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Activity of Phenolic Compounds in Figs (*Ficus carica* L.) as Antihyperlipidemic through in Silico Study

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ABSTRACT

Figs (Ficus carica L.) belongs to family Moraceae which contains a lot of phenolic compounds that have an antihyperlipidemic effect. However, the phenolic compounds of figs have not been intensively studied. The purpose of this study was to determine the activity of phenolic compounds in figs as antihyperlipidemic in inhibiting the work of the HMG-CoA reductase enzyme. This research uses an experimental technique with the in silico method. The in-silico method was performed to predict the physicochemical, pharmacokinetic, toxicity, and molecular docking properties by comparing the phenolic compounds in figs and Pravastatin with the HMG-CoA reductase receptor. Rutaretin, Pimpinellin dan Seselin has the highest affinity values, met the physicochemical, pharmacokinetic, and toxicity parameters compared to Psoralen, 8-Methoxypsoralen, Angelicin, Bergapten and Pravastatin control compounds. The presence of this binding enzyme was able to inhibit the work activity of HMG-CoA reductase with amino acid residues Cys526, Gln814, Ile536, Leu811, Ile762, Pro813, Ala763, Ala556, Val538, Pro535, Tyr533, Met534, Gly765, Tyr517, Val522, Cys527. These results suggest that phenolic compounds Rutaretin, Pimpinellin, and Seselin in figs could be an antihyperlipidemic on inhibiting the action of HMG-CoA reductase enzyme.

Keywords: Fig (Ficus carica L.), Phenolic, Antihyperlipidemic, HMG-CoA reductase

INTRODUCTION

Foods that are high in lipid content are currently very popular with the public. Some foods that are categorized as containing high lipids are foods with coconut milk, fried foods, meat, offal, and fast food (Setyaji et al., 2018). The existence of this diet causes an increase in lipid levels in the blood or what is often known as hyperlipidemic. This

situation can cause cardiovascular disease and can increase the human mortality ratio. Hyperlipidemic is a condition in which the distribution of lipids in the body increases, including Low-Density Lipoprotein, Very Low-Density Lipoprotein, free fatty acids, and triglycerides (Saputri & Sumiwi, 2019). The disorder is characterized by an increase in blood lipid levels (fats or fat-like compounds), especially cholesterol and triglycerides contained in the food consumed. An increase in triglyceride levels that exceeds normal levels (>200 mg/dl) indicates that the body is not working optimally to process food into energy (Refdanita et al., 2021; Sa'adah et al., 2018). If not treated properly, hyperlipidemic can cause coronary heart disease and stroke and can cause Alzheimer's disease, vascular dementia, and Parkinson's disease (Simatupang, 2017).

The treatment for hyperlipidemic is done through lifestyle and pharmacological changes. Controlling hyperlipidemic in the form of lifestyle changes includes avoiding foods that have a high-fat content, diligently exercising, and drinking lots of water and high fiber (Kumala et al., 2021). In addition to lifestyle changes, pharmacological therapy can be used by reducing plasma lipid profile levels and increasing plasma High-Density Lipoprotein levels (Rochim et al., 2021). One form of pharmacological therapy is by using statin treatment. Statins have a mechanism of action as the first line of hyperlipidemic therapy by inhibiting the action of the HMG-CoA reductase enzyme and increasing the activity of the LDL receptor (Maulana et al., 2019; Wulandari et al., 2015)

However, drugs based on statins, beta-blockers, and other lipid-lowering drugs can cause dangerous side effects such as liver damage, rhabdomyolysis, neoplasia, malaise, myopathy, hyperglycemia, hyperuricemia, flushing, and others (Sakaganta & Sukohar, 2021; Yuniarti et al., 2016). One type of statin-based drug that is often used by the public is pravastatin. The drug turned out to have a mechanism of action that is imperfectly absorbed in the gastrointestinal tract and undergoes first-pass metabolism in the liver so that it can cause the accumulation of statins in the liver. One alternative that is used to prevent side effects from synthetic chemical drugs is the use of plants as herbal therapy ingredients (Dwinanda et al., 2019). People assume that herbs are believed to have therapeutic effects, are easy to obtain, and are considered safer to overcome disease naturally and achieve optimal health to treat disease and improve health (Christina et al., 2016).

