Bioactive Compounds, Antioxidant Capacity and HMG-CoA Reductase Inhibitory Potential of Red Fruit Oil (*Pandanus conoideus* Lam.): An *In Silico* and *In Vitro* Study

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Abstract: *Cardiovascular disease, the leading cause of death worldwide, can result from dyslipidemia's ability to promote atherosclerosis. Therefore, it is important to address this issue by utilizing local food sources, such as red fruit oil, an endemic fruit from Papua, Indonesia. Red fruit oil contains some bioactive compounds, making it a promising candidate for use in functional foods. This study aimed to assess the bioactive components of red fruit oil, its antioxidant capacity, and its inhibitory potential against 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase enzyme, both* in silico *and* in vitro. *The results showed that red fruit oil contained total phenolics of 627.42 ± 61.78 mg GAE/g, flavonoids of 128.06 ± 8.94 mg QE/g, and an antioxidant capacity of 2316.15 ± 135.63 µmol TE/g. Based on the outcomes of* in silico *investigations, the suspected compounds capable of inhibiting HMG-CoA reductase were isochamaejasm, 6-acetylpicropolin, (−)-pinellic acid, and 2-monolinolein, with binding energies of −8.3620, −7.9660, −7.6980, and −7.6970 kcal/mol, respectively. The* in vitro *results showed that the inhibitory activity of red fruit oil was 48.36 ± 2.46, which was not significantly different from that of lovastatin 50.82 ± 2.46 (p = 0.288). The findings of this study suggest that red fruit oil may be able to manage dyslipidemia by inhibiting HMG-CoA reductase.*

Keywords: *bioactive compound; dyslipidemia; HMG-CoA reductase; red fruit oil*

■ INTRODUCTION

Dyslipidemia is defined as a condition in which there is an increase in total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides, as well as low high-density lipoprotein (HDL) cholesterol or a combination of these disorders [1]. Dyslipidemia increases the risk of developing atherosclerosis, which is characterized by the formation of lipid-rich plaques in the arteries. Dyslipidemia can lead to inflammation, oxidative stress, cardiovascular disease, and other metabolic dysfunctions [2]. Cardiovascular disease is the most common cause of death worldwide. Of the 17.9 million persons who died in 2019, approximately one-third (32%) died from cardiovascular diseases. Heart attacks and strokes account for 85% of all deaths [3].

Dyslipidemia can be treated non-pharmacologically through lifestyle modifications, such as increasing physical activity and improving diet, and pharmacologically by taking statin-class drugs, which are 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors. However, statin-class drugs show side effects, including myalgia, liver dysfunction, kidney dysfunction, diabetes mellitus, shortness of breath, pancreatitis, and peripheral neuropathy [4-5] Therefore, it is important to consider treating dyslipidemia with natural ingredients sourced from natural food sources.

Antioxidant-rich foods can aid individuals with dyslipidemia in preventing oxidative and inflammatory damage. They accomplish this by regulating fat metabolism, increasing antioxidant activity, and managing inflammation, all of which help protect against various problems [6]. One of the functional

foods that can be utilized for the treatment of dyslipidemia is red fruit (*Pandanus conoideus* Lam.). Red fruit contains various active components, including α-carotene, β-carotene, β-cryptoxanthin, and α-tocopherol, as well as unsaturated fatty acids. Furthermore, red fruit extract contains phytochemical compounds, including phenolics, flavonoids, triterpenoids, alkaloids, and saponins [7-8]. Flavonoids can limit the activity of HMG-CoA reductase by establishing hydrogen bonds with amino acids on the enzyme through hydrophobic interactions [9]. Active compounds such as oleic acid, luteolin, ascorbic acid, and α-tocopherol are also able to lower cholesterol levels by inhibiting HMG-CoA reductase [10]. Based on the foregoing description, red fruits are potential as functional food alternatives because of their bioactive content. Therefore, this study aims to evaluate its bioactive compound content including total phenolics, flavonoids, and antioxidant capacity using the cupric reducing antioxidant capacity (CUPRAC) method and to analyze the potential of red fruit oil to inhibit HMG-CoA reductase both *in silico* and *in vitro*.

■ EXPERIMENTAL SECTION

Materials

The materials used in this study were methanol and ethanol (pro analysis grade, ≥ 99%, Merck, Germany), $CuCl_2{\cdot}2H_2O$, 2,9-dimethyl-1,10-phenanthroline (neocuproine, Nc, ≥ 99%, Merck, Germany), ammonium acetate buffer (NH_4OAc, 99% purity, ACS Chemicals), 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (trolox, 97% purity, Thermo Scientific), aluminum chloride ($AlCl_3$, ≥ 98%, Merck, Germany), sodium nitrite ($NaNO_2$, ≥ 99.0%, Merck, Germany), sodium hydroxide (NaOH, ≥ 98.0%, Merck, Germany), quercetin (≥ 95.0%, Sigma-Aldrich, USA), Folin-Ciocalteu reagent (analytical grade, Merck, Germany), sodium carbonate (Na_2CO_3, ≥ 99.5%, Merck, Germany), gallic acid (≥ 98.0%, Sigma-Aldrich, USA), and the 3-hydroxy-3-methylglutaryl-CoA Reductase (HMGR) Inhibitor Screening Kit (Elabscience).

