Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 11 No. 2 August 2024, 230-241
DOI: 10.20473/jfiki.v11i12024.230-241
Available online at https://e-journal.unair.ac.id/JFIKI/

Analysis of Cayenne Pepper Fruit (*Capsicum frutescens*) in Inhibiting HMG-CoA Reductase Activity as a Treatment for Hypercholesterolemia

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Submitted: 6 Maret 2024
Revised: 5 July 2024
Accepted: 31 August 2024

Abstract

Background*: Hypercholesterolemia is a major cause of cardiovascular disease and its incidence continues to increase. Statins are a group of hypercholesterolemic therapies known to trigger various side effects; therefore, statin alternatives need to be investigated. The cayenne pepper (Capsicum frutescens) contains secondary metabolites that inhibit the activity of cholesterol-forming enzymes (HMG-CoA reductase).* ***Objective:*** *The aim of this study was to identify the ability of C. frutescens fruit to inhibit HMG-CoA reductase activity to prevent hypercholesterolemia.* ***Methods:*** *This was a true experimental study using a posttest-only control group design. The independent variables were n-hexane, methanol, and ethanol extracts of C. frutescens fruit, each with a concentration of 0.01%, with HMG-CoA reductase activity as the dependent variable. Enzymatic activity was measured enzymatically using spectrometry.* ***Results:*** *The mean values of % inhibition from n-hexane, methanol, and ethanol extracts of C. frutescens and pravastatin were 95.74%, 104.70%, 100.11%, and 99.27%, respectively. The average specific activities of n-hexane, methanol, and ethanol extracts of C. frutescens and pravastatin were 0.5765, 0.6029, 0.5513, and 0.5716 units/mgP, respectively. There was a significant difference between the sample groups in the inhibition of HMG-CoA reductase activity. HMG-CoA reductase inhibitory activity was highest in the methanol extract, followed by the n-hexane extracts. The activity of these extracts was higher than that of pravastatin alone.* ***Conclusion:*** *The methanol extract showed the best inhibitory activity****.*** *C. frutescens has been shown to have great potential in inhibiting the activity of the enzyme HMG-CoA reductase and preventing hypercholesterolemia.*

Keywords*: Capsicum frutescens, HMG-CoA reductase, hypercholesterolemia*

How to cite this article:
Albar, L. O. M., Tien & Eso, A. (2024). Analysis of Cayenne Pepper Fruit (*Capsicum frutescens*) in Inhibiting HMG-CoA Reductase Activity as a Treatment for Hypercholesterolemia. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 11(2), 230-241. http://doi.org/10.20473/jfiki.v11i12024.230-241

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

Hypercholesterolemia is a non-communicable disease caused by lipid metabolism disorders and is characterized by an increase in total cholesterol levels in the blood. As one of the causes of coronary heart disease (CHD), high cholesterol levels can increase the risk of death by up to three times (Jempormase et al., 2016). Globally, the highest incidence of hypercholesterolemia is in Europe, with a prevalence of 54%, America, with a prevalence of 48%, and Southeast Asia, with a prevalence of 30% (WHO, 2011). Locally, 36 million people, or about 18% of the Indonesian population, suffer from this blood fat disorder. Of that number, 80% of patients die suddenly from a heart attack and 50% have no previous symptoms (Jempormase et al., 2016).

Cholesterol biosynthesis requires the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme converts HMG-CoA into mevalonic acid through a series of condensation and rearrangements, and mevalonic acid is then converted into cholesterol (Baskaran et al., 2015).

Statins are cholesterol-lowering drugs that competitively reduce HMG-CoA reductase activity. Inhibition of this enzyme causes a series of reactions that trigger an increase in LDL receptor expression, which increases plasma LDL absorption, thereby decreasing plasma LDL cholesterol levels (Dewi and Merry, 2017). Despite being a guideline for cholesterol-lowering therapy, several studies have shown that long-term use of statins can lead to side effects, including hyperglycemia, leading to a new onset of diabetes mellitus, myopathy, renal failure, neurological side effects such as muscle pain (myalgia) and neurocognitive disorders, and hepatotoxic effects (Rizqi et al., 2014; Farida and Putri, 2016; Ward et al., 2019).