One of the plants that can be used as an ingredient in hyperlipidemia therapy is the fig or *Ficus carica* L. This plant belongs to the Moraceae family. Figs contain large amounts of phenolic compounds, namely polyphenols and flavonoids (Joseph & Raj, 2011; Kalaskar et al., 2010). Another study identified figs with high phytochemical content in phenols (Qusti et al., 2010). Research by Marrelli et al., (2012) stated that fig extract contains phenolic compounds in the form of Psoralen, 8-Methoxypsoralen, Angelicin, Bergapten, Rutaretin, Pimpinellin, and Seselin.

Drug design is an effort to get new drugs with better activity and the fewest side effects (Shofi, 2021a). The process of changing the structure of chemical compounds can reduce the risk of side effects from drug use (Pagadala et al., 2017).. One of the methods that can be chosen is to use a computational chemistry method, namely molecular docking. This method is a preliminary study that aims to improve research accuracy so that it can save energy, time, and costs (Putri, 2019; Shofi, 2021b).

Based on this description, this study aims to evaluate several bioactive compounds contained in figs through a molecular docking approach using the protein HMG-COA Reductase (PDB: 1DQ9). The results of the study are expected to be a reference for further research in finding drugs to reduce lipid content in the blood.

RESEARCH METHODS

This study used the in silico or molecular docking method by observing the interaction between phenolic compounds in figs such as Psoralen, 8-Methoxypsoralen, Angelicin, Bergapten, Rutaretin, Pimpinellin, and Seselin with the HMG-COA Reductase receptor protein (GDP: 1DQ9). This simulation uses the PyRx 0.08 application and AutoDock Vina 4.2.

The working procedure of the in-silico test of phenolic compounds on figs and a control compound in the form of Pravastatin (a compound against the HMG-COA Reductase receptor protein is as follows.

Receptor Determination

The receptor protein used in this study is HMG-COA Reductase with PDB code 1DQ9 (Navarro-González et al., 2014).

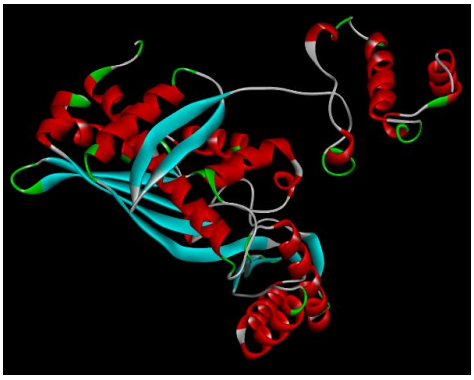


Figure 1. HMG-COA Reductase Receptor Protein (Source: Private Document)

Receptor Preparation

The three-dimensional structure of HMG-COA reductase (GDP: 1DQ9) was obtained from the protein database via the web server http://www.rcsb.org/pdb in pdb format. The pdb file obtained is then processed using AutoDock Vina 4.2. Furthermore, water molecules and ligands that are still attached to the receptor are removed and stored in pdb format. Polar hydrogen atoms are added and stored in pdbqt format (Shofi, 2021c).

Ligand Determination

The ligands used in this study were Psoralen, 8-Methoxypsoralen, Angelicin, Bergapten, Rutaretin, Pimpinellin, and Seselin (Marrelli et al., 2012) which are phenolic compounds in figs and a control compound in the form of pravastatin in the 3D form obtained from the PubChem webserver (http://pubchem.ncbi.nlm.nih.gov).

Receptor-Ligan Docking

The 3D structure of phenolic compounds in figs and Pravastatin was then converted using Open Babel and optimized using the PyRx program. The next process is the preparation of HMG-COA reductase protein by separating the native ligand from the protein structure using Autodock vina 4.2. Validation of the molecular docking method was carried out by re-docking native ligands to the removed protein using the Autodock 4.2 program. The phenolic compounds of figs and the control compounds resulting from the optimization were then docked on the proteins that had their native ligands removed using the PyRx program. The analysis results show the lowest conformational binding energy to bind to the target protein (Shofi, 2021b).