Instrumentation

Total phenolic and flavonoid analyses were performed using ultraviolet-visible (UV-vis) spectrophotometry. Bioactive compound profiling was conducted using liquid chromatography-mass spectrometry (LC-MS) UHPLC Vanquish Tandem Q Exactive Plus Orbitrap HRMS (Thermo Scientific). Antioxidant capacity and HMGR enzyme inhibition were measured using a multimode microplate reader (BioTek Synergy HTX, Agilent). Finally, *in silico* studies were performed using the YASARA Structure software on a desktop computer (DESKTOP-AE94SSE) equipped with an Intel® Core™ i9-9900K processor operating at 3.60 GHz, and 2D and 3D visualizations were created using Discovery Studio and PyMOL.

Procedure

Red fruit oil extraction

The red fruit was obtained from the Koya Barat District, Jayapura, Papua. Red fruit oil extraction was performed using a pressing method. A total of 2.8 kg of red fruit pulp was cleaned and steamed at 100 °C for 10 min. Subsequently, hot water at 80 °C was added at a 2:1 w/v ratio and pressing was performed at a pressure of 4,000–4,500 psi. Subsequently, centrifugation was performed at 3,000 rpm for 10 min for oil separation, and then evaporation was carried out at 50 °C for 15 min to remove any residual water from the red fruit oil.

Total phenolic content analysis

Red fruit oil was dissolved in ethanol at a 1:1 ratio in a 100 mL volumetric flask and used for flavonoid, phenolic, and antioxidant analyses. Flavonoid content analysis was performed according to the previous method described using the Folin-Ciocalteu method [11]. A total of 100 µL of the sample was pipetted into a test tube, and 2 mL of 10% Na_2CO_3 was added. The mixture was incubated for 5 min at room temperature in the dark. After incubation, 1 mL of Folin-Ciocalteu reagent was added and incubated again under the same conditions for 30 min. The absorbance was measured at 780 nm. The analysis was performed in triplicate

Total flavonoid content analysis

Total flavonoid content was analyzed using a previously described method [12]. A total of 1 mL of the sample was pipetted into a test tube, and 0.3 mL of 15% $NaNO_2$ was added and incubated for 6 min. After incubation, 0.3 mL of 10% $AlCl_3$ was added and incubated

for 1 h. Subsequently, 4 mL of 4% NaOH and 4 mL of H_2O were added, and the solution was vortexed and incubated for 15 min. The absorbance was measured at 420 nm. Quercetin concentrations of 0, 6.25, 12.5, 25, 50, 100, and 200 ppm were used as standards to determine the total flavonoid content. The analyses were performed in triplicate.

Antioxidant capacity analysis

Antioxidant capacity analysis was done using the CUPRAC method [13]. Trolox at concentrations of 0, 12.5, 25.0, 50.0, 100, 200, and 400 µmol was used as a standard to calculate antioxidant capacity in terms of TEAC (µmol TE/g extract). A total of 50 µL of the sample was pipetted into a 96-well microplate, followed by the addition of 50 µL of 0.01 M $CuCl_2{\cdot}2H_2O$, 50 µL of 0.0075 M Nc solution, and 50 µL of 1 M NH_4OAc buffer (pH 7). Subsequently, the mixture was incubated for 30 min at room temperature in the dark, and the absorbance was measured at 450 nm. The analysis was performed in triplicate.

Profiling of bioactive compounds

The red fruit oil was diluted at a 1:10 ratio in methanol and filtered through a 0.2 µm nylon filter. A 2 µL volume was then injected into an Accucore C18 column at a flow rate of 0.2 mL/min. The mobile phase consisted of H_2O + 0.1% formic acid (A) and acetonitrile + 0.1% formic acid (B) mixture. The analysis was performed in negative and positive ionization modes, with a mass range of 100–1,500 *m/z*. The compounds were identified by comparing their *m/z* values, retention times (RT), and fragmentation patterns with those in the ChemSpider and mzCloud databases. The compounds presented were selected based on their potential biological activities relevant to the objectives of this study.

In silico *study HMG-CoA reductase inhibition*

An *in silico* study was performed using the YASARA Structure, beginning with the preparation of the receptor and test ligands. This study used the 3D protein structure of HMG-CoA reductase obtained from the RSCB Protein Data Bank. Before use, the protein structure was prepared by removing water molecules and superfluous residues and adding hydrogen atoms to it. The test ligands used were bioactive compounds identified by LC-MS, and their structures were downloaded from PubChem and ChemSpider. Subsequently, the geometry of each ligand was optimized, and hydrogen atoms were added as part of the preparation. Before performing molecular docking on the test ligands, the grid box size was validated by redocking the native ligand to the receptor, starting with a size range of 1–10 Å at 0.5 Å intervals. The parameter for selecting the grid box size was based on the root mean square deviation (RMSD) value, which was considered valid if the superposition of the native ligand with the redocked ligand yielded an RMSD value of ≤ 2 Å [14]. After grid box validation, molecular docking was performed on the prepared test ligands in 100 repetitions. The molecular docking results were expressed as Gibbs free energy values ($\Delta G_{binding}$) and inhibition constants (Ki). The reference ligands used were HMG-CoA substrate and lovastatin. The selected value was the lowest (most negative) $\Delta G_{binding}$, which appears first in the output (log file). Subsequently, Ki was calculated from $\Delta G_{binding}$ using Eq. (1);

