In-Silico Screening of HMG-CoA Reductase Inhibition Potential from *Anredera cordifolia* (Ten.) Steenis and *Elephantopus scaber* Linn.

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ABSTRACT

Background. Hypercholesterolemia is one of the most important risk factors in causing coronary heart disease. Hypercholesterolemia occurs because cholesterol synthesis in the body increases. The key enzyme of the cholesterol synthesis is hydroxymethylglutaryl-CoA (HMG-CoA) reductase. Drugs that inhibit HMG-CoA reductase activity such as statins are effective in inhibiting cholesterol synthesis. The problem arises because these drugs have many side effects. The use of natural ingredients as traditional medicine has been practiced by communities for generations. This has led to massive exploration and scientific studies on the biological activities of these medicinal plants.

Objective. Using an in-silico method, this study aimed to explore the pharmacokinetic and toxicity predictions, as well as the HMG-CoA reductase inhibitor activity of "Binahong" (*Anredera cordifolia* [Ten.] Steenis.) and elephant's foot (*Elephantopus scaber* Linn.).

Methods. To collect samples, the Kanaya Knapsack database, USDA Dr Duke Phytochemical, PubChem, and Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) were used. To predict the activity of the active compounds, Pass Online software was used. To complete the drug-likeness analysis, the Lipinski rule of five and the Swiss Absorption, Distribution, Metabolism and Excretion (ADME) were employed. Protox II was used to predict the toxicity of the active compounds. Next, with PyRx v.0.9.8 software, molecular docking is utilized to do molecular screening. BioVia Discovery Studio 2019 was employed for data visualization.

Results. A number of the bioactive compounds of *Anredera cordifolia* and *Elephantopus scaber* had pa values >0.3 which indicate predicted activity as antihypercholesterolemic. The results of the pharmacokinetic analysis showed similar properties to drugs, allowing them to be absorbed well in the intestines and have no penetration into the blood-brain barrier. Toxicity prediction of the bioactive compounds was in the non-toxic category, although caution is required. The molecular docking results showed that three active compounds from *Anredera cordifolia* namely Ursolic acid, Calenduloside E, and Larreagenin A had a more negative binding energy compared to atorvastatin. Likewise, the active compounds from the *Elephantopus scaber* that had more negative binding energy than atorvastatin are Epifriedelanol, Stigmasterol glucoside, and Lupeol. However, the bioactive compounds of Larreagenin A and Lupeol do not have amino acid residues similar to the control on the active site of binding to the HMG-CoA reductase.

Conclusion. Both *Anredera cordifolia* and *Elephantopus scaber* plants showed potential as antihypercholesterolemic drugs through inhibition of HMG-CoA reductase activity, showed drug-likeness, and were able to be absorbed well in the intestines and had no penetration into the blood-brain barrier. Further studies are needed both in vitro and in vivo to examine the therapeutic effects of these two plants.

Keywords: HMG-CoA reductase inhibitor, in-silico, Anredera cordifolia, Elephantopus scaber

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INTRODUCTION

Coronary heart disease is the highest cause of death worldwide, and hypercholesterolemia is the third biggest risk factor in causing coronary heart disease.[1]

Hypercholesterolemia is a condition where there is an increase in cholesterol levels in the blood serum.[2,3] This can occur through increased cholesterol synthesis in hepatic cells. Cholesterol synthesis in cells is determined by the activity of a key enzyme, hydroxymethylglutaryl-CoA (HMG-CoA) reductase. This enzyme plays a role in converting acetyl CoA to mevalonate, the most important step in the de novo synthesis of cholesterol.[4]

Until now, drugs that are effective in lowering blood cholesterol are statins.[5] Statins (i.e., simvastatin, atorvastatin, fluvastatin) work by inhibiting the activity of the HMG-CoA reductase enzyme.[6,7] However, statins have several side effects including impaired liver function, myalgia, myopathy, and new-onset diabetes.[7,8] Therefore, efforts are needed to find new drugs that are effective with minimal side effects. The use of natural ingredients as traditional medicine has been going on for a long time and is hereditary. Based on WHO reports, 170 member countries report that the population in their countries has used traditional medicine in their daily lives.[9] In line with that, the exploration of natural materials as a source of new medicinal materials has developed very rapidly in recent years.[10-12]