Cayenne pepper (*Capsicum frutescens*) is a shrub that grows widely in Indonesia. This plant is part of the *Plantae* kingdom, *Solanaceae* family, and *Capsicum* genus (Simpson 2010). Several studies have shown the antioxidant effects of *C. frutescens* (Melannisa et al., 2011; Giovedi, 2016; Talitha, 2017) and its ability to inhibit the growth of *Staphylococcus aureus* (Munira et al., 2019; Taolin, 2019; Rahim and Nurmayanti, 2020). A number of studies using in silico docking methods have shown that secondary metabolites contained in *C. frutescens,* including flavonoids, terpenoids, alkaloids, and phenols, have the capacity to competitively reduce the activity of HMG-CoA reductase (Islam et al., 2015; Aqeel et al., 2018; Hariyati et al., 2018; Azmi et al., 2021; Shaik et al., 2020; Mannino et al., 2021). The catalytic activity of the enzyme against substrates in the form of HMG-CoA and NADPH co-substrates to form mevalonate can be prevented (Fridiana et al., 2019; Gesto et al., 2020; Marahatha et al., 2021).

This study aimed to identify the ability of n-hexane, methanol, and ethanol extracts of *C. frutescens* to inhibit HMG-CoA reductase activity and to determine the significant difference in the ability of *C. frutescens* extracts with statin class drugs such as pravastatin. This study can serve as a follow-up to in silico investigations of the numerous secondary metabolites detected in *C. frutescens fruit* with HMG-CoA reductase activity. This study can also serve as a source of scientific information about the *C. frutescens fruit*, enhancing public confidence in its use in everyday life.

MATERIALS AND METHODS

Materials

The material used in this study were *C. frutescens* obtained in Labaha Village, Watopute District, Muna Regency, Southeast Sulawesi. Plant taxonomy was determined at the Research Laboratory, Faculty of Pharmacy, Halu Oleo University, with sample code 017 and letter number 613. a/UN29.18/PP/2024. Other materials used in this research were the HMG-CoA reductase assay kit (Sigma Aldrich, Missouri, USA), ethanol (Merck), methanol (Merck), n-hexane (Merck), Meyer reagent, and Dragendorff reagent , Darmstadt, Germany).

Instrument

An ELISA reader (Thermo-Multiskan FC) was used to measure the HMG-CoA reductase enzyme activity.

Methods

This study was conducted at the Biomedical Laboratory of the Faculty of Medicine and Pharmacy Laboratory of the Faculty of Pharmacy, Universitas Halu Oleo.

Sample collection and preparation

C. frutescensi fruit were collected, then separated between the fruit and the stalks, then washed with running water to separate the fruit from the dirt attached to the sample. The samples were then dried out by being placed in an oven at 40°C. The drying process was carried out until the sample was completely dried and yielded a powder.

Extraction

The maceration method was applied in the extraction process by mixing *C. frutescens* plant powder with pure solvents (pro analysis) in the form of ethanol

P-ISSN: 2406-9388
E-ISSN: 2580-8303

(100%), methanol, and n-hexane at 1 g of dried powder per 10 mL of solvent for 48 h in the dark at room temperature. The extract was filtered through a filter paper until the filtrate was obtained. To obtain a thick extract, the concentration procedure was performed using a Rotary Vacuum Evaporator at 60 °C. To enhance solubility, the samples were diluted in DMSO.

Phytochemical screening

Phyochemical screening was performed as described by Wijaya et al. (2018) and Saripa et al. (2020).

Flavonoidstwo

Two drops of concentrated HCl were used to observe the color changes. The solution was then heated in a water heater for 15 min. The appearance of red, yellow, or orange after heating indicates the presence of flavonoid compounds.