$$Ki = e\left(\Delta G \times 1000/R \times T\right) \quad (1)$$

whereas R is ideal gas constant (1.985×10^{-3} kcal/mol K) and T is temperature (298.15 K). Only compounds that exhibited more negative binding energies than the substrate (HMG-CoA) were included in the results. After molecular docking, the bioavailability of the compounds with the best binding free energies was predicted using Lipinski's Rule of Five. Their ADMET properties were also predicted using the SwissADME website, developed by the Swiss Institute of Bioinformatics and the ProTox III platform [15-16].

In vitro *study of HMG-CoA reductase inhibition*

A HMG-CoA reductase inhibitor screening kit (catalog no: E-BC-D011) was used to conduct an *in vitro* study. The reaction solution consisted of a buffer solution, an enzyme, and a reaction working solution, which was a mixture of the buffer, substrate, and working accelerant solution. Lovastatin was used as a positive control, with an IC_{50} of approximately 10 µmol/L, and was dissolved in a buffer solution. The red fruit oil sample was dissolved in DMSO and buffer solution. Subsequently, 20 µL of the sample was pipetted into a 96-well microplate, followed by the addition of

20 µL of enzyme and 180 µL of reaction working solution. The blank consisted of 40 µL of buffer and 180 µL of the working solution. The total enzyme control consisted of 20 µL buffer, 20 µL enzyme, and 180 µL reaction working solution. The positive control consisted of 20 µL of lovastatin, 20 µL of enzyme, and 180 µL of the reaction working solution. After mixing all the solutions, the absorbance was measured using a multimode reader at 340 nm. The mixture was then incubated at 25 °C for 20 min. After incubation, the absorbance was measured again at 340 nm, and the change in absorbance for each well was calculated. The analysis was performed in triplicate. The percentage was calculated using Eq. (2);

$$\text{Inhibition rate } (\%) = \frac{\Delta A1 - \Delta A2}{\Delta A1} \times 100\% \quad (2)$$

whereas ΔA1 is ΔA total enzyme – Δ Blank while ΔA2 is Δ sample – Δ Blank.

■ RESULTS AND DISCUSSION

Total Phenolic, Flavonoid, and Antioxidant Capacity

The total flavonoid and phenolic contents were determined using spectrophotometric analysis. The flavonoid content was estimated based on a quercetin standard curve, while the phenolic content was estimated based on a gallic acid standard curve. The measurement results showed that the phenolic content in red fruit oil was higher than the flavonoid content, as shown in Table 1. Phenolics are a heterogeneous group of secondary metabolites produced during plant metabolism. These compounds are distinguished by having at least one aromatic ring with one or more connected hydroxyl groups, and their overall structure can be either aromatic or aliphatic [17]. Flavonoids are phenolic compounds responsible for characteristics such as color, aroma, and taste. Flavonoids have been demonstrated to provide several health benefits, including inflammation relief, cancer prevention, heart protection, and diabetes management [18-20].

Table 1. Total phenolic, flavonoid, and antioxidant capacity of red fruit oil

Parameter	Mean ± SD
Total phenolic (mg GAE/g extract)	627.42 ± 61.78
Total flavonoid (mg QE/g extract)	128.06 ± 8.94
Antioxidant capacity (µmol TE/g extract)	2316.15 ± 135.63

Antioxidant analysis using the CUPRAC method aims to evaluate a sample's antioxidant properties by observing its reducing power. This method assesses the antioxidant activity in a sample by measuring the reduction of cupric (Cu^{2+}) ions to cuprous (Cu^{+}) ions. It is suitable for measuring a wide variety of antioxidants, regardless of their chemical properties or hydrophobicity [21]. The CUPRAC technique is regarded as extremely selective because of its decreased redox potential. This allows it to oxidize only genuine antioxidants, such as phenolics. Furthermore, it can accurately assess both hydrophilic and lipophilic antioxidants at physiological pH, providing more realistic results [22]. The findings from the analysis indicated that the antioxidant capacity of red fruit oil was 2316.15 µmol TE/g extract. This high antioxidant capacity is related to the high total phenolic content of red fruit oil, which was 627.42 mg GAE/g extract. The total phenolic content in red fruit oil (*P. conoideus*) was higher compared to other members of the Pandanaceae family, such as the fruit extract of *Pandanus tectorius*, which contains approximately 160 µg GAE/g of sample, and *Pandanus amaryllifolius* Roxb., which contains 24.75 mg GAE/g [23-24]. This higher phenolic content contributes to the stronger antioxidant capacity of *P. conoideus*, as phenolic compounds are known to play a key role in scavenging free radicals and enhancing overall antioxidant activity.