Anredera cordifolia [Ten.] Steenis. *and Elephantopus scaber* Linn. are two plants that have been widely used as traditional medicines in tropical regions such as Indonesia. *Anredera cordifolia* [Ten.] Steenis. belongs to the Basellaceae family, originating from the South American region encompassing Paraguay, southern Brazil, Uruguay, and northern Argentina.[13,14] This plant is commonly known as "Binahong" in Indonesia, "Madeira vine" in South America, and "Dhen San Chi" in China. Common uses include the management of skin diseases, high blood pressure, swelling, and gout arthritis.[15] *Anredera cordifolia* leaves contain various secondary metabolites such as triterpenoids, steroids, saponins, alkaloids, flavonoids, polyphenols, quinones, monoterpenoids, sesquiterpenoids, coumarins, and polysaccharides.[16] This plant contains active compounds including phytol, α-pinene, and 6,10,14-trimethyl-2-pentadecanone.[17] *Elephantopus scaber* Linn. belongs to the Asteraceae family. This plant is commonly referred to as elephant's foot. The local name for *Elephantopus scaber* Linn. is “Tapak Liman.” This tropical plant is distributed across Europe, Asia, Australia, and Africa.[18,19] The air-dried powdered seeds' organic solvent extract, specifically acetone, contains terpenoids, flavonoids, steroids, glycosides, alkaloid, quinones, and phenols.[18] Numerous assertions suggest that these two plants have beneficial health properties, particularly as anti-cholesterol agents.[15,20,21] The aim of this study was to explore the pharmacokinetics and toxicity prediction and to test the HMG-CoA reductase inhibitory activity through molecular docking of bioactive compounds from *Anredera cordifolia* [Ten.] Steenis. and *Elephantopus scaber* Linn.

MATERIALS AND METHODS

Protein Target Preparation

The HMG-CoA reductase (HMGCR) protein's three-dimensional structure [PDB ID 1HW9] was obtained from a Protein Data Bank (www.rcsb.org) in PDB format. Proteins were pre-processed by removing water molecules, adding hydrogen atoms, and executing further operations using Biovia Discovery Studio Visualizer software.

Ligand Preparation

Ligand preparation is the preparation of 3-dimensional structures of active compounds from the natural plants used, namely *Anredera cordifolia* (Ten.) Steenis and *Elephantopus scaber* Linn., which were downloaded from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/).

The active substances structure of *Anredera cordifolia* (Ten.) Steenis and *Elephantopus scaber* Linn. were screened from published articles. In addition, a search for the active compounds from each plant was conducted using the Kanaya Knapsack database (http://knapsackfamily.com/KNApSAcK/) and USDA Dr Duke Phytochemical (https://phytochem.nal.usda.goc/). In the next step, the three-dimensional structure was downloaded from PubChem in SDF format. For the active compound ursolic acid used with Compound ID number (CID) 64945, Larreagenin A (CID: 14888779), Calenduloside E (CID: 176079), Epifridelanol (CID: 119242), Dotriacontanol (CID: 96117), 1-Triacontanol (CID: 68972), Vernoflexuoside (CID: 442320), Stigmasterol glucoside (CID: 6602508), Crepiside E (CID: 9845240), Lupeol (CID: 259846) and Stigmasterol (CID: 5280794).

Active Compound Prediction

Using the Pa (Probablility ‘to be active’), the active chemicals of *Anredera cordifolia* and *Elephantophus scaber* plants were predicted for their activity from Pass Online (http://way2drug.com/passonline/).[22] This server calculates a compound’s expected activity spectrum as probable inactivity (Pi) and probable activity (Pa). The PASS predicts this spectrum based on an investigation of the structure-activity connection of the training set, which includes over 205,000 compounds displaying over 3,750 different types of biological activities. The Pa and Pi values for probability range from 0.000 to 1.000. The predictions made by PASS were understood and applied with flexibility:

1. For a given molecule, only actions with Pa > Pi are deemed feasible.
2. There is an experimentally high possibility of finding activity if Pa >0.7.

3. The likelihood of finding activity is experimentally low if Pa is greater than 0.5 but less than 0.7, but the chemical is most likely distinct from well-known pharmacological drugs.
4. If Pa <0.5, there is little probability of finding activity in an experiment, but the chance to find a structurally new compound is greater.