Physicochemical Prediction

Physicochemical prediction of phenolic compounds in figs and control compounds in the form of Pravastatin using molecular weight (BM) <500, the logarithm of octanol/water partition coefficient (LogP) <5, hydrogen bond donor (HBD) <5, hydrogen bond acceptor (HBA) <10 and surface area < 140Å. The physiochemical prediction of the compounds contained in the phenolic compounds in figs is using Lipinski's rule of five which refers to the research of Hartati et al. (2021) and Shofi (2021a).

Pharmacokinetic Prediction

Pharmacokinetic prediction is used as a step to test the bioavailability and toxicity of an active compound using ADME parameters and prediction of toxicity based on the level of solubility in the intestine, metabolism of drug compounds, excretion in the liver, and toxicity and carcinogenicity of drug compounds (Shofi, 2021c; Sugiharto *et al*., 2021). Prediction of pharmacokinetic results (ADMET) using the webserver http://biosig.unimelb.edu.au/pkcsm/prediction by evaluating the phenolic compounds of fig

seeds and control compounds in the form of Pravastatin based on solubility in water. Absorption uses indicators of absorption potential through the intestine, distribution uses indicators of ability to penetrate BBB and the number of active compounds in unbound form, metabolism uses indicators of cytochrome P450 enzyme activation, excretion uses indicators of clearance of active compounds in the liver, kidneys and biliary tract. Toxicity uses hepatotoxic indicators and carcinogenesis potential (Pires *et al.*, 2015; Sugiharto *et al*., 2021). Determination of the LD50 value using the https://tox-new.charite.de/protox_II/ webserver by evaluating the LD50 value recorded on the webserver (Ruswanto *et al.*, 2017).

Data Analysis

Analysis of the data in the form of affinity values for phenolic compounds in figs and control compounds in the form of Pravastatin to the target protein HMG-COA reductase which was measured by comparing the value of free binding energy and the number of amino acid residues bound to phenolic compounds in figs and pravastatin. The result of molecular docking is the bond energy. The bond energy value shows the strength of the bond between the compound and the receptor. The lower the bond energy value, the stronger and more stable the bond will be (Shofi, 2021a). The data obtained were then analyzed descriptively by comparing the predicted physicochemical values, pharmacokinetic predictions, bond energy values and amino acid residues (Shofi, 2021a).

RESULT AND DISCUSSION

The results of the physicochemical predictions on the phenolic compounds contained in figs and the control compound Pravastatin are shown in Table 1, where the phenolic compounds in the form of Psoralen, 8-Methoxypsoralen, Angelicin, Bergapten, Rutaretin, Pimpinellin, and Seselin meet the 5 criteria in Lipinski's rule. While the control compound is pravastatin, only 4 criteria in Lipinski's rule are met, namely molecular weight, logP, torsion, hydrogen bond acceptors, and hydrogen bond donors. The fulfillment of Lipinski's law is to determine the physicochemical properties of ligands in determining the hydrophobic or hydrophilic character of a compound to pass through cell membranes by passive diffusion and to describe the solubility of compounds in penetrating cells through passive diffusion mechanisms (Sugiharto et al., 2021; Syahputra et al., 2014; Widiandani et al., 2013). The existence of physicochemical similarities between the phenolic compounds contained in figs and the control compounds can be said to have similarities so that they can be used as drug candidates. In addition, the insoluble nature of Pravastatin in water which is similar to the phenolic compounds in figs makes it difficult to absorb in the intestines so that these compounds can work effectively in the intestinal lumen.