Alkaloids

The residue was dissolved in 5 mL of HCl obtained by evaporating 2 mL of the test extract in a Petri dish. Divide into four tubes. Tube A (blank) was added to HCl. Dragendorff reagent was added with, Mayer reagent was added to tube C, and three drops of Wagner reagent were added to tube D. The white or orange precipitate formed indicated the presence of alkaloids in the test extract.

Terpenoids and sterols

A total of 0.5 mL of chloroform and 0.5 mL of $(CHCO_3)_2O$ were added to the test extract, which was then added to 2 mL of H_2SO_4. A bluish-green color indicates the presence of sterols. If a brown or purple ring forms at the boundary between the two solvents, the terpenoid content is present in the extract.

Phenol

One milliliter of extract (1000 µg/mL) was reacted with two drops of a 1% $FeCl_3$ solution. A strong red, green, or blue color is phenol-positive.

Saponins

The extract was cooled and shaken for 10 s in 10 ml of distilled water in a heated test tube. The foam formed with a height of 1-10 cm for 10 min was added with 2N HCl. The saponin content was considered positive if the foam did not disappear.

Tannins

One milligram was soaked in 96% ethanol. Three drops of a 1% FeCl3 solution were added. If a green or bluish-black color is formed, the tannins are positive.

Measurement of HMG-CoA Reductase Enzyme Activity

Ethanol, methanol, and n-hexane extracts (10 mg) from *C. frutescens* plants were evaporated and dissolved in 5 µL of 100% Dimethyl Sulfoxide (DMSO). The solution was then stirred to dissolve, diluted with 995 µL of deionized water, and stirred again until it dissolved.

Before starting the measurements, the ELISA reader was set at a temperature of 37 °C and wavelength of 340 nm. The work procedure was carried out with a 96 well plate sample measurement program, which was read every 20 s for 10 min. The reagent volumes for the components and samples to be tested are listed in Table 1.

Data analysis

Bioassay data were collected after three repetitions. Percent inhibition (%I) is a measure of the percentage of HMG-CoA reductase enzyme activity inhibited by the sample by estimating the difference between the absorbance value at the last measurement (A0) and the absorbance value at the first measurement (A10) of NADPH molecules in the reaction mixture within 10 min of measurement. Percent inhibition (%I) was estimated using the following formula: %I = [(control absorbance − sample absorbance)/control absorbance] × 100%.

Specific enzyme activity is the ability of the sample to inhibit the activity of the HMG-CoA reductase enzyme in enzyme units per milligram of protein, as determined by the difference between the absorbance value at the last measurement (A30) and the absorbance value at the first measurement (A1) of the NADPH molecules in the reaction sequence with 30 measurements over 10 min using an Elisa Reader (Thermo-Multiskan FC). The specific activity value of the HMG-CoA reductase enzyme was calculated using the following formula: specific activity (unit/mg P) = (ΔA(sample)/min) × volume total/12.44 x volume of enzyme × [enzyme] × light path (0.55 cm). The enzyme concentration was 0.6 mgP/mL.

Table 1. Volume of reagents and samples to be tested

	1 x *Assay Buffer*	Pravastatin / extract	NADPH	*HMG- CoA*	HMGR
Blanko	184 µl	-	4 µl	12 µl	-
Sample	181 µl	1 µl	4 µl	12 µl	2 µl

Abbreviations: NADPH, Nicotinamide adenine dinucleotide phosphate; HMGR, HMG CoA Reductase

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Statistical analyses were performed using the SPSS 25. This analysis aimed to compare the ability of HMG CoA-reductase inhibition among ethanol, methanol, n-hexane extracts, and pravastatin controls. This comparative analysis used a one-way ANOVA hypothesis test. The sample groups were considered distinct if the p-value was less than 0.05. If there were disparities in the sample variation, a post-hoc test was applied to continue the statistical analysis.

RESULTS AND DISCUSSION

Phytochemistry screening

As shown in Table 2, the secondary metabolite compounds in the three extracts of *C. frutescens* were alkaloids, saponins, terpenoids, and flavonoids. The types of secondary metabolites not contained in the three extracts of *C. frutescens* were tannins and steroids. Phenol is a secondary metabolite found only in the ethanol extract of *C. frutescens*.