Pharmacokinetic Prediction with ADME

The absorption, distribution, metabolism, and excretion (ADME) characteristics of active substances from *Anredera cordifolia* (Ten.) Steenis and *Elephantopus scaber* Linn. were tested via Swiss ADME online (https://www.swiss.ch). The active substances were predicted to be orally active or could be absorbed if they met at least two of Lipinski's rules: the molecular weight (MW) ≤ 500; the octanol/water partition coefficient (cLogP) ≤ 5; the number of donor hydrogen bonds (HBDs) ≤ 5; the number of hydrogen bond acceptors (HBAs) ≤ 10.6; and the topological polar surface area (TPSA) in the range of 20–130. Based on the analysis of these characteristics, the Swiss ADME software concluded the drug-likeness of each active substance.[23,24]

Pharmacokinetic Prediction with the Brain Or IntestinaL EstimateD (BOILED-Egg) model

Pharmacokinetic behaviors were also tested with the BOILED-Egg model, specifically gastrointestinal passive absorption (white region) and the permeability of the blood–brain barrier (yellow region). This approach also predicted descriptively whether the active substance of *Anredera cordifolia* (Ten.) Steenis and *Elephantopus scaber* Linn. were substrates of P-glycoprotein (PGP)-efflux transporter. Active substances that were identified as PGP-efflux transporter substrates might inhibit gastrointestinal absorption and/or unable to cross the blood-brain barrier.[25,26]

Toxicity Prediction

The toxicity of *Anredera cordifolia* (Ten.) Steenis and *Elephantopus scaber* Linn. active substances were tested using ProTox-II in silico (https://tox-new.charite.de/protox). The type of toxicity testing that was carried out include toxicity to the liver, toxicity to the immune system, as well as its ability to act as a mutagen and carcinogen. The test results were expressed as active or inactive. Acute toxicity prediction for oral administration within 24 hours was presented as lethal dose-50 or LD50 (mg/kg body weight (mg/kg bw)). LD50 was used for further analysis of toxicity classes, which range from I to VI (sequentially: I. fatal with LD50 less than 5 mg/kg bw, II. fatal with LD50 5 up to 50 mg/kg bw, III. Toxic with 50 < LD50 ≤ 300 mg/kg bw, IV. harmful with 300 < LD50 ≤ 2000 mg/kg bw, V. maybe harmful with 2000 < LD50 ≤ 5000 mg/kg bw, and VI. Nontoxic with > 5000 mg/kg bw). The toxicity predictions were compared with HMG-CoA reductase drugs: simvastatin, atorvastatin, and fluvastatin.[27]

Molecular Docking

The 3D structure of the target protein was obtained from the RCSB PDB database (https://www.rcsb.org/), namely HMG-CoA reductase (PDB code 1HW9). The 3D structures of each active plant compound and control were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Furthermore, the protein was pretreated by removing water molecules in Discovery Studio 2019 software (https://discover.3ds.com/discovery-studio-visualizer-download), while the ligand was energy minimized using Pyrx v.0.9.8 software (https://sourceforge.net/projects/pyrx/). Docking was performed using Autodock Vina integrated in Pyrx v.0.9.8. Docking was performed with a targeted docking method. The grid box size was adjusted to the position of amino acid residues based on the literature. The docking results were obtained in the form of binding affinity or affinity energy resulting from the interaction of compounds with proteins. Furthermore, the interaction between the compound and protein docking results was visualized using BioVia Discovery Studio 2019 software.[28-30]

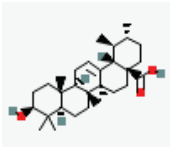
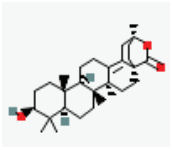
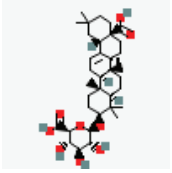
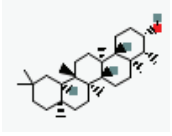
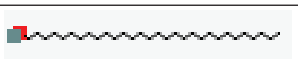
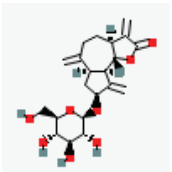
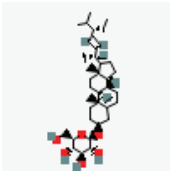
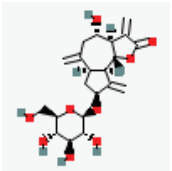
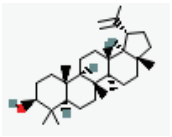
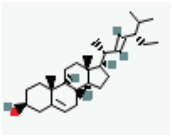
RESULTS