Table 1. Physicochemical Parameter Test Results (Lipinski Rule of Five) on Phenolic Compounds Contained in Figs

Compound	BM	LogP	Torsion	HBA	HBD	PSA(A^2)	Information
Psoralen	186.166	2.5392	0	3	0	78.555	Meet 5 Criteria
8-Methoxypsoralen	216.192	2.5478	1	4	0	90.034	Meet 5 Criteria
Angelicin	186.166	2.5392	0	3	0	78.555	Meet 5 Criteria
Bergapten	216.192	2.5478	1	4	0	90.034	Meet 5 Criteria
Rutaretin	262.261	1.573	1	5	2	108.600	Meet 5 Criteria
Pimpinellin	246.218	2.5564	2	5	0	101.512	Meet 5 Criteria
Seselin	228.247	2.9772	0	3	0	98.322	Meet 5 Criteria
Pravastatin	424.534	2.4404	10	6	4	177.991	Meet 4 Criteria

Note : BM = Molecular Weight (<500); LogP = logarithm of octanol/ water partition coefficient (< 5); Torsion = bond between rotating atoms; HBA = Hydrogen Bond Acceptors (<10); HBD = Hydrogen Bond Donors (< 5); PSA = Polar Surface Activity (< 140Å).

Lipinski (2004) said if the compound fails to meet the Lipinski Rule of Five, it is likely that there is a problem related to the absorption of the drug orally. However, a compound that complies with the Lipinski Rule of Five does not guarantee to have good activity because this law is not related to the specific chemical structure contained in a compound. Based on Chander et al. (2017) stated that clinically approved drugs must meet the requirements in the form of Molecular Weight between 130 to 725 g/mol, Hydrogen Bond Donors between 0 to 6, Hydrogen Bond Acceptors between 2 to 20, Log P between -2 to 6.5, and Atomic which can rotate between 0–15. Based on this statement, the phenolic compounds contained in the figs meet the requirements if they will be used as drug candidate compounds in inhibiting the HMG-CoA reductase enzyme based on physicochemical predictions. While the control compound Pravastatin is used as a clinical drug in reducing hyperlipidemic (Suprapti, 2018).

The next step is based on the absorption criteria for the phenolic compounds contained in figs and the Pravastatin absorption value exceeds 30%. This absorption value

shows how strongly drug compounds are absorbed in the intestine because the intestine is the main place for absorption of drugs given orally (Hardjono, 2017). The absorption value is said to be good if the molecule absorbed is more than 30% (Shofi, 2021c). This indicates that the compound is slightly absorbed in the intestine so that it can work optimally in the intestinal lumen.

The second criterion is skin permeability, to see that the compound has a skin permeability log Kp > -2.5 (Krihariyani et al., 2020; Pires et al., 2015) Based on the value of Skin Permeability (log Kp) of phenolic compounds contained in figs and pravastatin has a log Kp value of more than -2.5. This means that the phenolic compounds contained in figs and pravastatin have good skin permeability. Drug materials that have good skin permeability can be used as a consideration for the development of new drugs by transdermal administration (Krihariyani et al., 2020).

The next criterion is the Volume of Distribution at Steady State (VDSS), which is a volume that shows the value of a total dose of a drug that is thoroughly distributed and has a concentration like blood plasma (Krihariyani et al., 2020). The higher the VDSS value, the more the drug is distributed in the tissues than in the blood plasma (Pires et al., 2015). In the distribution profile, a compound is declared to have a high volume of distribution if the Log VDSS value > 0.45 and low if the Log VDSS < 0.15 (Hardjono, 2017). Based on table 2, it is known that the VDSS values of the phenolic compounds contained in figs, namely Psoralen, 8-Methoxypsoralen, Angelicin, Bergapten, Pimpinellin, and the control compound Pravastatin had low VDSS values, while rutaretin had high VDSS values and Seselin had moderate values. The existence of this can mean that all these compounds can be distributed evenly to provide the same concentration as in blood plasma (Nardina et al., 2021).

In addition to the VDSS value of drug compounds that need to be considered, the blood-brain barrier (BBB) also needs to be considered in predicting drug compounds. This is because the blood-brain barrier is very important. After all, it can determine the ability of these compounds to penetrate the brain and increase the pharmacological activity of drugs in the brain (Hartono et al., 2022). A compound is said to be non-toxic to the brain, namely if the blood-brain barrier value is > 0.3 because the compound can pass through the blood-brain barrier and can be deposited in the brain so that it can affect the performance of the brain (Abdullah et al., 2021). If the blood-brain barrier value is < -1, it indicates that the compound cannot penetrate the blood-brain barrier so it is not toxic to the brain (Carpenter et al., 2014). Psoralen and angelicin compounds have blood-brain barrier values exceeding 0.3, so these compounds are toxic to the brain. However, it was inversely proportional to the control compound, namely pravastatin, which had a value exceeding -1. The existence of this indicates that the control compound indicates that the compound cannot penetrate the Blood-Brain Barrier.

