herbs) to treat hypertension. One of the most often used medicinal plants to treat hypertension is cantaloupe (*Cucumis melo* var. *cantalupensis*) or Blewah in Javanese. However, thus far, the mechanism of how cantaloupe reduces blood pressure is still unknown. **Materials and Methods:** This research aimed to investigate the working mechanism of cantaloupe in reducing blood pressure through an *in silico* approach. **Results:** An enzyme activity analysis showed that the methanol extract from cantaloupe inhibited the activity of ACE in a dose-dependent manner. Moreover, the mapping analysis of the interaction between the bioactive compounds and their target proteins, using the STITCH and STRINGdb databases, suggested that L-glutathione (GSH) (reduced) interacted with proteins that are members of the superfamily of GSH S-transferase (GST). **Conclusion:** This protein family acts in detoxification and radical scavenging. Thus, the possible working mechanism of cantaloupe in reducing blood pressure is through the detoxification and radical scavenging pathways by GST.

KEY WORDS: Antihypertension, *Cucumis melo* var. *cantalupensis*, Glutathione S-transferase

GRAPHICAL ABSTRACT



Methanol cantaloupe extract inhibits ACE enzyme activity. The cantaloupe methanol extract suppressed ACE activity in a dose-dependent manner

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INTRODUCTION

Hypertension is a condition, in which a patient's systolic blood pressure reaches ≥140 mmHg and/or the diastolic

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blood pressure reaches ≥90 mmHg. This is the most common chronic disease[1] and it is commonly treated using synthetic chemical drugs. The classifications of drugs commonly used for hypertension therapy include angiotensin II receptor blockers (ARBs), angiotensin-I-converting enzyme (ACE) inhibitors,[2] combined ARBs and ACE-inhibitors,[3] diuretics,[4] beta-blockers,[5] calcium channel blockers,[6] alpha-adrenergic receptor agonists,[7] combined alpha- and beta-blockers,[8] inhibitors of renin,[9] vasodilators,[10] and others. ACE inhibitors are the most widely used type of antihypertensive drugs after diuretics.[11,12] ACE inhibitors suppress the conversion of angiotensin-I to angiotensin-II, acting as vasoconstrictors.[11] ACE inhibitors are considered safe for consumption when renal function and electrolyte levels are monitored.[11] In some patients, this drug causes side effects such as coughing,[13] hyperkalemia,[14] angioedema,[15] and skin rash.[16] The side effects are due to the inhibition of ACE, and they also impact the accumulation of bradykinin, which is an inflammatory factor.[17]

Indonesian people have long used natural ingredients, commonly called *Jamu* (herbs), to treated various diseases,[18] such as for antihypertensive therapy.[19] Plants commonly utilized as antihypertensive herbs include *Centella asiatica*, *Imperata cylindrica*,[19] *Morinda* sp., star fruit, and garlic.[20] Some people in Indonesia, mainly those in the rural areas of Java Island, use cantaloupe (*Cucumis melo* var. *cantalupensis*) for antihypertension therapy. These medicinal plants can be eaten directly, boiled, or made simplicia. These plants are also safe for the kidneys.[21] Several previous studies suggest that cantaloupe has a hypotensive effect through vascular tone regulation.[22] However, the working mechanism of how cantaloupe reduces blood pressure is still unknown. Indonesian people use this plant for hypertension therapy based on information passed down from their ancestors.

Several studies also indicate that cantaloupe potentially functions as an antioxidant,[23] anti-inflammatory,[24] and antimicrobial.[25] The active compounds in cantaloupe include phenols, flavonoids,[23] polyphenols, ortho-diphenols, and tannins.[26] This research aimed to examine its potential as an ACE inhibitor. Moreover, the study investigated the bioactive methanol extract from cantaloupe and predicted the target proteins to estimate the pathways that involve the bioactive compounds from cantaloupe in lowering blood pressure.

MATERIALS AND METHODS

Cantaloupe Extraction and ACE Enzyme Activity Test

The cantaloupe used in this research was obtained from Materia Medika Hall, Batu. A total of 200 g of dried cantaloupe were macerated using 3 L of absolute methanol for 3 days. Then, it was dried using a rotary evaporator. The dried extract was then dissolved using dimethyl sulfoxide at a concentration of 10%, which was then used for the ACE enzyme inhibition test. The ACE inhibition activity test was carried out based on the protocol from DOJINDO. The inhibitory activity of the ACE enzyme was carried out with four concentrations of the cantaloupe extracts (25, 50, 100, and 200 ug/ml).