The results of active compound prediction were shown in Table 1. Prediction to be active (Pa) values > 0.3 were

Table 1. Pass Online is Used to Predict the Active Compounds from *Anredera cordifolia* and *Elephantophus scaber* that have Antihypercholesterolemia Properties

Plant	Active Compounds	Pa	Activity
A. cordifolia	Ursolic acid	0.591	Cholesterol Antagonist
	Larreagenin A	0.357 0.454	Cholesterol synthesis inhibitor Cholesterol antagonist
	Calenduloside E	0.645 0.719	Antihypercholesterolemic Cholesterol antagonist
E. scaber	Epifriedelanol	0.390 0.470 0.547	Antihypercholesterolemic Cholesterol synthesis inhibitor Cholesterol antagonist
	Dotriacontanol	0.335 0.452 0.654	Cholesterol synthesis inhibitor Antihypercholesterolemic Cholesterol antagonist
	1-Triacontanol	0.335 0.452 0.654	Cholesterol synthesis inhibitor Antihypercholesterolemic Cholesterol antagonist
	Vernoflexuoside	0.603	Cholesterol antagonist
	Stigmasterol glucoside	0.554 0.985 0.990	Cholesterol synthesis inhibitor Cholesterol antagonist Antihypercholesterolemic
	Crepiside E	0.617	Cholesterol antagonist
	Lupeol	0.440 0.514	Cholesterol synthesis inhibitor Cholesterol antagonist
	Stigmasterol	0.670 0.965 0.970	Cholesterol synthesis inhibitor Cholesterol antagonist Antihypercholesterolemic

Table 2. The Molecule Structure of the Active Compounds

Plant	Compound/Ligand	Molecule structure
A. cordifolia	Ursolic acid	
	Larreagenin A	
	Calenduloside E	
E. scaber	Epifriedelanol	
	Dotriacontanol	
	1-Triacontanol	
	Vernoflexuoside	
	Stigmasterol glucoside	
	Crepiside E	
	Lupeol	
	Stigmasterol	

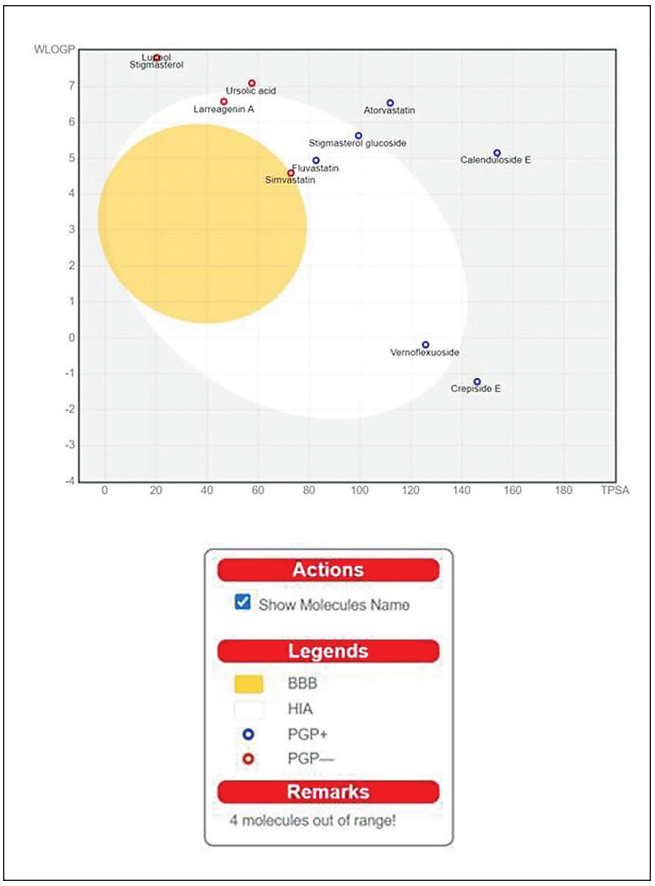


Figure 1. Predicted BOILED-Egg model of active compounds from *A. cordifolia*, *E. scaber*, and standard drugs, to evaluate two pharmacokinetic behaviors, specifically gastrointestinal passive absorption *(white region)* and the permeability of the blood–brain barrier *(yellow region/yolk)*.

observed for bioactive compounds of both plants, *Anredera cordifolia* and *Elephantopus scaber,* which showed as anti-hypercholesterol activity. Pa values calculate the likelihood that the examined compound is a member of the subclass of active compounds (molecular structures like those of the studied compound).