The ability of *C. frutescens* to reduce HMG-CoA reductase can be attributed to its high flavonoid content, which is known to have the capacity to reduce the enzyme significantly and competitively, similar to the ability of statin drugs to reduce cholesterol levels in the body (Nascimento et al., 2013; Wijaya et al., 2018; Rivera et al., 2019; Bansal, 2021). In a study conducted by Baskaran et al. (2015) on malabar spinach (*Basella alba*) with simvastatin as the positive control, it was found that *B. alba* inhibited HMG-CoA reductase activity, as seen from the % inhibition, which reached 74.1%, which was slightly lower than that of simvastatin (85.1 %). This was related to the secondary metabolite content of *B. alba*, one of the secondary metabolites present in *B. alba* with high levels of luteolin. This is in line with research conducted using samples in the form of *C. frutescens*, which is known to contain very high levels of flavonoids in the form of luteolin (Rivera et al., 2019). Molecular docking research conducted by Nematollahi et al. (2012) showed a very strong interaction between luteolin and the HMG-CoA reductase enzyme, making luteolin highly potential as an HMG-CoA reductase inhibitor.

Inhibition activity of HMG-CoA Reductase

Based on the analysis of research results, it was shown that ethanol, methanol, and n-hexane extracts from *C. frutescens* samples had the capacity to reduce HMG-CoA reductase, which can be seen from the % inhibition value of these three extracts. The mean % inhibition of n-hexane, methanol, and ethanol extracts from C. *frutescens* and pravastatin were 100.11%, 104.70%, 95.74%, and 99.27%, respectively (Figure 1). From the average % inhibition, the sample with the highest % inhibition value was the methanol extract of *C. frutescens*, and the sample with the second highest percentage inhibition was the n-hexane extract of C. frutescens and pravastatin. The sample with the lowest % inhibition value was the *C. frutescens* ethanol extract. The concentration of each extract used in this study was 10 mg in 1000 µL of solvent (0.01%).

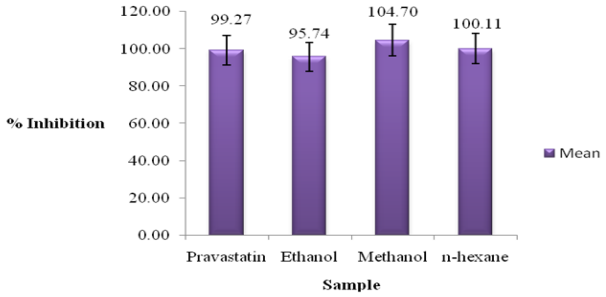

Figure 1. Graph of mean % inhibition values of pravastatin, n-hexane, methanol, and ethanol extracts of cayenne pepper (*C. frutescens*). Pravastatin as a positive control added at 1 µL and n-hexane, methanol, and ethanol extracts as test samples with a concentration of 10 mg in 1000 µL of solvent

Table 2. Phytochemical results of cayenne pepper (*C. frutescens*)

Compound Groups	Ethanol	Methanol	n-Hexane
Flavonoid	+	+	+
Alkaloid			
- Mayer	+	-	+
- Wagner	+	+	+
- *Dragendorff*	-	-	+
Terpenoid	+	+	+
Steroid	-	-	-
Fenol	+	-	-
Saponin	+	+	+
Tanin	-	-	-

Notes: +, detected; -, not detected

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 3. Post Hoc test results (multiple comparison) % inhibition value

Dependent variable: Inhibition % value		
Sample (n = 3)		***p-value****
Pravastatin	Ethanol	0.204
	Methanol	0.039
	n-Hexane	0.950
n-Hexane	Pravastatin	0.950
	Ethanol	0.099
	Methanol	0.082
Methanol	Pravastatin	0.039
	Ethanol	0.002
	n-Hexane	0.082
Ethanol	Pravastatin	0.204
	Methanol	0.002
	n-Hexane	0.099

Notes: *Post Hoc One Way ANOVA; significance if $p < 0.05$

This refers to a clinical dose of 10 mg of pravastatin. The inhibitory activity of the n-hexane and methanol extracts was quite high, reaching over 100%, surpassing the inhibitory activity of pravastatin. The crude extract had high inhibitory ability.