Affinity Test of the Cantaloupe Active Compounds Binding to ACE Proteins

The cantaloupe active compound was obtained through liquid chromatography–mass spectrometry (LC–MS). The structure of the active compound was then identified using the PubChem database (http://pubchem.ncbi.nlm.nih.gov/),[27] in which the canonical SMILES was copied to trace its potential as an ACE inhibitor in the online PASS database (http://www.pharmaexpert.ru/passonline/).[28] The 3D structures of the compounds that were potential ACE inhibitors were downloaded in Structure Data File (SDF) format and were used as ligands in the docking analysis with the ACE proteins as receptors (C-domain and N-domain). The 3D structure of the ACE protein was obtained from RSCB Protein Data Bank (PDB) (https://www.rcsb.org/),[29] with the PDB ID 1086 for the C-domain and the ID PDB 2C6N for the N-domain. The docking was carried out with the autodock4 algorithm using PyRx-0.8 software. The bond between the ligand and the receptor was observed using Discovery Studio software.

Protein network analysis

Target proteins from the cantaloupe active compounds were analyzed based on the compound-protein interaction from the STITCH database (http://stitch.embl.de/).[30] The compounds whose potentials were traced as ACE inhibitors were then submitted to the STITCH database to identify the target proteins. The proteins known to be targets of the active compounds of the cantaloupe methanol extract were then analyzed for their interactions using the STRINGdb database (https://string-db.org/).[31] The interaction between the proteins identified in the STRINGdb database was then analyzed further to describe the role of the network in blood pressure regulation.

RESULTS

Cantaloupe Extraction and the ACE Enzyme Activity Test

The extraction by maceration with a methanol solvent against 200 g of the cantaloupe powder simplicia produced 16.03 g of extract. The enzymatic activity test showed that the methanol extract from the cantaloupe inhibited the ACE activity in a dose-dependent manner. A further regression analysis showed that the R^2 was 0.7005 and the IC_{50} was 8.06 ppm [Figure 1]. After

learning that the methanol extract from the cantaloupe inhibited ACE activity, the next step was to analyze which compounds acted as the inhibitors.

The Binding Affinity of the Active Compounds to the ACE Protein

Based on the results from the LC–MS phytochemical test on the cantaloupe methanol extract [Figure 2], there were 434 types of active compounds, 30 of which were ACE inhibitors based on searches in PASS online [Table 1]. However, from the 30 compounds, only two types of compounds had Pa > 0.3, namely, octadecatrienoic acid methyl ester and L-glutathione (GSH) (reduced). Furthermore, the 3D structure of the two active compounds was analyzed using the PubChem database and was downloaded in SDF format and was used as a ligand in a docking analysis with the ACE protein receptors (C-domain and N-domain). The docking analysis showed that L-GSH (reduced) was better than captopril at binding ACE, which was determined by its lower affinity energy. This indicated that cantaloupe is a potential ACE inhibitor.

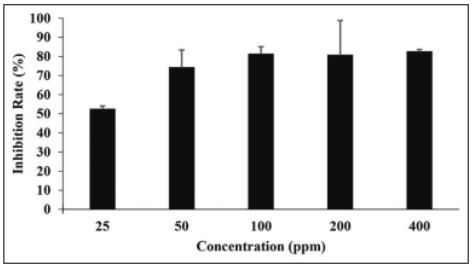

Figure 1: Methanol cantaloupe extract inhibits angiotensin-converting enzyme (ACE) enzyme activity. The cantaloupe methanol extract suppressed ACE activity in a dose-dependent manner (a), with a regression score of 0.7005 and an IC_{50} of 8.06 ppm (b)

To identify which active compounds might be ACE inhibitors, the interaction between the compounds and the ACE proteins that resulted from the docking analysis was analyzed. The observation showed that octadecatrienoic acid methyl ester and L-GSH (reduced) were bound to the active side of ACE. However, the binding pattern of the two compounds was different from the binding of captopril to ACE.

The next step was to analyze the interaction between the active compounds and the ACE protein active sites. Based on COFACTOR (https://zhanglab.ccmb.med.umich.edu/COFACTOR/),[32] the C-domain of ACE (1086) was predicted to have seven amino acids at the active site, namely, Gln281, His513, His353, Tyr523, Ala354, Glu384, and Glu411. Meanwhile, the N-domain of ACE (2C6N) was predicted to have five amino acids at the active site, namely, Lys172, Trp148, His236, Glu64, and Cys147. The seven amino acids on the C-domain of the ACE active site were bound to captopril, against 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester. Three amino acids on the C-domain of the ACE active site had the potential to bind, namely, His353, Gln281, and His513. Meanwhile, on L-GSH (reduced), five amino acids had the potential bind, namely, Glu384, Glu411, Tyr523, Ala354, and His513. Although the number of amino acids binding to L-GSH (reduced) was less than those binding to captopril, the energy affinity for the C-domain of ACE by L-GSH (reduced) was lower than the energy affinity of captopril [Table 2].