The chemical structure of the active compounds obtained from PubChem is shown in Table 2.

The pharmacokinetic (ADME) profile of the bioactive compounds is shown in Table 3 compared with the positive control such as simvastatin, atorvastin, and fluvastatin which represents the standard drug profile.

The Egan's BOILED-Egg permeation predictive model diagram demonstrates that some active chemicals from *Anredera cordifolia* and *Elephantopus scaber* such as Larreagenin A, Ursolic acid, Stigmasterol glucoside, and Vernoflexuoside have a high potential to be well-absorbed but not penetrate into the brain (Figure 1).

Figure 1 shows that Larreagenin A, Ursolic acid, Stigmasterol glucoside, and Vernoflexuoside are predicted as well-absorbed but not penetrate the brain; Lupeol, Stigmasterol, Calenduloside E, and Crpiside E are predicted as not absorbed and not brain penetrant; and some bioactive compounds as not absorbed and not brain penetrant because they are outside of the range of area.

Prediction of the toxicity of active chemicals based on a number of parameters, including hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity are shown in Table 4.

Molecular docking result analysis of binding interactions of the ligand with HMG-CoA reductase docked against PDB 1HW9 is shown in Table 5.

Figure 2 shows an example of the results of visualization of interactions between amino acid residues and several active compounds and their protein targets compared to the control (simvastatin), using molecular docking.

DISCUSSION

The aim of this research is to investigate the pharmacokinetic and toxicity predictions and to test the HMG-CoA reductase inhibitory activity through molecular docking of bioactive compounds from *Anredera cordifolia* (Ten.) Steenis. and *Elephantopus scaber* Linn. Based on analysis using Pass Online, three active compounds of *Anredera cordifolia* are predicted to have activity as anti-hypercholesterolemia, namely ursolic acid, Larreagenin A, and Calenduloside E.

Table 3. Physicochemical ADME Analysis of Ligands Compared with HMG-CoA Reductase Inhibitor Drugs

Ligands	MW	ilogP	ClogP	HBA	HBD	TPSA	N violations	Drug likeness
Simvastatin	418.57	3.84	4.13	5	1	72.83	0	Yes
Atorvastatin	558.64	3.81	4.99	6	4	111.79	1	Yes
Fluvastatin	411.47	2.89	3.76	5	3	82.69	0	Yes
Ursolic acid	456.70	3.71	5.88	3	2	57.53	1	Yes
Calenduloside E	632.82	3.11	4.18	9	5	153.75	1	Yes
Larreagenin A	440.66	4.10	5.74	3	1	46.53	1	Yes
Epifriedelanol	428.73	4.67	7.40	1	1	20.23	1	Yes
Dotriacontanol	466.87	8.10	11.23	1	1	20.23	1	Yes
1-Triacontanol	438.81	7.67	10.52	1	1	20.23	1	Yes
Vernoflexuoside	408.44	2.04	0.42	8	4	125.68	0	Yes
Stigmasterol glucoside	574.83	4.23	5.10	6	4	99.38	1	Yes
Crepiside E	424.44	2.06	-0.31	9	5	145.91	0	Yes
Lupeol	426.72	4.68	7.26	1	1	20.23	1	Yes
Stigmasterol	412.69	5.01	6.97	1	1	20.23	1	Yes