Bioactive Compound Profile of Red Fruit Oil

The identification of bioactive compounds in red fruit oil using LC-MS revealed 36 compounds (Table 2). The dominant class of compounds detected was fatty acyls, with 19 compounds. Fatty acids are a group of lipid molecules that consist of a hydrocarbon chain with a carboxyl group, and this class includes tens of thousands of lipid species [25]. Red fruit oil contains a high number of fatty acid compounds, as it is lipid in nature. The most abundant compounds in red fruit oil are oleic acid, oleoyl ethanolamide, and linoleyl ethanolamide, which are known to possess various health benefits [26-28]. In contrast, *P. tectorius* has been

Table 2. Bioactive compound profile of red fruit oil

Compound name	Formula	Compound class	Retention time (min)
Oleic acid	$C_{18}H_{34}O_2$	Fatty acids	22.39
Dioctyl adipate	$C_{22}H_{42}O_4$	Fatty acids	29.53
12-Hydroxystearic acid	$C_{18}H_{36}O_3$	Fatty acids	22.39
2-Hydroxybehenic acid	$C_{22}H_{44}O_3$	Fatty acids	27.18
Ricinoleic acid	$C_{18}H_{34}O_3$	Fatty acids	23.10
Furan fatty acid F6	$C_{22}H_{38}O_3$	Fatty acids	27.65
Palmitic acid	$C_{16}H_{32}O_2$	Fatty acids	27.07
(9*Z*)-Octadecenamide	$C_{18}H_{35}NO$	Fatty acids	25.53
13-Oxo-9,11-octadecadienoic acid	$C_{18}H_{30}O_3$	Fatty acids	20.62
13*S*-Hydroxyoctadecadienoic acid	$C_{18}H_{32}O_3$	Fatty acids	22.05
Juniperic acid	$C_{16}H_{32}O_3$	Fatty acids	24.15
Palmitamide	$C_{16}H_{33}NO$	Fatty acids	25.03
2,4-Dihydroxyheptadec-16-enyl acetate	$C_{19}H_{36}O_4$	Fatty acids	27.32
9-Oxo-octadeca-10,12-dienoic acid hydroxy-stearic acid	$C_{36}H_{68}O_4$	Fatty acids	27.33
Palmitelaidic acid	$C_{16}H_{30}O_2$	Fatty acids	25.05
2-Monolinolein	$C_{21}H_{38}O_4$	Fatty acids	24.13
15*S*-Hydroxyeicosatrienoic acid	$C_{20}H_{34}O_3$	Fatty acids	25.74
Mandenol	$C_{20}H_{36}O_2$	Fatty acids	27.17
(−)-Pinellic acid	$C_{18}H_{34}O_5$	Fatty acids	13.06
Anacardic acid	$C_{22}H_{36}O_3$	Benzenoids	27.04
Nafenopin	$C_{20}H_{22}O_3$	Benzenoids	25.67
2-Arachidonoylglycerol	$C_{23}H_{38}O_4$	Endoccannabinoid	27.03
Oleoyl ethanolamide	$C_{20}H_{39}NO_2$	Nitrogen compounds	24.29
Linoleyl ethanolamide	$C_{20}H_{37}NO_2$	Nitrogen compounds	22.38
Hexadecasphinganine	$C_{16}H_{35}NO_2$	Nitrogen compounds	15.75
1-Oleoyl-rac-glycerol	$C_{21}H_{40}O_4$	Glycerolipids	26.02
L-α-Palmitin	$C_{19}H_{38}O_4$	Glycerolipids	25.63
Phosphatidylcholine	$C_{44}H_{84}NO_8P$	Glycerophospholipids	27.05
Capsanthin	$C_{40}H_{56}O_3$	Prenol lipids	27.34
Farnesylacetone	$C_{18}H_{30}O$	Prenol lipids	20.86
10-Gingerol	$C_{21}H_{34}O_4$	Phenols	25.00
Oleoylglycine	$C_{20}H_{37}NO_3$	Carboxylic acids	23.58
L-(+)-Leucine	$C_6H_{13}NO_2$	Carboxylic acids	1.61
DL-Phenylalanine	$C_9H_{11}NO_2$	Carboxylic acids	2.40
6-Acetylpicropolin	$C_{24}H_{28}O_9$	Carboxylic acids	24.67
Isochamaejasmin	$C_{30}H_{22}O_{10}$	Flavonoids	1.01

reported to contain ethyl caffeate and dihydroconiferyl alcohol as major secondary metabolites, both of which have been identified as main peaks and are known to exhibit anti-inflammatory activity [29]. The 36 compounds of red fruit oil were prepared as test ligands to evaluate their inhibitory potential against HMG-CoA reductase receptors.

In Silico Study of HMG-CoA Reductase Inhibition

The HMG-CoA Reductase protein structure with code 1HW8 at 2.2 Å resolution was obtained from the RSCB Protein Data Bank for this study. HMG-CoA reductase is a tetrameric protein composed of subunits A, B, C, and D. Molecular docking was performed on the

enzyme's active site, which is located on the surface of two subunits that form dimers. The amino acid residues Glu559, Lys691, Asp769, and His866 form the catalytic site of the HMG-CoA reductase enzyme [30-31]. Before molecular docking was performed on the test ligands, the grid box size was validated at a range of 1–10 Å with an interval of 0.5 Å. The optimal grid box size was determined to be 7.5 Å, with an RMSD value of 1.96. This result is considered valid because the RMSD value was ≤ 2 Å [14]. The RMSD value is a comparison of the conformation of the redocked ligand with the actual ligand conformation, indicating the accuracy of the molecular docking method [32]. Fig. 1 shows the visualization of ligand superposition within a 7.5 Å grid box (26.5 × 26.5 × 26.5 $Å^3$) at the binding pocket on the interface of chains A and B.