The interactions between the ACE active sites and some of the active compounds from the cantaloupe extract were visualized using Discovery Studio [Figure 3]. The results showed that captopril formed Van der Waals bonds with His513, hydrogen bonds with His353, Tyr523, Tyr520, and Gln281, and

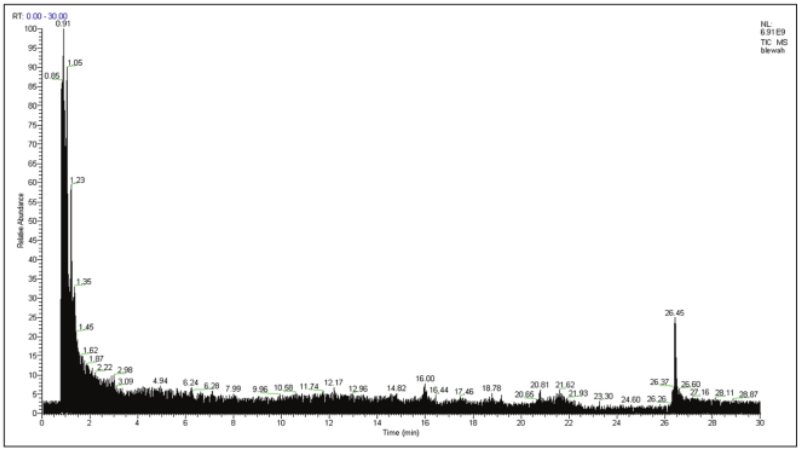

Figure 2: Chromatogram of the liquid chromatography–mass spectrometry cantaloupe results