Table 4. Toxicity Prediction by ProTox-II Server

Ligand	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	Predicted LD50 (mg/kg)	Predicted Toxicity class
Ursolic acid	Active	Active	Active	Inactive	Inactive	2000	5
Calenduloside E	Inactive	Inactive	Active	Inactive	Inactive	1750	4
Larreagenin A	Inactive	Active	Inactive	Inactive	Inactive	5000	5
Epifriedelanol	Inactive	Inactive	Inactive	Inactive	Inactive	940	4
Dotriacontanol	Inactive	Inactive	Inactive	Inactive	Inactive	1000	4
1-Triacontanol	Inactive	Inactive	Inactive	Inactive	Inactive	1000	4
Vernoflexuoside	Inactive	Inactive	Active	Inactive	Inactive	2000	5
Stigmasterol glucoside	Inactive	Inactive	Active	Inactive	Inactive	8000	6
Crepiside E	Inactive	Inactive	Active	Inactive	Inactive	590	4
Lupeol	Inactive	Inactive	Active	Inactive	Inactive	2000	5
Stigmasterol	Inactive	Inactive	Active	Inactive	Inactive	890	4
Simvastatin	Inactive	Active	Active	Inactive	Inactive	1000	4
Atorvastatin	Active	Inactive	Inactive	Inactive	Inactive	5000	5
Fluvastatin	Active	Inactive	Inactive	Inactive	Inactive	416	4