After the drug is distributed, the drug that enters the body undergoes metabolism. The metabolism of this drug is contradicted by the performance of the cytochrome P450 (Hardjono, 2017). Based on the criteria of metabolic properties, all of the test compounds and comparisons of Pravastatin did not activate or inhibit the CYP2D6 enzyme except for the compound bergapten. Extract compounds that can inhibit these cytochromes have the potential for drug interactions, thereby reducing the effectiveness of the drug properties (Abdullah et al., 2021; Ashour et al., 2017). The existence of this can affect the catalysis of cholesterol synthesis so that cholesterol levels in the blood will decrease (Hartono et al., 2022).

The total excretion value is used to predict the absorption of compounds through the liver, bile ducts, and kidneys as measured by the total excretion (CLtot) (Pires et al., 2015). The higher the excretion value, the faster the excretion process carried out by the liver, biliary and kidney (Novianty et al., 2022). Good compound excretion needs to be seen from the molecular weight and hydrophilicity value of the compound, the higher the molecular weight and hydrophobicity values, the smaller the excreted compound so that it can cause poisoning (Krihariyani et al., 2020). In Table 2 it can be seen that both the active compounds contained and the control compounds were able to predict the rate of excretion of these compounds.

Table 2. Pharmacokinetic Parameter Test Results on Phenolic Compounds Contained in Figs

Compound	**Intestinal absorption (human) (%)**	**Skin Permeability (log Kp)**	**VDss (human) (logL/kg)**	**BBB Permeability (logBB)**	**CYP2D6 substrate**	**CYP2D6 inhibitor**	**Total Clearence (log ml/min/kg)**	**Renal OCT2 substrate**	**AMES Toxicity**	**LD_{50} (mg/kg)**	**Class**
Psoralen	96.668	-2.216	-0.13	0.41	No	No	0.773	No	No	322	4
8-Methoxypsoralen	98.341	-2.336	-0.198	0.245	No	No	0.744	No	Yes	422	4
Angelicin	97.593	-2.214	-0.276	0.462	No	No	0.718	No	Yes	322	4
Bergapten	98.344	-2.419	-0.057	0.202	No	Yes	0.805	No	Yes	8100	6
Rutaretin	95.236	-2.797	0.909	0.146	No	No	0.584	No	No	1000	4
Pimpinellin	98.439	-2.461	-0.338	0.149	No	No	0.741	No	No	423	4
Seselin	97.946	-2.282	0.233	0.272	No	No	0.659	No	No	3850	5
Pravastatin	41.431	-2.736	-0.825	-1.056	No	No	1.25	No	No	8939	6

Organic Cation Transporter 2 (OCT2) is a transporter protein in the kidney that plays an important role in the disposal and clearance of endogenous drugs senta. OCT2 substrates have the potential to cause side effects when used with OCT2 inhibitors (Hardjono, 2017; Krihariyani et al., 2020). The phenolic compounds in figs and control compounds had no effect on the OCT2 substrate, so it could be interpreted that the compound was not an OCT2 substrate.

The toxicity of a drug compound can also be determined using the AMES toxicity test. AMES toxicity test is a method that is widely used to assess the mutagenic potential of a compound using bacteria (Krihariyani et al., 2020). If the AMES test result is positive, the compound is predicted to be mutagenic. Based on the results, all phenolic compounds in figs and control compounds did not cause mutagenicity except for 8-Methoxypsoralen, Angelicin, and Bergapten compounds.