Table 1: Compounds contained in the ACE-I potential cantaloupe extract

S. No.	Metabolite*	Molecular formula*	ΔMass* (Da)	CID**	Molecular formula**	Mw (g/mol)**	Pa
1.	(Similar to: 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester; ΔMass: 0.0063 Da)	-	292.2339	21718552	$C_{19}H_{32}O_2$	292.5	0.751
2.	(Similar to: 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester; ΔMass: 0.0063 Da)	-	292.2339	21718552	$C_{19}H_{32}O_2$	307.33	0.751
3.	(Similar to: L-GSH (reduced); ΔMass: 121.9825 Da)	-	185.1013	745	$C_{10}H_{17}N_3O_6S$	173.21	0.333
4.	(Similar to: N-acetyl-L-leucine; ΔMass: −113.0780 Da)	$C_{13}H_{26}N_4OS$	286.1832	70912	$C_8H_{15}NO_3$	173.21	0.16
5.	(Similar to: N-acetyl-L-leucine; ΔMass: −141.0723 Da)	$C_{15}H_{27}N_2O_3P$	314.1775	70912	$C_8H_{15}NO_3$	173.21	0.16
6.	(Similar to: L-saccharopine; ΔMass: 147.0558 Da)	-	129.0763	160556	$C_{11}H_{20}N_2O_6$	276.29	0.106
7.	(Similar to: Valine; ΔMass: −262.2215 Da)	$C_{23}H_{42}NOP$	379.3004	6287	$C_5H_{11}NO_2$	117.15	0.106
8.	(Similar to: L-lysine; ΔMass: 17.0292 Da)	-	129.0763	5962	$C_6H_{14}N_2O_2$	146.19	0.102
9.	(Similar to: L-lysine; ΔMass: 16.0452 Da)	$C_2H_6N_6O$	130.0603	5962	$C_6H_{14}N_2O_2$	146.19	0.102
10.	(Similar to: R-Palmitoyl-(1-methyl) Ethanolamide; ΔMass: 31.0480 Da)	-	282.2501	15667271	$C_{19}H_{39}NO_2$	313.5	0.08
11.	(Similar to: DL-3-Aminoisobutyric acid; ΔMass: −260.2060 Da)	$C_{13}H_{33}N_9O_3$	363.2693	64956	$C_4H_9NO_2$	103.12	0.079
12.	(Similar to: DL-3-Aminoisobutyric acid; ΔMass: −262.2216 Da)	$C_{13}H_{35}N_9O_3$	365.285	64956	$C_4H_9NO_2$	103.12	0.079
13.	(Similar to: Docosahexaenoyl glycine; ΔMass: 72.0068 Da)	$C_{18}H_{36}NOP$	313.2549	9908158	$C_{24}H_{35}NO_3$	385.5	0.074
14.	(Similar to: Docosahexaenoyl glycine; ΔMass: 0.0235 Da)	$C_{14}H_{37}N_5O_3P_2$	385.2382	9908158	$C_{24}H_{35}NO_3$	385.5	0.074
15.	(Similar to: R-Palmitoyl-(2-methyl) Ethanolamide; ΔMass: −3.9880 Da)	$C_{18}H_{40}NOP$	317.2861	18395309	$C_{19}H_{39}NO_2$	313.5	0.07
16.	(Similar to: 5,5,5-Trifluoronorvaline; ΔMass: 31.9926 Da)	-	139.0581	253377	$C_5H_8F_3NO_2$	171.12	0.066
17.	(Similar to: Palmitoylethanolamide; ΔMass: 0.0065 Da)	-	299.2759	4671	$C_{18}H_{37}NO_2$	299.5	0.066
18.	(Similar to: Nervonic acid; ΔMass: 84.0998 Da)	-	282.25	5281120	$C_{24}H_{46}O_2$	366.6	0.064
19.	(Similar to: Nervonic acid; ΔMass: 126.1458 Da)	-	240.204	5281120	$C_{24}H_{46}O_2$	366.6	0.064
20.	(Similar to: Nervonic acid; ΔMass: 84.0997 Da)	-	282.2501	5281120	$C_{24}H_{46}O_2$	366.6	0.064
21.	(Similar to: Nervonic acid; ΔMass: 64.1105 Da)	$C_{16}H_{34}N_2OS$	302.2393	5281120	$C_{24}H_{46}O_2$	366.6	0.064
22.	(Similar to: Stearoylbenzoylmethane; ΔMass: 28.0178 Da)	$C_{21}H_{43}O_2P$	358.3006	94050	$C_{26}H_{42}O_2$	386.6	0.062
23.	(Similar to: Oleoylethanolamide; ΔMass: 2.0225 Da)	$C_{20}H_{38}NP$	323.2756	5283454	$C_{20}H_{39}NO_2$	325.5	0.057
24.	(Similar to: Oleoyl ethanolamide; ΔMass: 0.0069 Da)	$C_{20}H_{40}NP$	325.2912	5283454	$C_{20}H_{39}NO_2$	325.5	0.057
25.	(Similar to: Erucamide; ΔMass: −4.9464 Da)	$C_{19}H_{39}N_2OP$	342.2808	5365371	$C_{22}H_{43}NO$	337.6	0.055
26.	(Similar to: Diisooctyl phthalate; ΔMass: −28.0220 Da)	$C_{26}H_{43}O_2P$	418.2991	33934	$C_{24}H_{38}O_4$ or $(C_8H_{17}COO)_2C_6H_4$	390.6	0.054

(*Contd...*)

Table 1: (*Continued*)

S. No.	Metabolite*	Molecular formula*	ΔMass* (Da)	CID**	Molecular formula**	Mw (g/mol)**	Pa
27.	(Similar to Ethyl oleate; ΔMass: 0.0067 Da)	$C_{20}H_{39}P$	310.2805	5363269	$C_{20}H_{38}O_2$	310.5	0.053
28.	(Similar to: Fumonisin B1; ΔMass: 388.0926 Da)	-	333.2959	2733487	$C_{34}H_{59}NO_{15}$	721.8	0.053
29.	(Similar to: 5(Z), 8(Z), 11(Z)-Eicosatrienoic acid ethanolamide; ΔMass: 28.0382 Da)	$C_{20}H_{36}NP$	321.2599	16061185	$C_{22}H_{39}NO_2$	349.5	0.052
30.	(Similar to Methyl palmitate; ΔMass: 0.0059 Da)	-	270.25	8181	$C_{17}H_{34}O_2$	270.5	0.052

*Data from the LC–MS results. **Data from PubChem. ACE: Angiotensin-converting enzyme

carbon-hydrogen bonds with His513. Captopril also formed Pi-cation bonds with Tyr523 and Pi-alkyl with His353 and Ala354. Both L-GSH (reduced) and 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester did not form Van der Waals bonds. However, L-GSH (reduced) formed hydrogen bonds with a similar pattern of hydrogen bonds shown by captopril. Moreover, L-GSH (reduced) formed Pi-sulfur bonds, while 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester formed alkyl bonds [Table 3].