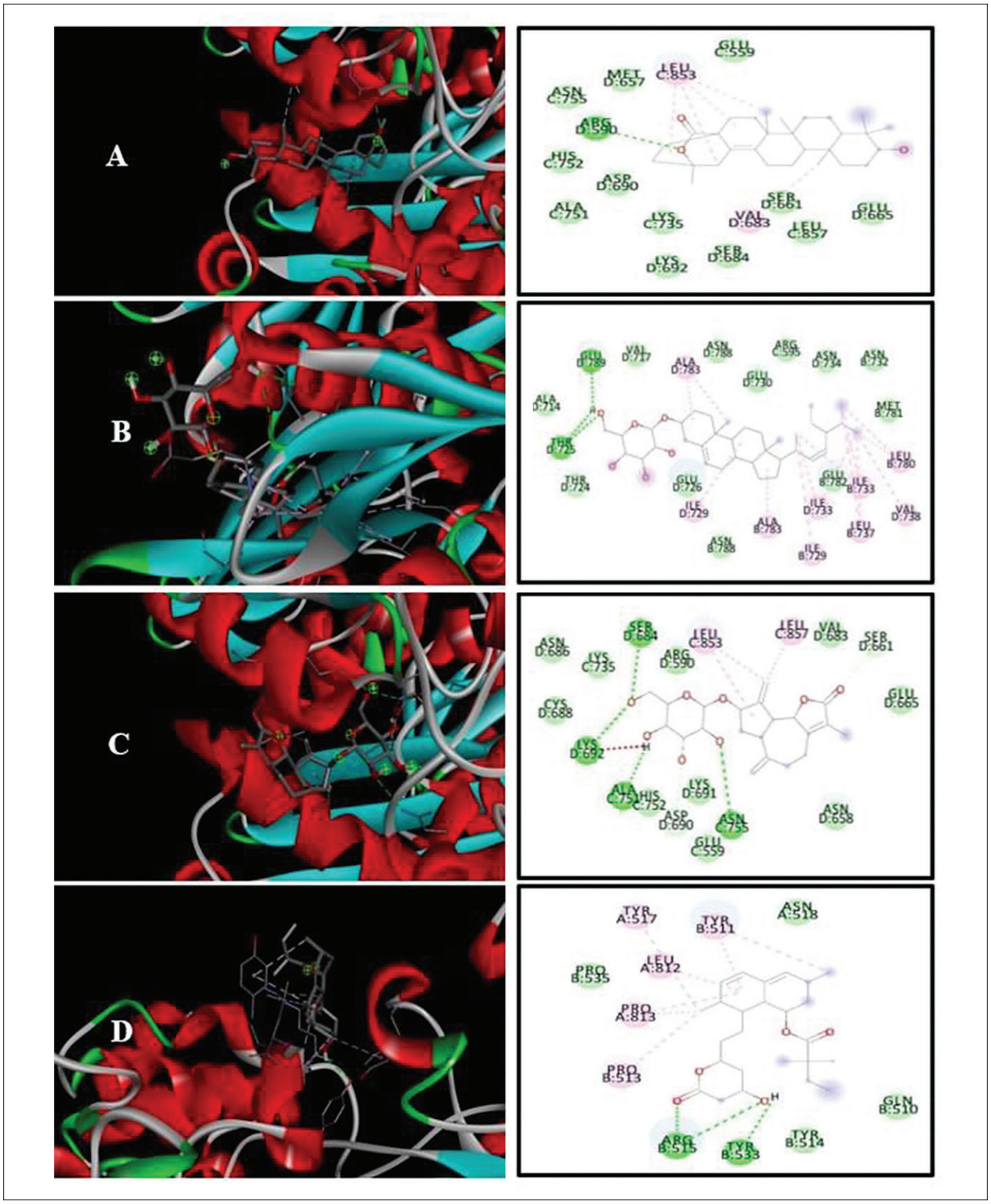


Figure 2. ***Molecular interactions using docking analysis.*** **(A)** HMG-CoA reductase interaction with Larreagenin A. **(B)** HMG-CoA reductase interaction with Stigmasterol glucoside.; **(C)** HMG-CoA reductase interaction with Vernoflexuoside. **(D)** HMG-CoA reductase interaction with simvastatin.

Table 5. Molecular Interaction of Ligands against HMG-CoA Reductase, Statin Class Drugs were Used as Controls

Plant	Ligand	Binding Energy	Interacting residues with protein target
Control	Simvastatin	-7.4	**Tyr517**, **Tyr511**, **Leu812**, Pro813, **Pro513**, Arg515, **Tyr533**
	Atorvastatin	-8.0	Glu610, Thr636, Lys606, **His635**, Ile699, Ser637, Gln632, **Ala585**, Asp586, Arg650, Ile638, Ser637
	Fluvastatin	-7.4	Ile729, Glu726, **Ala783**, Asn788, Asn788, Glu530, Glu782, Arg641, **Ala783**, **Ile729**, **Ile733**
A. cordifolia	Ursolic acid	-8.7	Phe615, **His635**, Lys633, **Ala585**
	Calenduloside E	-8.1	**Gln632**, Lys633, Asp586, **Gln632**, Gln648, Glu700, **His635**
	Larreagenin A	-8.4	Arg590, Leu853, Val683
E. scaber	Epifriedelanol	-8.2	**Ala585**, Lys633, Leu634, Phe615
	Dotriacontanol	-4.1	**Pro513**, **Tyr533**, Asp516, Arg515
	1-Triacontanol	-4.1	Gln510
	Vernoflexuoside	-7.6	Ser694, Lys692, Ala751, Asp690, Asn755, Leu853, Leu857, Ser661
	Stigmasterol glucoside	-8.8	Thr723, Glu789, **Ala783**, **Ile729**, **Ala783**, **Ile733**, **Ile729**, **Ile733**, Leu737, Val738, Leu780
	Crepiside E	-7.4	**Tyr511**, **Leu812**, **Tyr517**, Pro535, Asp516, **Tyr533**, **Pro513**, **Tyr533**
	Lupeol	-8.1	Phe615, Lys633, Leu634, Phe615, Lys633, Leu634, Phe615
	Stigmasterol	-7.8	**Ala783**, **Ile729**, **Ala783**, Met781

Note: Amino acid residues are bolded and colored red, green, and blue indicating similarities with control amino acid residues that interact with protein targets.

While the eight active compounds of *Elephantopus scaber* that are predicted to have activity as anti-hypercholesterolemia are Epifriedelanol, Dotriacontanol, 1-Triacontanol, Vernoflexuoside, Stigmasterol glucoside, Crepiside E, Lupeol, and Stigmasterol (Table 1).

Lipinski's Rule of Five illustrates a compound's oral bioavailability by indicating the degree of permeability or absorption of lipid bilayers found in the human body. The Lipinski rule, which states that a compound's maximal molecular weight cannot exceed 500, its log P cannot exceed 5, its donor hydrogen bond cannot exceed 5, and its number of hydrogen bond acceptors cannot exceed 10, will be satisfied by good bioavailability. Based on the results of ADME analysis using Lipinski's rules (Table 3), the active compounds of *Anredera cordifolia* and *Elephantopus scaber* showed drug-likeness.