In addition to the AMES test, to determine whether the compound has toxicity and mutagenicity, it can be seen through the LD_{50} value. The LD_{50} value indicates that the amount of compound given to experimental animals was able to kill 50% of the experimental animals. The prediction results of the LD_{50} value showed that Psoralen, 8-Methoxypsoralen, Angelicin, Rutaretin, and Pimpinellin were classified as toxicity 4 (300 < LD_{50} 2000 mg/kg) which indicated their toxicity was relatively low and dangerous when ingested (Ruswanto et al., 2017). Seseline compound belongs to category 5 (2000 < LD_{50} 5000 mg/kg) which indicates that it can be harmful if swallowed. Meanwhile, the bergapten compound and the control compound, namely pravastatin, were included in category 6 (LD_{50} > 5000 mg/kg) which is not mutagenic or non-toxic when ingested. This means that all phenolic compounds in figs and control compounds have low toxicity because the higher the LD50 value of the compounds, the lower the toxicity level for these compounds (Ruswanto *et al*., 2017; Supandi *et al.*, 2018).

Table 3 shows that the bioactive compounds 8-Methoxypsoralen, Bergapten, Rutaretin, and Seselin in figs have lower binding energies than control compounds, namely Pravastatin. That means that the compound can ware used as an inhibitor of the HMG-COA reductase enzyme. The binding energy of the control compound and protein HMG-COA reductase was -6.4. The amount of binding energy (ΔG) was an indicator of the binding of the active compound to the target protein (Hartati et al., 2021). Protein-ligand binding only occurs when the change in the Gibbs free energy (ΔG) of the system is negative when the system reaches equilibrium at constant pressure and temperature. The magnitude of negative ΔG determines the degree of protein-ligand association. The ΔG can ware considered to determine the stability of the existing protein-ligand complex or the binding affinity of the ligand to certain acceptors (Matter & Güssregen, 2018).. Based on these statements, 8-Methoxypsoralen, Bergapten, Rutaretin, and Seselin compounds in figs can predict spontaneous binding to the active site of the HMG-COA reductase receptor protein to form a stable protein-ligand complex.

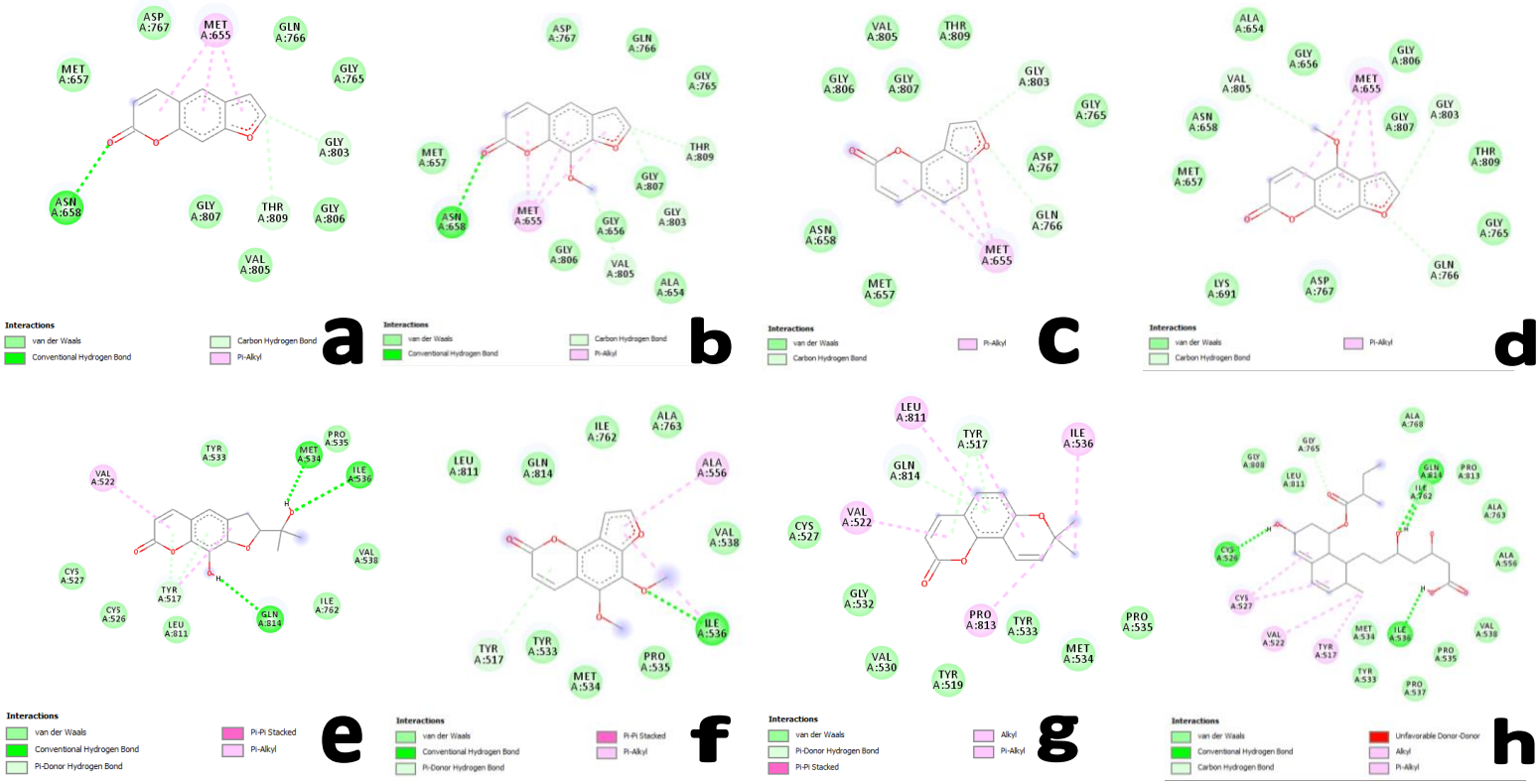
The ability to bind a receptor-ligand is called affinity, which was determined by the free bond energy, inhibition constant, surface interactions, and the number of bound amino acid residues. If the value of the free bond energy is less than or equal to -7kcal/mol, the compound's affinity for the enzyme had expected to be high. That means that energy describes the spontaneity and stability of the bond (Purnomo et al., 2015).. The low inhibitory constant indicates that the barrier between the ligand and protein is small, so it is easy to bind to the receptor (Arrasyid et al., 2020; Muttaqin, 2019).