In a study conducted by Wijaya et al. (2018) on variations in the concentration of the ethanol extract of bay leaves (*Syzygium polyanthum*), it was found that *S. polyanthum* has the ability to inhibit the activity of HMG-CoA reductase, which can be seen from the % inhibition of bay leaves at different concentrations. One of them was that at a concentration of 600 ppm, the ethanol extract of *S. polyanthum* could inhibit the enzyme with a % inhibition value of 82.76%. This is related to the secondary metabolite content of *S. polyanthum*, where quercetin is one of the secondary metabolites present in S. polyanthum at high levels. This is in line with research carried out using samples in the form of *C. frutescens*, which is known to contain very high levels of flavonoids in the form of quercetin (Nascimento et al., 2013).

Islam et al. (2015) explored the ability of luteolin and quercetin, flavonoid polyphenols, to inhibit HMG-CoA reductase activity. Based on the results obtained, it was found that luteolin and quercetin have a fairly high affinity for the active section of the amino acid residue of the enzyme, which causes the enzyme's catalytic activity to not occur toward the substrate and cosubstrate. This shows that luteolin and quercetin have an excellent ability to inhibit enzyme activity so that they can prevent cholesterol synthesis.

The high activity of *C. frutescens* extract in polar (methanol), nonpolar (n-hexane), and semipolar (ethanol) solvents can be attributed to the high levels of flavonoids in *C. frutescens*. Flavonoids are secondary metabolites that have two different polarities, polar and nonpolar, so that they can dissolve easily in polar, nonpolar, and semipolar solvents (Nascimento et al., 2013; Arifin and Ibrahim, 2018; Rivera et al., 2019). The *C. frutescens* extract in a polar solvent (methanol) had the highest ability with a % inhibition value exceeding that of pravastatin and was statistically significantly different from pravastatin, indicating that the flavonoid content in the *C. frutescens* samples used in this study is thought to be dominated by flavonoids in the form of glycosides, so they are more soluble in polar solvents. Apart from flavonoids, the *C. frutescens* studied is also known to contain a number of secondary metabolite compounds that have the capacity to interact with the active section of HMG-CoA reductase, including phenols, alkaloids, and terpenoids. The results of in silico research show that secondary metabolites in the form of flavonoids, phenols, alkaloids, and terpenoids can interact with the active section of the enzyme, thus inhibiting the catalytic activity of the enzyme against substrates in the form of HMG-CoA and cosubstrates in the form of NADPH (Islam et al., 2015; Hariyanti et al., 2018; Aqeel et al., 2021; Mannino et al., 2021).

The P value between n-hexane extract and ethanol extract ($p > 0.05$) and n-hexane extract and methanol extract ($p > 0.05$) showed that of the three groups of *C. frutescens* extract samples, the HMG enzyme was inhibited by two distinct groups of extracts. The different CoA reductases were ethanol extract and methanol extract ($p < 0.05$), and one group had the same capacity to reduce the enzyme as the other group, namely the n-hexane extract.

Specific activity of HMG-CoA reductase

Based on Figure 2, the enzyme specific activity of the ethanol, methanol, and n-hexane extract samples of *C. frutescens* and pravastatin are shown with the average enzyme specific activity in the following order: 0.5513 mgP; 0.6029 mgP, 0.5765 mgP, and 0.5716 mgP, respectively. Specific activity is the standard of enzyme purity in a series of reactions that contribute to

P-ISSN: 2406-9388
E-ISSN: 2580-8303

the transformation of a particular substance. The specific activity of the enzyme was determined by the number of enzyme units per milligram of protein (units/mg P). Enzymes are proteins and their catalytic activity depends on the integrity of their structure, so the probability that the content of HMG-CoA reductase as an enzyme protein will be high if there is inhibition of the use of NADPH by the inhibitors used in the reaction series. The higher the specific activity of the enzyme, the purer the enzyme contained in the reaction, indicating that the reacted enzyme is not used in the conversion process of a particular compound. Inhibition of enzyme activity by the sample by preventing the reaction between HMG-CoA reductase, HMG-CoA, and NADPH can increase the purity of the enzyme in the reaction. Thus, the higher the specific activity of the enzyme, the higher the ability of the inhibitor to inhibit enzyme activity (Djarkasi et al., 2021).