The results of molecular docking performed on 36 bioactive compounds from red fruit oil showed that four compounds have the potential to be HMG-CoA reductase inhibitors, with a stronger binding energy than that of lovastatin (−7.5640 kcal/mol, see Table 3). The identified compounds included isochamaejasmin, a flavonoid compound with a binding energy of −8.3620 kcal/mol, followed by 6-acetylpicropolin, (−)-pinellic acid, and 2-monolinolein, which are fatty acids. Ligand-protein binding occurs when $\Delta G_{binding}$ is negative, indicating that the binding of the ligand to the protein is spontaneous and releases energy. The more negative the $\Delta G_{binding}$ value, the stronger and more stable the bond [33]. The Ki is the inhibitor's equilibrium constant for complexation with the receptor and is a parameter used to measure ligand-receptor binding affinity. The Ki value is inversely proportional to the $\Delta G_{binding}$; the more negative the $\Delta G_{binding}$ value, the smaller the Ki value, and the greater the binding affinity of the ligand to the receptor [34-35].

Isochamaejasmin interacts with the HMG-CoA reductase receptor, forming 21 interactions with amino acid residues, as shown in Fig. 2(a). The interactions formed include 11 van der Waals interactions, 5 hydrogen bonds, 3 hydrophobic interactions, and 2 ionic interactions. Isochamaejasmin interacts with the catalytic region of HMG-CoA reductase, creating π–anion interactions with the Glu559 residue at a distance of 6.47 Å, π–cation interactions with the Lys691 residue at a distance of 6.85 Å, and van der Waals connections with the Asp767 residue. The 6-acetylpicropolin formed 14 van der Waals interactions, 3 hydrogen bonds, 1 π-alkyl interaction, 1 alkyl interaction, and 1 π-sulfur interaction between the π-electron system on the aromatic ring of 6-acetylpicropolin and the sulfur atom on the Cys561 (Fig. 2(b)). The 6-acetylpicropolin also forms two

Table 3. Molecular docking results of test ligands and reference ligands

Compound	$\Delta G_{binding}$ (kcal/mol)	Ki (μM)
Isochamaejasmin	−8.362	0.66
6-Acetylpicropolin	−7.966	1.30
(−)-Pinellic acid	−7.698	2.25
2-Monolinolein	−7.697	2.26
Lovastatin (positive control)	−7.564	2.99
HMG-KoA (substrate)	−7.366	4.00

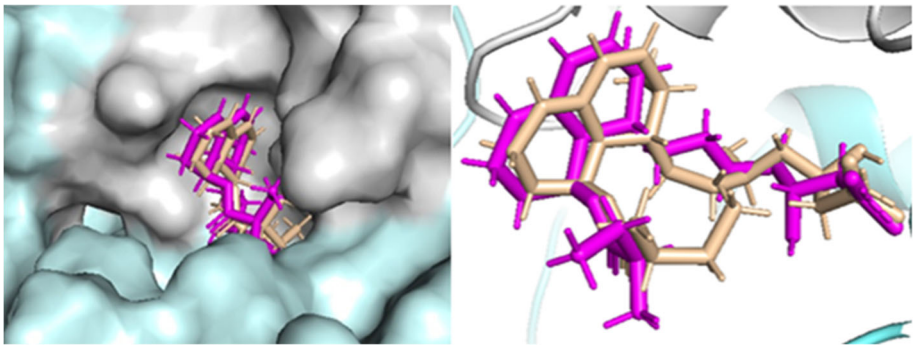

Fig 1. Superposition visualization of the native ligand (magenta) and redocked ligand (wheat) in the binding pocket at the dimer interface of chain A (cyan) and chain B (gray)