Furthermore, in an effort to understand the antihypertensive potential of these compounds in addition to being ACE inhibitor, the STITCH database was used to predict the target proteins from the compounds contained in the cantaloupe methanol extract. The analysis showed that L-GSH (reduced) was the most interacting active compound with the proteins from the GSH S-transferase (GST) family. In the N-domain of ACE, bonds were also formed with L-GSH (reduced) and 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester, but not on the active site amino acids.

DISCUSSION

These results indicated that cantaloupe inhibited ACE dose dependently. In addition, the data from this study scientifically proved that cantaloupe functions as a potential antihypertensive drug. ACE hydrolyzes peptides by removing a dipeptide from the C-terminus, as when ACE converts angiotensin I inactive decapeptide to angiotensin II octapeptide by removing the His-Leu dipeptide.[33] Angiotensin II that has been active can interact with the angiotensin II receptor Type 1 in arterial smooth muscle cells, triggering some reactions that generate vasoconstriction and, ultimately, increase blood pressure.[34] The inhibition of this enzyme decreases the level of angiotensin II.[11] Therefore, ACE inhibition potentially leads to a decrease in blood pressure.

Based on the results of the LC–MS phytochemical test on the cantaloupe methanol extract, there were 434 types of active compounds, 30 of which were ACE inhibitors based on searches in the online PASS [Table 1]. However, among the 30 compounds, only two types of compounds had Pa > 0.3, namely, octadecatrienoic acid methyl ester and L-GSH (reduced). Furthermore, the 3D structure of the two active compounds was analyzed using the PubChem database and was downloaded in the SDF format and was used as a ligand in the docking analysis with the ACE protein receptors (C-domain and N-domain). The docking analysis showed that L-GSH (reduced) was better than captopril at binding ACE, with an almost similar binding pattern as that of captopril. However, L-GSH (reduced) did not bind to any of the

Table 2: Docking molecular score of the two cantaloupe bioactive compounds that were potential ACE inhibitors

S. No.	Metabolite	9(Z), 11(E), 13(E)-Octadecatrienoic acid methyl ester		L-glutathione (reduced) (CID 745)		Captopril	
		1O86	2C6N	1O86	2C6N	1O86	2C6N
1.	Binding energy (kcal/mol)	0,7	−3.6	−6.6	−5.3	−5.8	−5.8

ACE: Angiotensin-converting enzyme

Figure 3: Interaction between the C-domain of angiotensin-converting enzyme (ACE) and 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester (a), interaction between the C-domain of ACE and L-glutathione (GSH) (reduced) (b), interaction between the C-domain of ACE and captopril (c), interaction between the N-domain of ACE and 9(Z), 11(E), 13(E)-octadecatrienoic acid methyl ester (d), interaction between the N-domain of ACE and L-GSH (reduced) (e), and interaction between the N-domain of ACE and captopril (f)

amino acids on the active site of ACE. Above all, the affinity energy in the bond between L-GSH (reduced) and ACE was lower than that of the bond between captopril and ACE.

L-GSH (reduced) is a reduced form of GSH. GSH is a type of antioxidant that already exists in almost every cell in the body that plays a role in the detoxification of drugs and xenobiotics. Meanwhile, reduced GSH acts

as a hydrogen donor in the detoxification of hydrogen peroxide.[35] Several experimental and clinical studies have highlighted the role of oxidative stress in the development of hypertension. Our body utilizes protective antioxidant mechanisms to counteract the production of reactive oxygen species (ROS). One such system is that GST functions as a detoxification enzyme. GST activity is demonstrated in vascular tissue and is a major cellular defense mechanism against oxidative injury.[36]

The analysis of the interaction between the active compound of the cantaloupe methanol extract and the target proteins carried out using the STITCH and STRINGdb databases suggests that at least four active compounds have a target protein [Figure 4]. However, the most interactive compound was reduced GSH, which interacted with hematopoietic prostaglandin D synthase (HPGDS), glutathione S-transferase zeta 1, glutathione S-transferase A1, glutathione S-transferase A2, glutathione S-transferase A3, alpha-aminoadipic semialdehyde synthase (AASS), arginase 1 (ARG1), hydroxyacylglutathione hydrolase, glutathione reductase, and glutathione synthetase. Eight of the 10 proteins interacted with each other and most belonged to the family of GSTs – a superfamily of enzymes involved in the detoxification of hazardous compounds and confers protection against oxidative damage,[37,38] GSTs are divided into three superfamilies, namely, cytosolic, mitochondrial, and MAPEGs (microsomal GSTs). Cytosolic GSTs are divided into 13 classes, namely, alpha, beta, delta, epsilon, zeta, theta, mu, nu, pi, sigma, tau, phi, and omega. Mitochondrial GSTs are included in the kappa class, while MAPEGs consist of four subgroups, namely, I-IV.[39,40]