Data analysis was performed to determine the specific activity of the enzyme. Based on research by Feng et al. (2013) on a mutated uricase enzyme, it is known that measuring the specific activity of the enzyme can help measure the catalytic activity of the enzyme with high sensitivity, even at low activity levels. The basic pathomechanism of hyperuricemia is mutation of the uricase enzyme; therefore, measuring the catalytic activity of the uricase enzyme is essential for determining the progression of the uricase enzyme mutation. The relatively small number of enzymes in cells makes it difficult to determine their presence and concentration. However, the ability to rapidly convert thousands of molecules of a particular substrate into a product makes it easier for each enzyme to detect its presence.

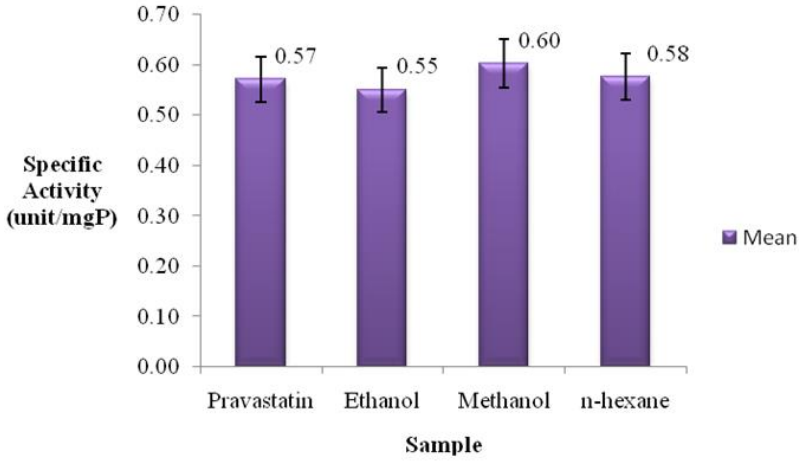

Figure 2. Graph of mean enzyme specific activity of pravastatin, n-hexane, methanol, and ethanol extracts of cayenne pepper (*C. frutescens*)

Table 4. Results of Post Hoc Test (Multiple Comparison) Enzyme Specific Activity

Dependent variable: Enzyme Specific Activity		
Sample (n = 3)		***p-value****
Pravastatin	Ethanol	0.203
	Methanol	0.039
	n-Hexane	0.951
n-Hexane	Pravastatin	0.951
	Ethanol	0.098
	Methanol	0.081
Methanol	Pravastatin	0.039
	Ethanol	0.002
	n-Hexane	0.081
Ethanol	Pravastatin	0.203
	Methanol	0.002
	n-Hexane	0.098

Notes: *Post Hoc One Way ANOVA; significance if $p < 0.05$

P-ISSN: 2406-9388
E-ISSN: 2580-8303

The measurement of enzyme catalytic activity is often used in clinical and research laboratories (Murray et al., 2012). The correlation between specific activity and enzyme catalytic activity, which is directly proportional, shows that exploration of the specific activity of enzymes will greatly assist the development of biotechnology, which is oriented towards progressing clinical aspects in determining the diagnosis or prognosis of diseases related to the metabolism of a particular enzyme.