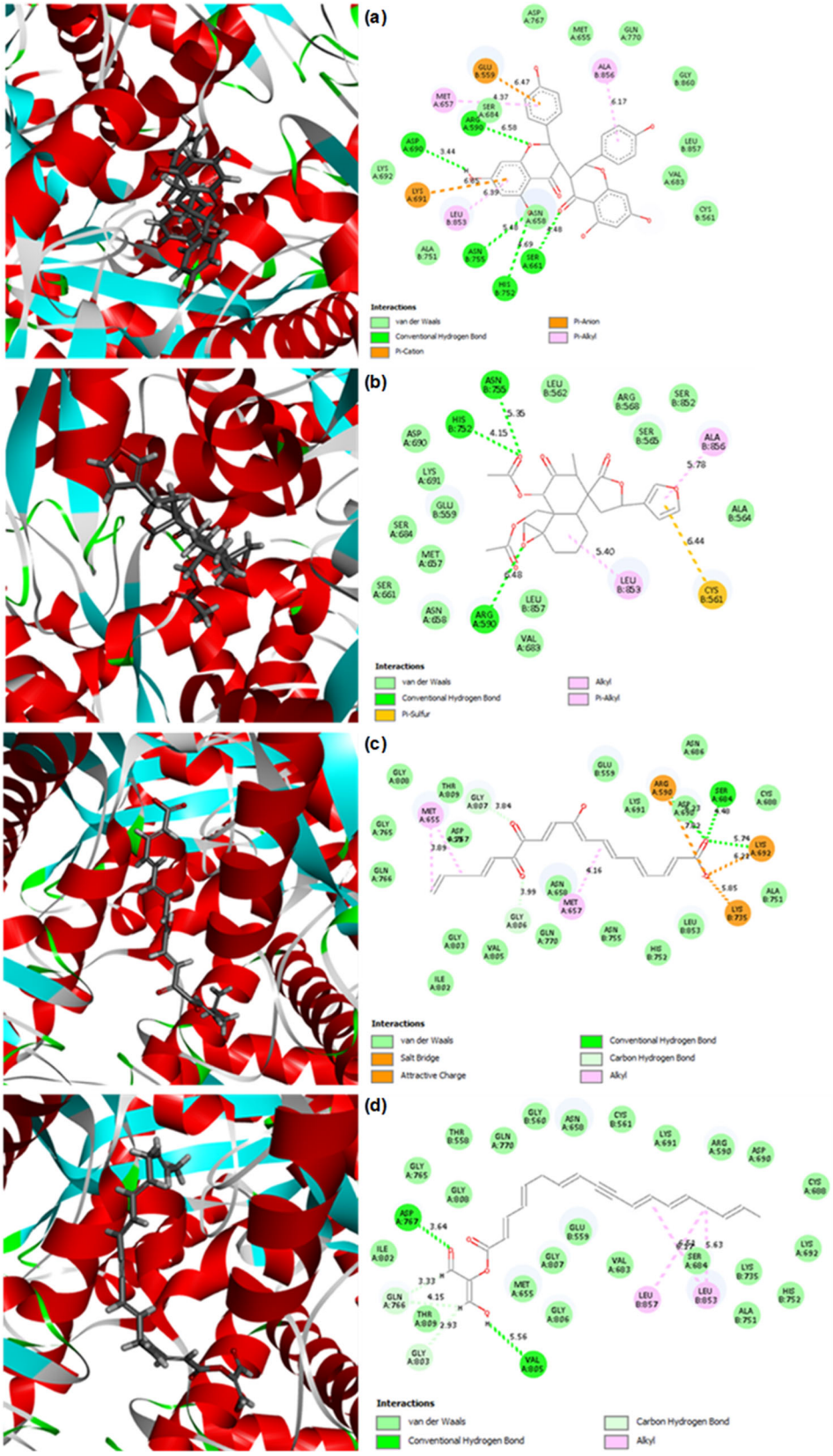

Fig 2. 3D and 2D visualization of the interaction of (a) isochamaejasmin, (b) 6-acetylpicropolin, (c) (–)-pinellic acid, and (d) 2-monolinolein with the HMG-CoA reductase receptor

van der Waals interactions with the enzyme's catalytic site at the Glu559 and Lys691 residues. The (−)-pinellic acid (Fig. 2(c)) forms 19 van der Waals interactions, 1 hydrogen bonds, 2 carbon-hydrogen bonds, 2 hydrophobic interactions, and 2 salt bridges. The interactions formed with the enzyme's catalytic site were van der Waals interactions with Glu559, Lys691, and Asp767. The 2-monolinolein (Fig. 2(d)) forms 23 van der Waals interactions, 2 hydrogen bonds, 2 carbon-hydrogen bonds, and 2 hydrophobic interactions. The 2-monolinolein formed a hydrogen bond with the catalytic site of the HMG-CoA reductase receptor at the Asp767 residue with a distance of 3.64 Å and van der Waals interactions with the Glu559 and Lys691 residues.

Several factors influence the strength and durability of ligand-receptor complexes, including bond type, specific interactions, and binding area. 2D visualization of molecular docking results aims to identify the interactions that occur between the ligand and receptor, such as hydrogen bonds, hydrophobic interactions, and van der Waals interactions. A hydrogen bond is an interaction between a hydrogen atom bonded to an electronegative donor atom and an acceptor's lone pair of electrons. Hydrogen bonds contribute significantly to ligand-receptor binding [36-37]. This description is supported by the molecular docking data acquired in this study, which showed that isochamaejasmin, which exhibited the strongest binding, formed five hydrogen bonds with the HMG-CoA reductase.

Hydrophobic interactions occur because of the driving force for nonpolar groups to cluster within the protein structure, minimizing contact between nonpolar residues and water molecules. The hydrophobic interactions formed between the ligand and receptor in this study are pi-alkyl and alkyl interactions. These interactions can also increase the stability of ligand binding to the receptor [38]. In addition to hydrogen bonds and hydrophobic interactions, the molecular docking results also showed the presence of a salt bridge interaction formed by the compound (−)-pinellic acid. A salt bridge is a non-covalent connection that includes two interactions, i.e., electrostatic attraction between chemical groups or atoms with opposite charges and hydrogen bonding. Thus, its binding strength exceeds that of hydrogen bonds alone [39]. Salt bridges are typically found at positively charged basic amino acid residues, such as Lys or Arg, or negatively charged amino acids, such as Glu and Asp [40]. The 2D visualization results showed that (−)-pinellic acid formed a salt bridge with Lys692. A salt bridge can stabilize the ligand-protein bond by acting as a molecular clip, thereby ensuring that the ligand can bind strongly to the receptor [41].