The boiled egg may be applied to assess brain penetration (BBB) and passive gastrointestinal absorption (HIA). The yolk (yellow region) has a higher chance of brain penetration, whereas the white part has a higher possibility of passive absorption by the GIT. Furthermore, the spots are colored red if P-gp is projected to be non-substrate and blue if P-gp is predicted to be actively effluxing (PGP+). Based on Figure 1, the Egan's BOILED-Egg permeation predictive model diagram demonstrates that some active chemicals from *Anredera cordifolia* and *Elephantopus scaber* such as Larreagenin A, Ursolic acid, Stigmasterol glucoside, and Vernoflexuoside have a high potential to be well-absorbed but not penetrate the brain.

A web server called ProTox-II uses machine learning methods to forecast a chemical compound's level of toxicity. To evaluate key toxicity endpoints, such as acute toxicity (LD50 values), organ toxicity (hepatotoxicity), carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. The results of the analysis using Protox II, based on the LD50 values of the active compounds analyzed, the toxicity classification is at a value between 4-6, from the level of danger, possibly dangerous and non-toxic (Table 4). This indicates that in general, the active compounds are in the safe category, although caution is required. However, based on its toxic effects on organs, cellular proteins, and other biomolecules, it was found that ursolic acid was hepatotoxic, carcinogenic, and immunotoxic. Larreagenin A is predicted to be carcinogenic, while several other compounds namely vernoflexuoside, stigmasterol glucoside, crepiside E lupeol, and stigmasterol are predicted to be immunotoxic.

The results of previous studies on Ursolic Acid showed cytotoxic activity, and the synthetic compounds of the Ursolic Acid derivates have anti-cancer activity.[31] Table 5 showed that the active compounds Ursolic acid (-8.7) and Calenduloside E (-8.1) showed strong binding to the active site of the HMG-CoA reductase enzyme similar to atorvastatin. Ursolic acid had two amino acid residues in common with atorvastatin namely His635 and Ala585, while Calenduloside E had three amino acid residues namely Gln632, Gln632 and His635. This result is different from the results of molecular docking analysis of the active compounds catechins and schisandrin from *Piper crocatum* Ruiz & Pav.[32] Crepiside E showed a strong binding with HMG-CoA reductase which was characterized by its binding affinity value of -7.4 and binding sites on amino acid residues that correspond to simvastatin, namely Tyr511, Leu812, Tyr517, Tyr533 and Pro513. Stigmasterol glucoside and Stigmasterol showed strong binding to the active site of the HMG-CoA reductase

enzyme similar to Fluvastatin, namely at amino acid residues Ala783, Ile729, Ala783, Ile733, Ile729, Ile733 for Stigmasterol glucoside and Ala783, Ile729, Ala783 for Stigmasterol. Unlike the Larreagenin A, Lupeol and Vernoflexuoside, although they had a very strong binding affinities (-8.4, -8.1 and -7.6, respectively), there are no amino acid residues similar to the three control drugs at the binding site with the target protein. The results of previous studies showed that molecular docking analysis of ursolic acid against six target genes associated with osteoporosis, namely CASP3, IL6, MAPK8, JUN, TP53 and VEGFA proved to have strong binding activity.[32] The results of docking analysis of synthetic compounds of Ursolic Acid derivatives (3β-(L-prolyloxy)-urs-12-en-28-oic acid methyl ester hydrochloride) against estrogen receptors showed to have stronger binding activity than estradiol. The ursolic acid derivative compound was produced through the substitution process of several amino acids and dipeptides at the C-3 position of the steroid skeleton.[33,34]

The more negative the binding affinity and the higher the level of similarity of amino acid residues between the active compound and the control (simvastatin, atorvastatin or fluvastatin) which binds to HMG-CoA reductase indicates that the active compound is the best drug candidate as an HMG-CoA reductase inhibitor such as Stigmasterol glucoside and Crepiside E.

CONCLUSIONS

Both *Anredera cordifolia* and *Elephantopus scaber* plants showed potential as anti-hypercholesterolemic drugs through inhibition of HMG-CoA reductase activity. Several active compounds such as Ursolic acid, Calenduloside E, Stigmasterol glucoside, and Crepiside E showed more potential results as HMG-CoA reductase inhibitors compared to the others. The active compounds from *Anredera cordifolia* and *Elephantopus scaber* showed drug-likeness, were able to be absorbed well in the intestines, and had no penetration into the blood-brain barrier. Further studies are needed both in vitro and in vivo to examine the therapeutic effects of these two plants.

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