Significant differences in the specific activity of HMG-CoA reductase from n-hexane, methanol, and ethanol extracts of *C. frutescens* and pravastatin can be identified by looking at the p value from the one-way ANOVA test. The one-way ANOVA test on the sample data revealed that the specific activity of the enzyme was significantly different between the sample groups, as shown in Table 4. Based on data analysis, the average specific activities of the enzyme from n-hexane, methanol, and ethanol extracts of *C. frutescens* and pravastatin, respectively, were as follows: 0.5765 units/mgP, 0.6029 units/mgP, 0.5513 units/mgP, and 0.5716 units/mgP. The sample with the highest specific enzyme activity was the methanol extract of *C. frutescens* with an average specific enzyme activity of 0.6029 units/mgP, followed by the n-hexane extract of *C. frutescens* with an average specific enzyme activity of 0.5765 units/mgP. Both extracts had higher specific enzyme activity than pravastatin with an average specific activity of 0.5716 units/mgP. The average specific enzyme activity of the ethanol extract of *C. frutescens* was lower than that of pravastatin, with an average value of 0.5513 units/mgP. The analysis of specific enzyme activity data showed that the methanol extract and n-hexane extract of *C. frutescens* had the best potential for inhibiting the enzyme.

The results of the phytochemical tests carried out on three groups of *C. frutescens* extract samples showed variations in the content of different secondary metabolite compounds from each extract. *C. frutescens* ethanol extract is a sample that contains the most varied secondary metabolite compounds with secondary metabolite compounds in the form of flavonoids, phenols, alkaloids (positive in the Mayer and Wagner method), terpenoids and saponins. The n-hexane extract of *C. frutescens* is a sample that contains the second most varied secondary metabolite compounds after ethanol with secondary metabolite compounds in the form of flavonoids, alkaloids (positive in the Mayer, Wagner and Dragendorff methods), terpenoids and saponins. The methanol extract of *C. frutescens* contained the smallest variation in secondary metabolite compounds. Flavonoids, alkaloids (positive in the Wagner method), terpenoids, and saponins were some of the secondary metabolites found in the methanol extract of C. frutescens.

Based on the data on the % inhibition value and specific activity of the enzyme obtained, the extract samples with the best potential for inhibiting the enzyme were the methanol extract and n-hexane extract of *C. frutescens*. The sample with the smallest potential for enzyme inhibition was the ethanol extract of *C. frutescens*. This indicates that the high variation of secondary metabolite compounds found in the extract samples in this study does not determine their bioactive capabilities, especially when it comes to enzyme inhibition.

In addition, the characteristics of secondary metabolite compounds which have synergistic and antagonistic properties are known to be one of the factors that determine the potential bioactivity of these secondary metabolite compounds (Kopjar et al., 2016).

In a study conducted by Tavadyan and Minasyan (2019), using the Square Wave Voltammetry (SWV) method on the antioxidant ability of isolated flavonoids, it was found that there was a decrease in the potential bioactivity of flavonoid-derived secondary metabolite compounds in the form of quercetin after adding ascorbic acid (vitamin C). The interaction of a series of chemical groups of the aglycone properties of quercetin as a secondary metabolite derived from flavonoids with vitamin C causes a decrease in the antioxidant activity of quercetin. This shows that the interactions between secondary metabolite compounds and other compounds contained in plants can determine their potential bioactivity.

CONCLUSION

Based on the percentage inhibition value and enzyme-specific activity, the methanol extract of C. frutescens had the best HMG-CoA reductase inhibition capability, with an average inhibition capability of 104.70% and an enzyme-specific activity of 0.60 units/mgP. In addition, there was a substantial difference in HMG-CoA reductase inhibition between the pravastatin and *C. frutescens* extracts.

ACKNOWLEDGMENT

The authors would like to thank the Faculty of Medicine, Halu Oleo University for supporting this research.

AUTHOR CONTRIBUTIONS

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Conceptualization, L.O.M.A., T.; Methodology, L.O.M.A., T.; Software, L.O.M.A., A.E.; Validation, L.O.M.A., A.E.; Formal Analysis, L.O.M.A., A.E.; Investigation, L.O.M.A., T; Resources, L.O.M.A., T.; Data Curration; L.O.M.A., T.; Writing - Original Draft, L.O.M.A.; Writing - Review & Editing, T.; Visualization, L.O.M.A., T.; Supervision, T.; Project Administration, T.; Funding Acquisition, T.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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