Bioavailability and Toxicity Prediction of Compounds

The inhibitory potential of a compound can be influenced by its stability. Lipinski's Rule of Five predicts whether a compound has good oral bioavailability, which is its ability to be efficiently absorbed from the intestine into the bloodstream. A molecule is deemed well-absorbed if it has a molecular mass of less than 500 Da, less than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, a log P value of less than 5, and a molar refractivity of 40–130 [42]. The molecular weight reflects a compound's ability to penetrate membranes; the heavier the molecular mass of a compound, the more difficult it is for the compound to pass through the cell membrane. The log P value is related to a compound's hydrophobic properties; a high log P value indicates that a compound is hydrophobic, which can potentially increase toxicity because the compound remains on the cell membrane for a longer period. Furthermore, the number of hydrogen bond donors and acceptors is directly proportional to the energy required during the absorption process [43]. Based on the results of the bioavailability prediction for the test ligands (Table 4), one compound violated more than one of Lipinski's rules: isochamaejasmin. With a molecular weight of 542.496 Da (> 500 Da), 6 hydrogen bond donors (> 5), and a molar refractivity value of 141 (> 130), this compound is considered to have poor bioavailability. Another compound that violated Lipinski's rule was 2-monolinolein, with a molar refractivity value of 25.82 (< 40). Nevertheless, this compound is still classified as having good bioavailability because it only violates one of Lipinski's rules.

Table 4. Bioavailability and toxicity prediction of compounds with the strongest binding

Parameter	Compounds			
	Isochamaejasmin	6-Acetylpicropolin	(−)-Pinellic acid	2-Monolinolein
	Bioavailability			
Molecular mass	542.49	460.47	330.46	354.52
H-bond donor	6	0	4	2
H-bond acceptor	10	9	5	4
Log P	4.48	2.52	3.02	4.70
Molar refractivity	141	111.21	93.42	105.72
	ADMET prediction			
Human intestinal absorption	Low	High	High	High
BBB permeant	−	−	−	+
CYP1A2 inhibitor	−	−	−	−
CYP2C19 inhibitor	−	−	−	−
CYP2C9 inhibitor	+	−	−	−
CYP2D6 inhibitor	−	−	+	−
CYP3A4 inhibitor	+	+	−	−
Hepatotoxicity (probability)	−0.76	−0.89	−0.74	−0.91
Neurotoxicity (probability)	−0.86	−0.85	−0.97	−0.96
Carcinogenicity (probability)	−0.69	−0.51	−0.55	−0.59
Immunotoxicity (probability)	−0.98	0.83	−0.99	−0.90
Mutagenicity (probability)	−0.71	−0.72	−0.95	−0.80
Cytotoxicity (probability)	−0.98	−0.66	−0.58	−0.84

Forecasting a compound's absorption, distribution, metabolism, and toxicity (ADMET) parameters provides information about a compound's properties and is an important step in the quality control of compounds with the potential to be used as drugs. Based on the ADMET prediction results for the test ligands presented in Table 4, three of the four test compounds, 6-acetylpicropolin, (−)-pinellic acid, and 2-monolinolein were found to have a high level of intestinal absorption. In contrast, isochamaejasmin exhibited low absorption. This is influenced by its molecular weight, which is 542.496 Da (> 500 Da), as an increase in molecular weight leads to a decrease in compound permeability. In addition to its molecular weight, isochamaejasmin has a high number of hydrogen bond donors (> 5), and compounds with many hydrogen bonds tend to be more soluble in water, with an excessive number also reducing the permeability of the compound.

It is critical to comprehend how different substances interact inside the cytochrome P450 (CYP) enzyme system, as these interactions determine how a compound is metabolized and eliminated from the body. If a compound can inhibit this enzyme, the elimination process may be disrupted, leading to toxicity [16,44]. The prediction results indicated that isochamaejasmin has potential inhibitory activity against CYP2C9 and CYP3A4, 6-acetylpicropilin shows potential as a CYP3A4 inhibitor, and (−)-pinellic acid is predicted to inhibit CYP2D6. In contrast, 2-monolinolein can be readily metabolized in the liver and removed from the body because they do not block any of the five P450 isoforms. The toxicity prediction results showed that isochamaejasmin, 6-acetylpicropolin, (−)-pinellic acid, and 2-monolinolein were not hepatotoxic, neurotoxic, carcinogenic, mutagenic, or cytotoxic. Toxicity is an undesirable effect of a compound or chemical and is influenced by the dose, frequency, and duration of exposure [45].

In Vitro Study of HMG-CoA Reductase Inhibition

The *in vitro* study aimed to assess the inhibitory efficacy of red fruit oil against HMG-CoA reductase.