Table 3. Molecular Docking Test Results on Phenolic Compounds Contained in Figs with Pravastatin

Ligan	Binding Affinity (Kkal/mol)	Amino Acid Residue	Total Amino Acid Residues Compared to Pravastatin	Percentage of Amino Acid Similarities (%)
Psoralen	-6.2	• Conventional Hydrogen Bond : Asn658 • Van der Waals : Met657, Asp767, Gln766, **Gly765**, Gly806, Gly807, Val805 • Carbon Hydrogen Bond : Gly803, Thr809 • Pi-Alkyl : Met655	1	9.09
8-Methoxypsoralen	-6.7	• Conventional Hydrogen Bond : Asn658 • Van der Waals : Met 657, Asp767, Gln766, **Gly765**, Gly807, Gly656, Ala654, Gly806 • Carbon Hydrogen Bond :Thr809, Gly803, Val805 • Pi-Alkyl : Met655	1	7.69
Angelicin	-6.3	• Van der Waals : Gly806,Val805, Gly807, Thr809, **Gly765**, Asp767, Met657, Asn658 • Carbon Hydrogen Bond : Gly803, Gln766 • Pi-Alkyl : Met655	1	9.09
Bergapten	-6.4	• Van der Waals : Met657, Asn658, Ala654, Gly656, Gly806, Gly807, Thr809, **Gly765**, Asp767, Lys691 • Carbon Hydrogen Bond : Val805, Gln766 • Pi-Alkyl : Met655	1	7.69
Rutaretin	-7.1	• Conventional Hydrogen Bond : **Met534**, **Ile536**, **Gln814** • Van der Waals : **Tyr533**, **Pro535**, **Val538**, **Ile762**, **Leu811**, **Cys526**, **Cys527** • Pi-Donor Hydrogen Bond : **Tyr517** • Pi-Alkyl : **Val522**	12	100
Pimpinellin	-6.2	• Conventional Hydrogen Bond : **Ile536** • Van der Waals : **Leu811**, **Gln814**, **Ile762**, **Ala763**, **Val538**, **Pro535**, **Met534**, **Tyr533**	11	100