HPGDS is a bifunctional enzyme that catalyzes the conversion of PGH2 to PGD2. PGD2, if interacting with

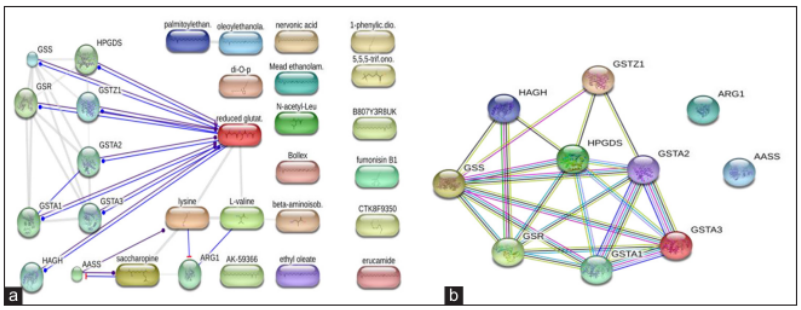

Figure 4: Interaction between the cantaloupe active compounds with the target proteins (a), interaction between the target proteins of cantaloupe active compounds (b)

Table 3: Bonds between captopril and the cantaloupe active compounds with ACE

S. No.	Bond type	9(Z), 11(E), 13(E)-Octadecatrienoic acid methyl ester (CID 21718552)		L-glutathione (reduced) (CID 745)		Captopril	
		1O86	2C6N	1O86	2C6N	1O86	2C6N
1.	Van der Waals	-	-	-	-	His513	-
2.	Attractive charge	-	-	-	-	Glu411	Asp140
3.	Conventional hydrogen bond	Lys511	-	Glu384 Glu411 His383 Tyr523 Asp415	Ala332 Gln355 His331 Ser123	His353 Tyr523 Tyr520 Gln281	Csy330 Ala332 His331
4.	Carbon hydrogen bond	-	Thr144	Ala354	Ser123	His513	-
5.	Unfavorable Donor-donor	His353 Gln281	-	-	His331	Lys511 Gln281	-
6.	Pi-cation	-	-	-		His383 Tyr523	-
7.	Pi-sulfur	-	-	His513	Trp257 His331	His387 His383	Tyr122
8.	Alkyl	His513	-	-	-		Leu139
9.	Pi-alkyl	Val380	Trp257	-	-	His353 Ala354	Phe490 His331 Tyr122

the prostaglandin D_2 receptor 1, causes vasodilatation effects and inhibits cell migration, smooth muscle relaxation, and eosinophil apoptosis.[41] AASS and ARG1 appear to have no interactions with other proteins.

Based on the results of the analysis of the protein-protein interactions above, cantaloupe is a potential antihypertensive drug that acts through the tissue damage protection pathway damage to prevent oxidative stress. In the pathophysiology of hypertension, oxidative stress plays a major role.[42] In the cardiovascular system, ROS controls endothelial function, vascular tone, and cardiac function, and pathophysiological roles in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis, angiogenesis, and rarefaction, all of which are important processes that contribute to endothelial dysfunction and cardiovascular remodeling in hypertension.[42]

This research describes that cantaloupe contains various active compounds that target some proteins involved in the protection system due to the adverse effects of oxidative stress. This is an advantage for cantaloupe in hypertension therapy because it works systematically, which is in comparison to the antihypertensive drugs that are available on the market. For example, ACE inhibitors work specifically to target the ACE proteins, which cause side effects that include coughing, due to the accumulation of bradykinin.[13,16] In contrast, the cantaloupe methanol extract works by targeting several proteins at once so that it achieves a more balanced reaction.

CONCLUSION

The methanol extract from *C. melo* var. *cantalupensis* inhibits ACE activity. It is estimated that the L-GSH (reduced) contained in the methanol extract from *C. melo* var. *cantalupensis* acts as an antihypertensive agent through the stimulation of the GST pathway, which plays a role in detoxification and radical scavenging.

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