HMG-CoA reductase is an enzyme that catalyzes the reduction of HMG-CoA to mevalonate, which contributes to cholesterol production. Therefore, inhibiting its activity is a therapeutic target for reducing blood cholesterol levels [46]. Lovastatin, used as a comparative ligand, is a statin drug commonly used to treat cardiovascular diseases. This drug works by inhibiting HMG-CoA reductase, which can significantly reduce LDL-C and triglyceride levels and increase HDL levels in patients [5]. *In vitro* analysis showed that lovastatin inhibited HMG-CoA reductase with an inhibitory activity of 50.82% (Table 5). Lovastatin competitively inhibits HMG-CoA reductase by binding to the active site where its substrate (HMG-CoA) reacts with the enzyme, thereby inhibiting the conversion to mevalonate and limiting cholesterol synthesis [47-48].

Based on the analysis results, red fruit oil was also found to be able to inhibit the HMG-CoA reductase enzyme with an inhibitory activity of 48.36%. Statistically, there was no significant difference in inhibitory activity between lovastatin and red fruit oil ($p > 0.005$). Meanwhile, a previous study on *P. tectorius* fruit reported a higher inhibitory activity of 65.63% [49]. These findings suggest that while *P. tectorius* exhibited stronger enzyme inhibition, *P. conoideus* remains superior in terms of total phenolic content, which contributes significantly to its antioxidant capacity. The higher phenolic content in *P. conoideus* oil enhances its ability to neutralize free radicals and may provide additional cardioprotective benefits beyond enzyme inhibition. This indicates that, although *P. tectorius* shows stronger direct inhibition of HMG-CoA reductase, *P. conoideus* offers a broader spectrum of bioactivity due to its richer composition of phenolic compounds with dual roles as antioxidants and lipid metabolism modulators. Red fruit oil can stimulate eNOS phosphorylation and increase NO production in endothelial cells, which leads to vasodilation. This is important in conditions of dyslipidemia, as it can help improve the endothelial dysfunction that frequently occurs in this condition. Additionally, red fruit oil is also able to reduce oxidative stress and decrease oxidative DNA damage caused by genotoxins [50]. Red fruit oil contains various bioactive components that play a role in inhibiting the HMG-CoA reductase enzyme, one of which is the flavonoid class of compounds. The *in silico* study previously conducted in this research showed that the compound with the most negative binding energy was isochamaejasmin, a flavonoid compound. Isochamaejasmin was able to form ionic interactions with the enzyme's catalytic site and also formed 5 hydrogen bonds, which contributed most significantly to the ligand-receptor binding. This gives it the potential to be an HMG-CoA reductase enzyme inhibitor that can competitively bind with HMG-CoA.

Table 5. HMG-CoA reductase enzyme inhibition of red fruit oil

Sample	%Inhibition	*p*-Value
Lovastatin	50.82 ± 2.46	0.288
Red fruit oil	48.36 ± 2.46	

Based on the molecular docking results, other compounds with a better binding affinity than lovastatin are (−)-pinellic acid and 2-monolinolein, both of which are fatty acyl compounds. The 2-monolinolein is a monoglyceride in which the linolenoyl group forms the 2-acyl group. Functionally, this compound is related to linoleic acid, a common omega-6 fatty acid found in plant-based oils. Pinellic acid is a hydroxyoctadecanoic acid with hydroxyl groups at the C-9, C-12, and C-13 positions, as well as an *E* (cis) double bond at position 10. This compound functions as an adjuvant and an anti-inflammatory agent. Results showed that pinellic acid provided significant anti-inflammatory activity by inhibiting prostaglandin D2 production with an IC_{50} of 40.8 μM [44]. By inhibiting prostaglandin D2 production, pinellic acid directly suppresses the inflammatory pathway that can be caused by dyslipidemia, thereby potentially helping to minimize the risk of atherosclerosis and cardiovascular disease.

■ CONCLUSION

Red fruit oil has the potential to be an anti-dyslipidemia agent because its bioactive components can competitively inhibit cholesterol synthesis. The oil contains a total phenolic content of 627.42 mg GAE/g, flavonoids of 128.06 mg QE/g, and an antioxidant capacity of 2316.15 μmol TE/g. Based on LC-MS

identification results, a total of 36 bioactive components were found in red fruit oil, the majority of which were from the fatty acyls class, with compounds from the flavonoid and phenolic classes also being present. The results of molecular docking performed on the 36 compounds against the HMG-CoA reductase receptor showed that four candidate compounds had a more negative binding affinity than the HMG-CoA substrate, namely isochamaejasmin, 6-acetylpicropolin, (−)-pinellic acid, and 2-monolinolein. Through the *in vitro* assay, red fruit oil showed an inhibitory activity of 48.36%, and the positive control, lovastatin, showed 50.82%, which indicates no significant difference. The findings of this study show that red fruit oil is a potential HMG-CoA reductase inhibitor, making it a promising functional food for addressing problems associated with dyslipidemia and cardiovascular diseases.

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■ CONFLICT OF INTEREST

The authors state that there is no conflict of interest regarding the publication of this manuscript.

■ AUTHOR CONTRIBUTIONS

Ribka Tande conducted the experiment, analyzed the data and wrote the manuscript. Rimbawan, Eny Palupi and Rini Kurniasih did supervision, conceptualization of this work, wrote and revised the manuscript. Nur Haerati conducted the experiment. All authors agreed to the final version of this manuscript.

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