Ligan	Binding Affinity (Kkal/mol)	Amino Acid Residue	Total Amino Acid Residues Compared to Pravastatin	Percentage of Amino Acid Similarities (%)
		• Carbon Hydrogen Bond :**Tyr517** • Pi-Alkyl :**Ala556**		
Seselin	-6.8	• Van der Waals : **Cys527**, Pro535, **Met534**, **Tyr533**, Tyr519, Val530, Gly532, **Gln814**, **Tyr517** • Alkyl dan Pi-Alkyl : **Val522**, **Leu811**, **Ile536**, **Pro813**	9	69.23
Pravastatin	-6.4	• Conventional Hydrogen Bond : **Cys526**, **Gln814**, **Ile536** • Van der Waals : Gly808, **Leu811**, **Ile762**, Ala768, **Pro813**, **Ala763**, **Ala556**, **Val538**, **Pro535**, Pro537, **Tyr533**, **Met534** • Carbon Hydrogen Bond : **Gly765** • Alkyl dan Pi-Alkyl : **Tyr517**, **Val522**, **Cys527**	19	100

The high surface interaction indicates a high probability of the active compound interacting with the target protein. Based on the intermolecular interactions between drugs and proteins, amino acid residues determine the active site of the enzyme (Ishmahdina et al., 2021). Determination of amino acid residues that bind to the HMG-COA reductase target protein and determine the strength of the bond between the active compound and the target protein. The strong binding to the target protein can occur by hydrogen bonding with the same amino acid residues compared to the control reference active compound, namely Pravastatin. The results of the amino acid residue bonding can be seen in Figure 1.



Gambar 1. Interaksi Ligan-Protein (a) Psoralen, (b) 8-Methoxypsoralen, (c) Angelicin, (d) Bergapten, (e) Rutaretin, (f) Pimpinellin, (g) Seselin, dan (h) Pravastatin (Senyawa Kontrol)

Table 3 shows that the control compound pravastatin binds to the active site of the target protein by hydrogen bonding with the following amino acid types Cys526, Gln814, and Ile536; via Van der Waals with the amino acids Gly808, Leu811, Ile762, Ala768, Pro813, Ala763, Ala556, Val538, Pro535, Pro537, Tyr533, and Met534; through the Carbon Hydrogen Bond, namely Gly765; and Alkyl and Pi-Alkyl namely Tyr517, Val522, Cys527. Based on various amino acid residues, the test compounds and control compounds had similarities including Cys526, Gln814, Ile536, Leu811, Ile762, Pro813, Ala763, Ala556, Val538, Pro535, Tyr533, Met534, Gly765, Tyr517, and Val522, Cys527. The similarity of these residues can be predicted that the compounds Rutaretin, Pimpinellin, and Seselin have a high degree of similarity with the control compounds so that they can be used to inhibit the work of the HMG-COA reductase enzyme.

Bioactive compounds ware predicted to have strong binding to the target receptor if they can bind tightly via hydrogen bonds and bind to one amino acid residue from the active site compared to a reference or inhibitor compounds. A hydrogen bond is an electrostatic interaction between a hydrogen atom bonded to an electronegative atom and another electronegative atom. The strength of the hydrogen bond is below that of the covalent bond, but its presence is significant. Its presence contributes to the structure and characteristics of the molecule. Hydrogen bonding in medicine plays a role in studying the design and interactions between drug molecules and metabolic systems in the body (Kharisma et al., 2018). Therefore, phenolic compounds in figs such as Rutaretin, Pimpinellin, and Seselin can be used as drug candidate compounds to inhibit the action of the HMG-COA reductase enzyme because there are hydrogen bonds from amino acid residues that are similar to control compounds.

CONCLUSION

Based on the results of the research and discussion, it can be concluded that from all the parameters studied, the compounds Rutaretin, Pimpinellin, and Seselin met the physicochemical, pharmacokinetic (ADME) properties, toxicity, and affinity values of antilipidemic drug compounds. These results indicate that figs are safe for consumption to inhibit the action of the HMG-COA reductase enzyme in lowering blood lipid levels.

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